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EDITORIAL

Risk factors for herpes simplex virus transmission to pregnant women: A couples study
David A. Baker, MD
Stony Brook, NY

Environmental contaminants and maternal thyroid function
Brian Casey, MD
Dallas, TX

EDITORS’ CHOICE

Risk factors for herpes simplex virus transmission to pregnant women: A couples study
Carolyn Gardella, MD, MPH, Zane Brown, MD, Anna Wald, MD, MPH, Stacy Selke, MS, Judy Zeh, PhD, Rhoda Ashley Morrow, PhD, Lawrence Corey, MD
Seattle, WA

Among susceptible pregnant women with serologically discordant partners, having a partner with oral herpes and duration of sexual partnership 1 year or less were risk factors for herpes simplex virus-1 and herpes simplex virus-2 acquisition, respectively.

Dioxin-like activity and maternal thyroid hormone levels in second trimester maternal serum
Warren G. Foster, PhD, Alison C. Holloway, PhD, Claude L. Hughes, Jr, MD, PhD
Hamilton, Ontario, Canada, and Greenville, NC

This study demonstrates that environmental contaminants with dioxin-like activity are detectable in an overwhelming majority of second-trimester maternal serum samples.

Commentary
Foster et al found that more than 95% of women had measurable levels of dioxin in their serum in the second trimester. We asked Dr Brian Casey to comment on the clinical implications of this observation.
Damage to ovarian reserve associated with laparoscopic excision of endometriomas: A quantitative rather than a qualitative injury

Guido Ragni, MD, Edgardo Somigliana, MD, Francesca Benedetti, MD, Alessio Paffoni, BS, Walter Vegetti, MD, Liliana Restelli, BS, Pier Giorgio Crosignani, MD

Milan, Italy

Laparoscopic excision of endometriomas is associated with a quantitative but not a qualitative damage to ovarian reserve.

Commentary
The potential deleterious effects on ovarian function associated with the excision of ovarian endometriomas have long been a subject of debate. The study of Ragni et al demonstrated that a quantitative reduction in ovarian reserve based on the number of follicles and oocytes retrieved during IVF cycles was associated with laparoscopic excision of endometriomas. However, it was reassuring that there was no adverse qualitative changes in ovarian reserve.

CLINICAL OPINION
To the point: Medical education reviews—Dealing with student difficulties in the clinical setting

Patricia J. Hicks, MD, Susan M. Cox, MD, Eve L. Espey, MD, Alice R. Goepfert, MD, Jessica L. Bienstock, MD, Sonya S. Erickson, MD, Maya M. Hammoud, MD, Nadine T. Katz, MD, Paul M. Krueger, DO, James J. Neutens, PhD, Edward Peskin, MD, Elizabeth E. Puscheck, MD

Dallas, TX, Albuquerque, NM, Birmingham, AL, Baltimore, MD, Denver, CO, Bronx, NY, Stratford, NJ, Knoxville, TN, Worcester, MA, and Ann Arbor and Detroit, MI

Strategies for identification, assessment, intervention, and prevention of problems associated with the difficult student are discussed.

REVIEW ARTICLE
Etiology and prevention of stillbirth

Ruth C. Fretts, MD, MPH

 Wellesley, MA

GENERAL OBSTETRICS AND GYNECOLOGY: GYNECOLOGY
The direct cost of stress urinary incontinence among women in a Medicaid population

Kraig S. Kinchen, MD, MSc, Stacey Long, MS, Stella Chang, MPH, Tammy K. Girts, PharmD, MS, Barbara Pantos, RN, MS

Indianapolis, IN, Hampden, ME, Washington, DC, and Ridgefield, CT

Utilization and costs of stress urinary incontinence treatment remain low among women enrolled in Medicaid.
Analysis of knowledge and attitudes of adult groups before and after attending an educational presentation regarding adolescent sexual activity
Patricia J. Sulak, MD, Sara Herbelin, MS, Alicia L. Kuehl, BS, Thomas J. Kuehl, PhD
Temple, TX

Educating adults on the ramifications of adolescent sexual activity results in significant improvement in knowledge and a shift in attitude favoring adolescents delaying sexual activity.

Glycodelin reduces carcinoma-associated gene expression in endometrial adenocarcinoma cells
Hannu Koistinen, DSc, Markku Seppälä, MD, Balint Nagy, PhD, Johanna Tapper, MD, Sakari Knuutila, PhD, Riitta Koistinen, PhD
Helsinki, Finland

Transfection of glycodelin cDNA into glycodelin-negative endometrial adenocarcinoma cells reduces cell proliferation and carcinoma-associated gene expression.

Neovascularization and mast cells with tryptase activity increase simultaneously with pathologic progression in human endometrial cancer
Domenico Ribatti, MD, Nicoletta Finato, MD, Enrico Crivellato, MD, Andrea Marzullo, MD, Domenica Mangieri, PhD, Beatrice Nico, PhD, Angelo Vacca, MD, Carlo A. Beltrami, MD
Bari and Udine, Italy

Mast cells, angiogenesis, and endometrial cancer.

GENERAL OBSTETRICS AND GYNECOLOGY: OBSTETRICS

Noninvasive prenatal RHD genotyping by real-time polymerase chain reaction using plasma from D-negative pregnant women
Lan Zhou, MD, PhD, John A. Thorson, MD, PhD, Clark Nugent, MD, Robertson D. Davenport, MD, Suzanne H. Butch, MA, MT (ASCP) SBB, W. John Judd, FIBMS, MIBiol
Ann Arbor, MI, and Cleveland, OH

Prenatal noninvasive RHD genotyping by real-time polymerase chain reaction on maternal plasma predicts the fetal Rh status with 94% accuracy.

Simulation of therapy in a model of a nonhydropic and hydropic recipient in twin-twin transfusion syndrome
Jeroen P. H. M. van den Wijngaard, MSc, Michael G. Ross, MD, MPH, Jos A. P. van der Sloot, MD, PhD, Yves Ville, MD, Martin J. C. van Gemert, PhD
Amsterdam, The Netherlands, Torrance, CA, and Poissy, France

Mathematical modeling of twin-twin transfusion syndrome predicts different therapeutic responses to select treatment options dependent on the presence of a nonhydropic versus hydropic recipient twin.

Risk during pregnancy—Self-report versus medical record
Tay K. McNamara, PhD, E. John Orav, PhD, Louise Wilkins-Haug, MD, PhD, Grace Chang, MD, MPH
Boston, MA

Self-report on the T-ACE alcohol screening questionnaire identifies more women at risk for prenatal alcohol use than information documented in the medical record.

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**Electrical inhibition of preterm birth: Inhibition of uterine contractility in the rabbit and pup births in the rat**  
Jeffrey Karsdon, MD, Robert E. Garfield, PhD, Shao-Qing Shi, MD, William Maner, BS, George Saade, MD  
New York, NY, and Galveston, TX

An electrical current can inhibit in vivo spontaneously contracting preterm and term uterine tissue.

**Increasing prepregnancy body mass index: Analysis of trends and contributing variables**  
John Yeh, MD, James A. Shelton, MS  
Buffalo, NY

A population-based analysis demonstrates an increased prepregnancy body mass index in almost all subgroups of patients who delivered a live birth in the last 5 years.

**Cervical anti-inflammatory cytokine concentrations among first-trimester pregnant smokers**  
Hyagriv N. Simhan, MD, MSCR, Steve N. Caritis, MD, Sharon L. Hillier, PhD, Marijane A. Krohn, PhD  
Pittsburgh, PA

Smoking in pregnancy is associated with an alteration of cervical innate immunity, as represented by 3 anti-inflammatory cytokines, which may impact the host response to infection.

**Citalopram use in pregnancy: Prospective comparative evaluation of pregnancy and fetal outcome**  
Anna Sivojelezova, BSc, Samar Shuhaiber, MSc, Lorig Sarkissian, BSc, Adrienne Einarson, RN, Gideon Koren, MD  
Ontario, Canada

Citalopram is not associated with a major teratogenic risk in pregnancy; however, late pregnancy use can lead to an increased risk of poor neonatal adaptation syndrome, recently described with other selective serotonin reuptake inhibitors.

**Activity of hepatic enzymes from week sixteen of pregnancy**  
Aнгесеs Ruiz-Estremerа, MD, Маriа Lореz-Garridо, MD, Еntriqueta Barranco, MD, Маriа D. Quinterо, MD, Еsther Ocetе-Hita, MD, Палома Muñoz de Ruedа, PhD, Ana Gila, MD, Javier Salmerón, MD  
Granada, Spain

Study of hepatic enzyme activity from week 16 of pregnancy and mother-child repercussions of increased alanine-aminotransferase levels.

**Adipose tissue from pregnant women with and without gestational diabetes mellitus: Insulin-sensitive but resistant to hyperosmolarity**  
Anthony W. Russell, PhD, H. David McIntyre, MB, BS, Jon P. Whitehead, PhD, Johannes B. Prins, PhD  
Brisbane and South Brisbane, Australia

Insulin-stimulated glucose uptake in adipose tissue is not impaired in pregnancy or gestational diabetes mellitus, but hyperosmolar-stimulated glucose uptake is impaired in these conditions.
CLASSIC PAGES IN OBSTETRICS AND GYNECOLOGY

Endocrine functions of the human fetoplacental unit
Egon Diczfalusy
Ronninge, Sweden
An excerpt from Federation Proceedings 1964;23:791-8, with a commentary by Laurence D. Longo, MD, followed by My Life with the fetal-placental unit by Egon Diczfalusy, MD.

TRANSACTIONS FROM THE 31st ANNUAL SCIENTIFIC MEETING
OF THE SOCIETY OF GYNECOLOGIC SURGEONS

Presidential Address: The Chickens
Thomas G. Stovall, MD
Memphis, TN

Racial differences in pelvic morphology among asymptomatic nulliparous women as seen on three-dimensional magnetic resonance images
Lennox Hoyte, MD, MSEECS, John Thomas, MD, Raymond T. Foster, MD, Susan Shott, PhD, Marianna Jakab, MSEECS, Alison C. Weidner, MD
Boston, MA, Durham, NC, and Chicago, IL
Differences in female pelvic soft tissue bulk and morphology are seen in age matched African-American and white nulliparous women. Whether these differences are related to reported differences in the prevalence of pelvic floor dysfunction among races needs further evaluation.

Is previous cesarean section a risk for incidental cystotomy at the time of hysterectomy?: A case-controlled study
Christopher M. Rooney, MD, Adam T. Crawford, MD, Brett J. Vassallo, MD, Steven D. Kleeman, MD, Mickey M. Karram, MD
Cincinnati, OH, and Park Ridge, IL
Previous cesarean section is an independent risk factor for incidental cystotomy at the time of hysterectomy.

Bleeding complications with the tension-free vaginal tape operation
Dieter Kölle, MD, Karl Tamussino, MD, Engelbert Hanzal, MD, Ayman Tammaa, MD, Oliver Preyer, MD, Arnim Bader, MD, Hermann Enzelsberger, MD, PhD, George Ralph, MD, Paul Riss, MD, for the Austrian Urogynecology Working Group
Innsbruck, Vienna, Steyr, Leoben, and Mödling, Austria
The rate of reinterventions for bleeding complications with the tension-free vaginal tape operation was 0.8%.

Rectoceles and the anatomy of the posterior vaginal wall: Revisited
Steven D. Kleenan, MD, Cynthia Westermann, MD, Mickey M. Karram, MD
Cincinnati, OH
There is no histologic evidence of fascia in the posterior vaginal wall, and the tissue used for vaginal repair of anterior rectal wall prolapse is the dissected layers of adventitia and fibromuscular layers from the vagina.

A six-year study of surgical teaching and skills evaluation for obstetric/gynecologic residents in porcine and inanimate surgical models
Gretchen M. Lentz, MD, Lynn S. Mandel, PhD, Barbara A. Goff, MD
Seattle, WA
A comprehensive curriculum for training and testing resident's surgical skills may improve performance as evaluated by bench skill testing and objective structured assessment of technical skills.

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Ovarian remnant syndrome 2062
Paul M. Magtibay, MD, Jessica L. Nyholm, MD, Jose L. Hernandez, Karl C. Podratz, MD, PhD
Scottsdale, AZ, and Rochester, MN

Surgical management of ovarian remnant syndrome in 186 patients with a prior history of bilateral salpingo-oophorectomy produced relief of continued symptoms in more than 90%.

Regret, satisfaction, and symptom improvement: analysis of the impact of partial colpocleisis for the management of severe pelvic organ prolapse 2067
Thomas L. Wheeler II, MD, Holly E. Richter, PhD, MD, Kathryn L. Burgio, PhD, David T. Redden, PhD, C. C. Grace Chen, MD, Patricia S. Goode, MD, R. Edward Varner, MD
Birmingham, AL

Patients who undergo partial colpocleisis, levator myorrhaphy, and perineorrhaphy report a low rate of regret, high rate of satisfaction, and significant urogenital symptom improvement.

Fecal incontinence in US women: A population-based study 2071
Jennifer L. Melville, MD, MPH, Ming-Yu Fan, PhD, Katherine Newton, PhD, Dee Fenner, MD
Seattle, WA, and Ann Arbor, MI

In community-dwelling women, fecal incontinence is a prevalent condition that is significantly associated with age, major depression, urinary incontinence, medical illness, and operative vaginal delivery.

Safety and efficacy of cytoreductive surgery for epithelial ovarian cancer in elderly and high-risk surgical patients 2077
Sameer Sharma, MD, Deborah Driscoll, BA, Kunle Odunsi, MD, PhD, Arun Venkatadri, BS, Shashikant Lele, MD
Buffalo, NY

Age, medical comorbidities, previous surgical history, and advanced stage should not preclude patients with epithelial ovarian cancer from maximal surgical effort.

Sacral neuromodulation for the treatment of refractory urinary urge incontinence after stress incontinence surgery 2083
Neil D. Sherman, MD, Margaret G. Jamison, PhD, George D. Webster, MB, FRCS, Cindy L. Amundsen, MD
Durham, NC

Sacral neuromodulation is a feasible management option for refractory urinary urge incontinence after surgery for stress urinary incontinence.

Factors associated with incontinence frequency in a surgical cohort of stress incontinent women 2088
Holly E. Richter, PhD, MD, Kathryn L. Burgio, PhD, Linda Brubaker, MD, Pamela A. Moalli, MD, PhD, Alayne D. Markland, MD, Veronica Maller, MD, Shawn A. Menefee, MD, Harry W. Johnson, MD, Muriel K. Boreham, MD, Kimberly J. Dandreco, MSc, Anne M. Stoddard, ScD, for the Urinary Incontinence Treatment Network (NIDDK, NICHD)
Birmingham, AL, Maywood, IL, Pittsburgh, PA, San Antonio and Dallas, TX, Dearborn, MI, San Diego, CA, Baltimore, MD, and Boston, MA

Incontinence severity in a surgical cohort of women was positively associated with body mass index and smoking status and negatively associated with prolapse stage and Q-tip displacement.
Abdominal sacral suspensions: Analysis of complications using permanent mesh
Giti Bensinger, MD, Larry Lind, MD, Martin Lesser, PhD, Marsha Guess, MD, Harvey A. Winkler, MD
Manhasset and Bronx, NY
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Dr. Gardella and colleagues present data in couples to determine the risk for the acquisition of both oral (labial) and genital herpes during pregnancy. This is important and a break-through paper in our understanding of herpes transmission to the mother during pregnancy and for finding methods to prevent neonatal herpes. Both pregnant women and newborns continue to be at risk of acquiring herpes infection. The incidence of neonatal herpes in the United States cannot be accurately estimated because it is not a reportable disease. However, in some areas of the United States, the incidence is as high as 1 in 3200 live births. Likewise, about 70% of infected infants are born to women who are asymptomatic at delivery and have no history of genital herpes infection.

The current management guidelines recommended by the American College of Obstetricians and Gynecologists (ACOG) rely on patients’ history as a screening method to determine pregnant women who are at risk for transmitting herpes to their newborn. On the basis of the current study and a study by Fleming et al, history is an unreliable method for identifying those who are infected with genital herpes. Most importantly, it fails completely in identifying the women most at risk of transmitting herpes, the serodiscordant woman who acquires herpes simplex virus (HSV)-1 or HSV-2 from her partner during pregnancy, to their newborn.

The study also highlights the difficulty in determining the serostatus of pregnant women and their partners. Large differences in the prevalence of genital herpes (as defined by being antibody positive to HSV-2) are seen in different racial and socioeconomic populations. In the current study, the high rate of discordant couples (22% of women were HSV susceptible with serologically discordant partners) and the high rates of acquisition of HSV-1 (2.4%) and HSV-2 (14%) is alarming. Certainly additional studies to determine susceptibility rates for other populations outside the Seattle, Washington, area will be helpful. The authors comment on the high number of at-risk women in their study. They agree that HSV seroprevalence rates vary with race and socioeconomic status. In addition, this study provides new information with regard to the high incidence of asymptomatic infection (68%) and genital infection with HSV-1 during pregnancy. These new data call for changes in the current management of pregnant women to prevent maternal and newborn HSV infections.

Only 47% of the male partners consented to be tested. Four women who acquired HSV infection developed antibodies that did not match those of their tested partners, suggesting exposure from another source, a complicating social issue as it related to sexually transmitted diseases.

The current paper clearly states “demographic and clinical factors were not a viable surrogate for serologic testing of the couple.” Prevention of transmission herpes infection from the male partner to the susceptible pregnant women can reduce the incidence of neonatal...
herpes by 60% to 80%. The first and most important step is the determination of serostatus of the pregnant women to determine susceptibility. Although “routine serologic testing for pregnant and their partners should be performed was not the focus of this investigation,” it seems evident that the only way to determine susceptibility of the pregnant woman is to screen for antibodies to HSV-1 and HSV-2 during early pregnancy. Thus, in screening for HSV during pregnancy, both infected and susceptible pregnant women will be identified.

The authors use a Western blot assay, a technique reserved for research laboratories, for serologic testing. Newer and more accurate type-specific tests, based on glycoprotein G, are now available from commercial laboratories. These tests, now easily available, offer the advantages of convenience over previously available tests. The introduction of these new tests (with sensitivity ranging from 92% to 100% and specificity ranging from 87% to 98% for HSV-2) will enable physicians to make a more accurate diagnosis of genital herpes.

The Centers for Disease Control and Prevention (CDC) provides guidelines on the use of type-specific serologic tests. The CDC recognizes the significance of using serologic testing for the following: (1) to confirm clinical diagnoses, (2) to diagnose people with unrecognized infection, and (3) to manage sex partners of persons with genital herpes. Because cultures are frequently false negative, serologic tests can be useful in confirming a clinical diagnosis. The guidelines note that some specialists believe that type-specific serologic tests are useful to identify pregnant women at risk for HSV infection and help counseling with regard to the risk of acquiring genital herpes during pregnancy.

Since the 1999 publication of the ACOG practice bulletin, entitled Management of Herpes in Pregnancy, significant new information has become available.

Because at-risk women can now be accurately identified by the new and more accurate type-specific serologic tests, effective prevention strategies should be instituted to minimize risk of transmission to the neonate. Newer studies demonstrate the safety and clinical and cost-effectiveness of antiviral suppressive therapy used in HSV-infected women in the last several weeks of pregnancy. There was a significant decrease in clinical recurrences, a decrease in viral shedding at delivery, and a decrease in the need for cesarean sections. The combination of condom use and antiviral suppressive therapy reduces the transmission of genital herpes to the susceptible sexual partner.

These studies in nonpregnant women can be applied to the couple with discordant results in which the female partner is in early pregnancy but has not yet become infected with HSV. The highest risk is that of neonatal transmission from a mother experiencing an initial genital HSV-1 or HSV-2 infection in late pregnancy. Conversely, the rate of neonatal transmission from women with recurrent genital herpes infection is low (less than 1%). Because genital herpes is so common, the absolute total number of cases of neonatal herpes from women with recurrent disease remains high.

Once a mother is identified as being infected with HSV-2, the health care providers, both pediatricians and obstetricians, can be alerted to the potential risk of neonatal herpes infection. If the mother is identified as susceptible, intervention can then be initiated to prevent infection of the mother and thereby transmission to the newborn during pregnancy.

This detailed and large study makes it clear that maternal infection from the male partner plays a major role in neonatal herpes infection. It is time to address these new findings from the current paper and to implement changes in the current management protocols to prevent neonatal infection. The ACOG, CDC, and American Academy of Pediatrics have the ability to call an advisory board to draft new guidelines for the prevention of neonatal herpes by identifying the asymptomatic/susceptible woman.

References

Environmental contaminants and maternal thyroid function

Brian Casey, MD

University of Texas Southwestern Medical Center at Dallas, Dallas, TX

Dioxin and dioxin-like substances are often byproducts of industrial processes and are considered highly toxic. The major source of human exposure is through the diet as these substances are concentrated in fatty tissues of beef, poultry, pork and fish. Another important contributor of dioxin-like substance exposure is cigarette smoking. Though industrial sources of these substances have been significantly reduced in the last 20 years, exposure to them has been linked to several adverse health effects. Of particular interest and relevant to this issue is the report by Foster et al concerning the potential endocrine disruption by these substances, especially thyroid function. There have been numerous animal studies linking prenatal exposure to dioxin-like substances with suppressed serum T3 and T4 levels in progeny in the postnatal period. Similar relationships between prenatal and lactational exposure to dioxin-like substances and thyroid function in humans have also been reported. For example, higher levels of 2 polychlorinated biphenyl (PCB) congeners in umbilical cord blood have been associated with higher thyrotropin levels in newborn infants. In addition, maternal T3 levels were recently reported to be inversely associated with several PCBs, whereas thyroid hormone levels in cord blood were not different. Therefore, there is some evidence that supports that exposure to at least some levels of dioxin and dioxin-like substances may be associated with thyroid dysfunction in mothers and their offspring.

Another reported consequence of fetal or neonatal exposure to dioxin-like compounds concerns neurobehavioral problems in children. Prenatal exposure to PCBs has been linked to lower psychomotor scores on Bayley developmental scales, and it has been inversely correlated with full scale and verbal IQ scores at age 11 years. Because of what has been reported about the effects of dioxin-like substances on thyroid function, it has been suggested that the underlying mechanism for these learning and developmental difficulties may be the disruption of the normal action of thyroid hormone during pregnancy. Certainly, it is well-established that thyroid insufficiency caused by severe iodine deficiency or other reasons during pregnancy can cause neurobehavioral deficiencies in offspring. It is also known that maternal thyroxine is critical to fetal neurodevelopment in early pregnancy at a time when the fetal thyroid cannot synthesize iodothyronines. Several recent studies in women with various degrees of hypothyroidism or hypothyroxinemia during the first half of pregnancy have raised concern that even mild maternal hypothyroidism might lead to intellectual impairment in offspring.

The study by Foster et al in this issue of the American Journal of Obstetrics and Gynecology investigates the association between prenatal exposure to dioxin-like substances and maternal thyroid deficiency. The authors hypothesized that this may be the link between prenatal exposure to dioxin-like substances and neurologic impairment in exposed offspring. Detectable dioxin-like activity was identified in almost all (96.7%) second-trimester maternal serum samples. This finding certainly suggests that dioxin-like substances are ubiquitous in the environment. Still, overall dioxin-like activity in this...
study was relatively low across all groups of women studied. Although this may be a reflection of the analytical methods used for measuring dioxin-like toxie equivalence, it may also be that the exposure to them did not exceed the threshold for manifestation of endocrinologic effects. The incidence of hypothyroidism (4%) and subclinical hypothyroidism (8%) in this study are higher than others reported in pregnancy; however, the women studied had a mean age of 38 years, and this may explain their unusually high incidence of thyroid dysfunction.

At this time, the impact of maternal dioxin-like substance exposure as well as subclinical hypothyroidism on fetal neurodevelopment are controversial. Concerns regarding intellectual impairment in offspring of women with undiagnosed thyroid dysfunction are based largely on studies in women with variously defined hypothyroidism. They have led to conflicting and confusing position statements as to whether all pregnant women should be screened for hypothyroidism and treatment prescribed for those found to have subclinical hypothyroidism. According to the American College of Obstetricians and Gynecologists: “It is important to acknowledge the limitations of the current understanding of this issue. The data available are observational. There have been no intervention trials to demonstrate the efficacy of screening and treatment to improve neuropsychologic performance in the offspring of hypothyroid women.” The one issue on which there is clear consensus is that well-controlled trials are necessary to determine whether treatment of subclinical hypothyroidism will result in improvement in intellectual function of offspring born to such women. Until such studies are completed, it is imprudent to embark on such a screening policy and premature to treat pregnant women.

The study by Foster et al does not establish a connection between low-level dioxin exposure and maternal thyroid dysfunction. Therefore, at least in women with relatively low exposure, hypothyroidism likely does not play an important role in the neurobehavioral problems in offspring of exposed women. Further studies will be necessary to elucidate the site and mechanism of action of these environmental chemicals during brain development and to establish thresholds for these effects.

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Risk factors for herpes simplex virus transmission to pregnant women: A couples study

Carolyn Gardella, MD, MPH,a,* Zane Brown, MD,a Anna Wald, MD, MPH,b,c,d Stacy Selke, MS,d Judy Zeh, PhD,a Rhoda Ashley Morrow, PhD,d Lawrence Corey, MDb,d,f

Departments of Obstetrics and Gynecology,a Medicine,b Epidemiology,c Laboratory Medicine,d Statistics,e University of Washington; Program in Infectious Diseases, Fred Hutchinson Cancer Research Center,f Seattle, WA

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KEY WORDS
Herpes
Pregnancy
Risk factors

Objective: This study was undertaken to determine risk factors for herpes simplex virus (HSV) acquisition among at risk pregnant women.

Study design: Women in a prospective study of HSV acquisition in pregnancy invited their sexual partners for HSV type-specific serologic testing. Risk factors for HSV susceptibility, exposure, and acquisition were examined.

Results: A total of 3192 couples enrolled; 22% included women at risk for HSV-1 or HSV-2. Among 582 HSV-1 seronegative women with HSV-1 seropositive partners, 14 (3.5% adjusted for gestation length) acquired HSV-1. Having a partner with a history of oral herpes was associated with HSV-1 acquisition (odds ratio [OR] 8.1, 95% CI: 1.8-36.0) and accounted for 75% of incident infections. Among 125 HSV-2 seronegative women with HSV-2 seropositive partners, 17 (20% adjusted for gestation length) acquired HSV-2. Duration of partnership of 1 year or less was associated with HSV-2 acquisition (OR 7.8, 95% CI: 2.3-25.7) and accounted for 63% of incident infections. No combination of clinical characteristics could identify the majority of susceptible women with serologically discordant partners.

Conclusion: HSV acquisition rates in pregnancy are high in discordant couples, especially for HSV-2. Interventions that address risk factors for HSV acquisition should be studied in pregnancy. Clinical profiles cannot replace serologic screening to identify susceptible women with serologically discordant partners.

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Maternal acquisition of herpes simplex virus 1 (HSV-1) or HSV-2 near the time of delivery accounts for 60% to 80% of cases of neonatal HSV infection.1,2 Although HSV acquisition at the end of pregnancy is relatively infrequent, the efficiency of transmission from mother to infant is high in this situation.3 As such, an effective strategy to reduce neonatal HSV infection may be to prevent maternal HSV acquisition during pregnancy.

Previously, we reported the risk of seroconversion to HSV-1 or HSV-2 among pregnant women to be 3.7%.3 This number included all women susceptible to HSV-1 or
HSV-2 and did not define HSV risk by male partners’ serologic status. As such, women who lacked a partner with HSV and therefore who were not exposed to HSV during pregnancy were included. These women were not at risk for HSV acquisition. To further define the risk of HSV acquisition among pregnant women, we conducted a cohort study to determine the frequency of and risk factors for exposure to HSV-1 or HSV-2 among susceptible women during pregnancy as well as the frequency of and risk factors for HSV acquisition by susceptible women with serologically discordant partners. These data may help identify couples for targeted interventions to prevent HSV transmission during pregnancy.

Materials and methods

Subjects, setting, and procedures

This couples’ study complemented a prospective study of HSV seroconversion among pregnant women. We obtained serum samples at the first prenatal visit and at the time of labor from all women receiving prenatal care at University Hospital in Seattle, WA, between January 1992 and September 2000 and at Madigan Army Hospital in Tacoma, WA, between March 1994 and September 1997. Swabs for culture of HSV from the external genitalia and cervix were collected from women when they presented in labor. For the couples’ study, study nurses were able to approach 8674 women in this cohort to invite their male sexual partners to submit a serum sample for HSV serologies, of whom, 4065 (47%) participated. For 83% of participating partners, this sample was obtained at the time of delivery and reported postpartum. For the remainder, the sera were obtained predelivery, stored, and tested postpartum. Couples completed a short demographic and lifestyle questionnaire at the time of partner serum sampling. Women received their antibody results and HSV counseling from their prenatal providers and a patient education sheet about HSV in pregnancy as part of routine clinical care. Chart review for symptoms or signs of orolabial or genital HSV infection was performed in a blinded manner for all women with seroconversion.

Written approval for the study protocol was obtained according to the guidelines of the Human Subjects Review Board of the University of Washington.

Laboratory

Antibodies to HSV-1 and HSV-2 were detected by Western blot. Prenatal and delivery sera for women were paired and assayed together. For all women whose initial serum sample was positive for HSV-1 but in whom antibodies to HSV-2 later developed, seroconversion was confirmed by absorption blot. Isolation and typing of HSV was performed as previously described.

Definitions

A woman was considered HSV-1 susceptible and exposed (at risk) if she lacked antibody to HSV-1 and her partner had antibody to HSV-1 only or to both HSV-1 and HSV-2. She was considered at risk for HSV-2 infection if she lacked antibody to HSV-2 and her partner had antibody to HSV-2 only or both HSV-1 and HSV-2. A woman was considered at risk for both HSV-1 and HSV-2 infection if she lacked antibody to HSV-1 and HSV-2 and her partner had antibodies to both.

Acquisition of HSV was defined as development of culture-proven HSV infection or new evidence of HSV type-specific antibodies (seroconversion) during pregnancy. Among women with symptomatic disease, the date of acquisition was defined as the first report of genital or oral lesions. For subclinical disease, the date of acquisition was defined by trimester of the first positive antibody test.

Statistical analysis

For inclusion in the analyses, both prenatal and delivery sera as well as partner’s serum had to be available. The frequency of HSV acquisition was adjusted for length of gestation, assuming a constant rate of acquisition over the course of pregnancy, because the mean interval between first prenatal visit and delivery was shorter than the length of pregnancy. This method may result in underestimation of the true frequency of acquisition because the interval between conception and the first prenatal visit may be a time of normal or increased sexual activity that then declines as pregnancy progresses.

Categorical variables were compared using $\chi^2$ or Fisher exact test as appropriate. Comparisons of the distribution of continuous variables between 2 groups were made with the Mann-Whitney U test. Rates of acquisition were compared by permutation tests. Standard errors for those rates were estimated by bootstrap resampling. All statistical tests were 2-tailed.

Odds ratios (ORs) and adjusted ORs (aORs) for HSV-1 and HSV-2 acquisition and for exposure to HSV-1 among HSV-1 seronegative women and exposure to HSV-2 among HSV-2 seronegative women were determined with multivariate logistic regression with separate models for each HSV type. For these analyses, the dataset was restricted to include only women with complete data on maternal and paternal age and duration of partnership. Bayes Information Criterion (BIC) was used to select the final models. BIC provides a consistent estimate of the number of predictors in the model, independent of the size of the dataset being analyzed. They are more useful for prediction than less parsimonious models that may include risk factors of marginal significance in a particularly large dataset. Models that included interactions were rejected by BIC.
so they are not discussed further. Missing data in categorical predictors were coded separately, except for history of oral or genital herpes and race, which had too few missing values to support separate categories. Missing values in history of herpes and maternal race were assigned to the most frequent category. Missing values in paternal race were set equal to the maternal race because the study population included few multiracial couples. We did not report ORs for the missing data categories because none were statistically significant. Results from analyses with these assignments were very similar to results that omitted cases with missing values.

To evaluate the potential impact of risk reduction among women who are at highest risk of HSV acquisition, we calculated the attributable risk percent and the population attributable risk percent for the strongest risk factors for HSV-1 or HSV-2 acquisition.

Binary recursive partitioning, which used serologic testing as the gold standard, generated a classification tree of demographic and clinical characteristics to predict the risk of HSV susceptibility and exposure.\textsuperscript{11} This method creates a classification tree by choosing, at each step, a split in 1 of the risk stratifiers that maximally distinguishes the women in the 2 branches in terms of their risk for HSV. The resulting classification tree shows which predictors are most important (those determining the first few splits), which are least important (those that do not appear in the tree), and to which risk class women in a branch tend to belong. The length of the branches at each split is based on the change of deviance between the parent and child nodes. Thus, longer branches contribute more to explaining the percentages at the terminal nodes than shorter branches. Unlike logistic regression, tree-based models can handle the 3 risk classes simultaneously. Classes were defined as: (1) Not at risk for HSV: Women were seropositive for HSV-1 and HSV-2, the partner was HSV seronegative, or the couple was seroconcordant; (2) at risk for HSV-1: Women were HSV-1 seronegative and their partners were HSV-1 seropositive; and (3) at risk for HSV-2: Women were HSV-2 seronegative with HSV-2 seropositive partners. Maternal and paternal age, ethnicity, and history of oral and genital herpes symptoms, duration of partnership, marital status, gravidity, study site, smoking status, use of alcohol or drugs, and history of other sexually transmitted diseases during pregnancy were the risk stratifiers.

Results

Characteristics of the study population

Figure 1 illustrates the study population. After excluding couples in which only 1 maternal serum sample was obtained and therefore we could not determine maternal

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**Figure 1**  Study population. *MAMC*, Madigan Army Medical Center; *UWMC*, University of Washington Medical Center.
seroconversion, a total of 3192 couples were available for analysis.

Compared with women who delivered at the study hospitals but did not participate in the study (because they were not approached for enrollment [64%], they declined [11%], they did not have a partner [3%], or an available partner [3%]) women who had partners that participated more often were white (71% vs 57%, \( P < .001 \)), married (84% vs 64%, \( P < .001 \)), nulliparous (51% vs 45%, \( P < .001 \)), carried private insurance (41% vs 28%, \( P < .001 \)), and were HSV seronegative (32% vs 20%, \( P < .001 \)). Participants and nonparticipants were similar with respect to maternal history of genital HSV (7%-9%) or other sexually transmitted diseases (32%-34%), cesarean section rate (22%-23%), maternal age (median 25-26 years), gestational age at delivery (median 39-40 weeks), and neonatal birth weight (median 3200-3400 g).

Notably, 4 women who acquired HSV developed antibodies that did not match those of their partners, suggesting exposure from another source. In each case, antibody results from both partners were verified by retesting. Specifically, 3 women had antibodies to HSV-2 develop but their partners were seronegative for HSV-2 and another woman acquired HSV-1 although her partner was HSV seronegative. The partners were tested initially at 131 days before delivery, 1 day postpartum, 10 days postpartum, and 3 days postpartum, respectively. These women were excluded from the analyses because we lacked information about the source partner.

**Frequency of serologic discord between partners**

Forty-eight percent (1517/3192) of couples had discordant HSV serologies. The median duration of sexual partnership was 4 years among couples who were serologically concordant, compared with 3 years among discordant couples. The serodiscordant couples included 582 women at risk for HSV-1 acquisition and 125 women at risk for HSV-2 acquisition. Among these were 10 women at risk for acquisition of both HSV-1 and HSV-2. Overall, 22% of women were HSV susceptible with serologically discordant partners. The remaining serodiscordant couples placed the male partner at risk of HSV acquisition (Table I).

**Frequency of HSV acquisition during pregnancy**

Of the 582 women at risk for HSV-1 acquisition, 14 (2.4%; 3.5% adjusted for length of gestation) acquired HSV-1. Of the 125 women at risk for HSV-2 acquisition, 17 (14%; 20% adjusted for length of gestation) acquired HSV-2 (Table II).

<table>
<thead>
<tr>
<th>Maternal prenatal serology</th>
<th>HSV negative</th>
<th>Heterologous antibody present</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquisition of: HSV-1</td>
<td>Observed</td>
<td>Adjusted rate*</td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>13/403</td>
<td>(3.2%)</td>
<td>14/582</td>
</tr>
<tr>
<td>Adjusted rate*</td>
<td>4.7%</td>
<td>(2.2%-7.3%)</td>
<td>3.5%</td>
</tr>
<tr>
<td>HSV-2</td>
<td>Observed</td>
<td>Adjusted rate*</td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>6/32</td>
<td>(19%)</td>
<td>17/125</td>
</tr>
<tr>
<td>Adjusted rate*</td>
<td>28%</td>
<td>(10%-49%)</td>
<td>20%</td>
</tr>
</tbody>
</table>

* Adjusted for length of gestation; adjusted rate is followed by 95% CI in parentheses.

### Table I

<table>
<thead>
<tr>
<th>Partner serology</th>
<th>HSV (-)</th>
<th>HSV-1 (+)</th>
<th>HSV-2 (+)</th>
<th>HSV-1 &amp; HSV-2 (+)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal serology</td>
<td>590</td>
<td>393</td>
<td>22</td>
<td>10*</td>
<td>1015</td>
</tr>
<tr>
<td>HSV-1 (+)</td>
<td>470</td>
<td>899</td>
<td>39</td>
<td>54*</td>
<td>1462</td>
</tr>
<tr>
<td>HSV-2 (+)</td>
<td>61</td>
<td>99*</td>
<td>79</td>
<td>80*</td>
<td>319</td>
</tr>
<tr>
<td>HSV-1 &amp; HSV-2 (+)</td>
<td>67</td>
<td>131</td>
<td>91</td>
<td>107</td>
<td>396</td>
</tr>
<tr>
<td>Total</td>
<td>1188</td>
<td>1522</td>
<td>231</td>
<td>251</td>
<td>3192</td>
</tr>
</tbody>
</table>

* Indicates women susceptible and exposed to HSV-2.
3 had genital lesions, and 1 had oral lesions. Of the 10 women with subclinical HSV-1 acquisition, 6 had genital specimens collected for culture at delivery, and all 6 were culture negative.

One case of neonatal herpes occurred among the study population. The mother of this neonate was asymptomatic and HSV seronegative at delivery but HSV-2 was isolated from a culture of genital secretions at delivery.

Risk factors for HSV acquisition among at risk women

The only significant independent risk factor for HSV-1 acquisition during pregnancy was having a partner with a history of oral herpes (aOR 7.7, 95% CI: 1.7-34.7, adjusted for duration of partnership, Table III).

Duration of sexual partnership was strongly associated with HSV-2 acquisition. The odds of HSV-2 acquisition were nearly 8 times greater among women who had been with their partners for 1 year or less compared with women who had been with their partners for more than 1 year (OR 7.76, 95% CI: 2.35-25.7; aOR 5.34, 95% CI: 1.49-19.2, adjusted for partner age). Women who acquired HSV-2 were significantly younger, more likely to be unmarried, primigravid, have a younger partner, and be in relationships of 1 year or less than women who were at risk but did not become infected. However, after adjustment for duration of partnership, these risk factors for HSV acquisition among HSV-1 seronegative women with HSV-1 seropositive partners and HSV-2 seronegative women with HSV-2 seropositive partners

<table>
<thead>
<tr>
<th></th>
<th>HSV-1 acquisition</th>
<th></th>
<th>HSV-2 acquisition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N = 14)</td>
<td>No (N = 568)</td>
<td>aOR* (95% CI)</td>
<td>Yes (N = 17)</td>
</tr>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (y)</td>
<td>21</td>
<td>24</td>
<td>1.10 (0.98-1.23)</td>
<td>22</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71%</td>
<td>73%</td>
<td>1.0 (ref)</td>
<td>53%</td>
</tr>
<tr>
<td>Black</td>
<td>14%</td>
<td>14%</td>
<td>1.37 (0.29-6.50)</td>
<td>18%</td>
</tr>
<tr>
<td>Other</td>
<td>14%</td>
<td>13%</td>
<td>1.21 (0.26-5.73)</td>
<td>29%</td>
</tr>
<tr>
<td>Unmarried</td>
<td>38%</td>
<td>24%</td>
<td>2.14 (0.69-6.61)</td>
<td>53%</td>
</tr>
<tr>
<td>Primigravida</td>
<td>46%</td>
<td>39%</td>
<td>1.33 (0.45-3.91)</td>
<td>47%</td>
</tr>
<tr>
<td>Smoked in pregnancy</td>
<td>25%</td>
<td>22%</td>
<td>1.13 (0.31-4.18)</td>
<td>18%</td>
</tr>
<tr>
<td>Used alcohol</td>
<td>8%</td>
<td>9%</td>
<td>1.05 (0.13-8.42)</td>
<td>12%</td>
</tr>
<tr>
<td>in pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illicit drug use in pregnancy</td>
<td>17%</td>
<td>5%</td>
<td>5.02 (0.98-25.7)</td>
<td>0%</td>
</tr>
<tr>
<td>STD in pregnancy</td>
<td>42%</td>
<td>38%</td>
<td>1.35 (0.42-4.38)</td>
<td>50%</td>
</tr>
<tr>
<td>Partner characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of oral HSV</td>
<td>86%</td>
<td>43%</td>
<td>7.70 (1.71-34.7)</td>
<td>31%</td>
</tr>
<tr>
<td>History of genital HSV</td>
<td>7%</td>
<td>5%</td>
<td>1.74 (0.21-14.3)</td>
<td>19%</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>24</td>
<td>26</td>
<td>1.05 (0.96-1.15)</td>
<td>28</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64%</td>
<td>67%</td>
<td>1.0 (ref)</td>
<td>53%</td>
</tr>
<tr>
<td>Black</td>
<td>21%</td>
<td>19%</td>
<td>1.71 (0.44-6.62)</td>
<td>33%</td>
</tr>
<tr>
<td>Other</td>
<td>14%</td>
<td>14%</td>
<td>1.63 (0.33-7.97)</td>
<td>13%</td>
</tr>
<tr>
<td>Duration of partnership</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3 y</td>
<td>14%</td>
<td>42%</td>
<td>1.0 (ref)</td>
<td>24%</td>
</tr>
<tr>
<td>≤ 3 y</td>
<td>86%</td>
<td>58%</td>
<td>3.97 (0.87-18.0)</td>
<td>13%</td>
</tr>
<tr>
<td>≥ 1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bold items are statistically significant. STD, Sexually transmitted disease.

* ORs were determined from logistic regressions restricted to the 568/582 (98%) at risk women with data on maternal and paternal age and duration of partnership, including all 14 women who acquired HSV-1. aOR for HSV-1 acquisition are adjusted for partner history of oral HSV, unless otherwise indicated.

† ORs were determined from logistic regressions restricted to the 122/125 (98%) women at risk for HSV-2 acquisition with data on maternal and paternal age and duration of partnership, including all 17 women who acquired HSV-2. aOR for HSV-2 acquisition are adjusted for duration of sexual partnership as a categorical variable, unless otherwise indicated.

‡ OR compares 1 year younger.

§ Adjusted for duration of partnership.

‖ Adjusted for partner age.
factors were no longer statistically significant (Table III).

### Estimating the potential for prevention of HSV acquisition during pregnancy

Among women at risk for HSV-1 infection who had partners with histories of oral herpes, this risk factor accounted for 87% of HSV-1 acquisitions. In our cohort, 44% of women at risk for HSV-1 acquisition had a partner with a history of oral herpes and therefore 75% of HSV-1 incident infections were attributable to that risk factor. Among the women at risk for HSV-2 acquisition and in partnerships of 1 year or less, 83% of HSV-2 acquisitions were attributable to this risk factor.

Among women at risk for HSV-2 acquisition, 36% were in partnerships for 1 year or less; therefore 63% of the incident HSV-2 infections were attributable to that factor in our cohort.

### Risk factors for HSV exposure among susceptible women

Risk factors for HSV exposure, defined as having a partner with HSV, are shown in Table IV. Partner history of oral herpes and nonwhite ethnicity were the strongest predictors of maternal HSV-1 exposure after adjustment for confounding factors. The strongest independent risk factor for HSV-2 exposure was having a partner with a history of genital herpes. Duration of

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**Table IV** Risk factors for HSV-1 exposure among HSV-1 seronegative women and for HSV-2 exposure among HSV-2 seronegative women during pregnancy

<table>
<thead>
<tr>
<th>Partner status:</th>
<th>HSV-1</th>
<th></th>
<th>HSV-2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (N = 752)</td>
<td>Positive (N = 582)</td>
<td>aOR*</td>
<td>Negative (N = 2352)</td>
</tr>
<tr>
<td>Median maternal age^1 (y)</td>
<td>26</td>
<td>24</td>
<td>1.08 (1.04-1.12)</td>
<td>24</td>
</tr>
<tr>
<td>Median partner age^2 (y)</td>
<td>27</td>
<td>26</td>
<td>1.08 (1.05-1.12)</td>
<td>26</td>
</tr>
<tr>
<td>Maternal ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85%</td>
<td>73%</td>
<td>1.0 (ref)</td>
<td>74%</td>
</tr>
<tr>
<td>Black</td>
<td>6%</td>
<td>14%</td>
<td>1.31 (0.73-2.37)</td>
<td>8%</td>
</tr>
<tr>
<td>Asian</td>
<td>4%</td>
<td>5%</td>
<td>0.82 (0.45-1.52)</td>
<td>8%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3%</td>
<td>5%</td>
<td>0.94 (0.47-1.89)</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>3%</td>
<td>0.67 (0.28-1.64)</td>
<td>4%</td>
</tr>
<tr>
<td>Partner ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>86%</td>
<td>67%</td>
<td>1.0 (ref)</td>
<td>74%</td>
</tr>
<tr>
<td>Black</td>
<td>8%</td>
<td>19%</td>
<td>2.69 (1.84-3.92)</td>
<td>10%</td>
</tr>
<tr>
<td>Asian</td>
<td>1%</td>
<td>3%</td>
<td>2.61 (1.18-5.78)</td>
<td>5%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3%</td>
<td>7%</td>
<td>3.07 (1.73-5.43)</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>4%</td>
<td>3.98 (1.89-8.40)</td>
<td>5%</td>
</tr>
<tr>
<td>Smoked in pregnancy</td>
<td>16%</td>
<td>22%</td>
<td>1.25 (0.90-1.74)</td>
<td>16%</td>
</tr>
<tr>
<td>Alcohol use in pregnancy</td>
<td>8%</td>
<td>9%</td>
<td>0.90 (0.57-1.42)</td>
<td>6%</td>
</tr>
<tr>
<td>Illicit drug use in pregnancy</td>
<td>3%</td>
<td>5%</td>
<td>1.14 (0.58-2.32)</td>
<td>2%</td>
</tr>
<tr>
<td>STD in pregnancy</td>
<td>31%</td>
<td>38%</td>
<td>1.17 (0.90-1.53)</td>
<td>31%</td>
</tr>
<tr>
<td>Unmarried</td>
<td>13%</td>
<td>25%</td>
<td>1.14 (1.00-2.01)</td>
<td>14%</td>
</tr>
<tr>
<td>Primigravida</td>
<td>38%</td>
<td>39%</td>
<td>0.95 (0.73-1.23)</td>
<td>37%</td>
</tr>
<tr>
<td>Duration of partnership</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 y</td>
<td>30%</td>
<td>17%</td>
<td>1.0 (ref)</td>
<td>25%</td>
</tr>
<tr>
<td>4-6 y</td>
<td>24%</td>
<td>24%</td>
<td>1.79 (1.24-2.59)</td>
<td>27%</td>
</tr>
<tr>
<td>2-3 y</td>
<td>27%</td>
<td>28%</td>
<td>1.66 (1.12-2.41)</td>
<td>28%</td>
</tr>
<tr>
<td>≤1 y</td>
<td>19%</td>
<td>31%</td>
<td>2.47 (1.63-3.75)</td>
<td>21%</td>
</tr>
<tr>
<td>Partner h/o oral HSV</td>
<td>24%</td>
<td>44%</td>
<td>2.71 (2.10-3.49)</td>
<td>1%</td>
</tr>
<tr>
<td>Mother HSV-2 positive</td>
<td>19%</td>
<td>31%</td>
<td>1.62 (1.20-2.18)</td>
<td>58%</td>
</tr>
<tr>
<td>Partner h/o genital HSV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother HSV-1 positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bold items are statistically significant. STD, Sexually transmitted disease; h/o, history of.

* Odds ratio adjusted for maternal and partner age, partner ethnicity and history of oral herpes, duration of partnership, and maternal HSV-2 serostatus; 733/752 (97%) of the unexposed and 568/582 (98%) of the exposed women were included in the logistic regression analyses for HSV-1 exposure after screen for missing age and duration of partnership data.

^1 Odds ratio adjusted for partner age, ethnicity and history of genital herpes, and duration of partnership; 2275/2352 (97%) of the unexposed women and 122/125 (98%) of the exposed were included in the logistic regression analyses for HSV-2 exposure after screening for missing values.

^2 OR compares age with one year younger.

^3 OR compares age with 1 year older.
partnership of 3 years or less, partner of black or Hispanic ethnicity and older partner age also were significant independent risk factors for HSV-2 exposure.

**Use of demographic and clinical characteristics to predict HSV risk status in pregnancy**

To determine whether demographic and clinical characteristics alone could identify women who were HSV susceptible with serologically discordant partners, we constructed a classification tree, shown in Figure 2. With the use of serologic testing as the gold standard, only 2 sets of characteristics identified women who had greater than 25% chance of susceptibility and exposure to HSV-2. One group was women with a history of oral herpes and with partners with a history of genital herpes or whose genital herpes history was unknown; 29% of these women were HSV-2 seronegative with HSV-2 seropositive partners. The other group included women with no known history of oral or genital herpes and whose partner had no known history of oral herpes but may have had a history of genital herpes; 38% of these women were HSV-2 seronegative with HSV-2 seropositive partners. Demographic and clinical characteristics identified a group of women with the maximum chance of being HSV-1 seronegative with HSV-1 seropositive partners of 39%. In all but 1 combination of risk factors, some risk of HSV-1 or HSV-2 susceptibility and exposure remained.

**Comment**

This study, which evaluates risk factors for HSV acquisition among pregnant women in a large cohort of serodiscordant couples, makes several important observations. First, among at-risk pregnant women, the observed rates of HSV-1 or HSV-2 acquisition were 2.4% and 14%. Second, we identified risk factors for HSV-1 (partner history of oral herpes) and HSV-2 acquisition (duration of partnership <1 year) that accounted for most incident HSV infections. Third, we were unable to develop clinically useful risk factor profiles that could replace or direct serologic testing to identify women at high risk of HSV susceptibility and exposure.

This is the first study to report HSV-1 acquisition rates during pregnancy among women known to be at risk for infection. Partner history of oral herpes as the main risk factor for HSV-1 acquisition reflects the increased likelihood of viral shedding observed among persons with symptomatic HSV-1 infection and is consistent with data from nonpregnant populations that oral-genital contact is a risk factor for HSV-1 acquisition. Of the 4 women in our study who experienced symptomatic HSV-1 acquisition, 3 had genital lesions, consistent with the finding that half of symptomatic new HSV-1 infections may be genital. The HSV-2 acquisition rate of 14% is similar to the previously published annualized incidence rate of 11%
among a smaller group of at-risk pregnant women\textsuperscript{12} and similar to these rates for nonpregnant women at risk for HSV-2 infection.\textsuperscript{16-18} Duration of partnership 1 year or less as a risk factor for HSV-2 acquisition is consistent with the previously reported median duration of relationship of 3 months before acquisition of genital herpes in a nonpregnant population\textsuperscript{10} and may relate to increased sexual contact early in relationships.

Calculations of population attributable risk percent depend on the frequency of the risk factor among couples at risk for HSV. The prevalence of duration of partnership 1 year or less and partner history of oral herpes in other US populations at risk for HSV acquisition during pregnancy is unknown. Compared with nonpregnant populations in which 55% to 62% of HSV-1 seropositive persons report a history of oral herpes, the frequency of oral herpes symptoms among HSV-1 seropositive partners in this study was lower (44%).\textsuperscript{20,21} Alternatively, it is possible that our study sample was biased toward couples in which the male partner had a history of oral herpes because these couples were concerned about HSV transmission. If so, the frequency of this risk factor in a general population of at-risk pregnant couples may be lower and thus the percent of incident HSV-1 infections attributable to this risk factor would be less.

Several possible study limitations merit discussion. Selection bias may have affected HSV serodiscordance rates among participating couples. The number of women at risk for HSV acquisition in our study cohort (22%) was higher than previous estimates. HSV seroprevalence rates vary with race and socioeconomic status.\textsuperscript{20-23} Women of lower socioeconomic status and nonwhite race are more likely to acquire HSV earlier in life and, therefore, not be at risk for HSV acquisition in pregnancy. Women who participated in the couples’ study were more likely to be white, carry private insurance, and be HSV seronegative; thus, they may have been more likely to be serodiscordant with their partners. HSV seronegative women with new partners or partners with symptoms of genital herpes may have been more likely to participate in the study because of the perceived increased risk of HSV infection. Participation provided free partner serotesting that may have been of interest to the women and their prenatal providers. Thus, our study cohort may have been at greater risk of HSV acquisition than the whole prenatal population at the 2 study sites.

The study cohort recruited from the Army Hospital may be more representative of a general prenatal population because the proportion of this prenatal population that participated was greater. Analyses for susceptibility and exposure to HSV were stratified by study site to explore the effect of study site and possible selection bias. However, the results generated for each study site were not significantly different than those generated with combined data suggesting that the risk factors were similar for both study sites and may be applicable to a broader patient population.

We may have failed to detect additional risk factors for HSV acquisition because the relatively small sample size of women who acquired HSV-1 (N = 14) or HSV-2 (N = 17). Further, we did not collect data regarding sexual behavior in pregnancy and therefore were unable to determine the contribution of oral sex to HSV-1 acquisition, or the effect of condom use.

Despite these limitations, we believe that the identified risk factors for HSV acquisition during pregnancy are likely to be applicable to the general population based on the strength of the associations, their biologic plausibility, and consistency with data from non-pregnant cohorts.

The main implication of this study is that most cases of HSV acquisition among susceptible pregnant women with serologically discordant partners may be attributable to partner history of oral HSV and duration of partnership of 1 year or less. Therefore, interventions that address these risk factors might significantly reduce the rate of HSV acquisition during pregnancy. At risk women with a partner with a history of oral HSV could be counseled to avoid receptive oral genital contact and/or to use viral suppressive therapy among their partners. Pregnant women at risk for HSV-2, and especially those in relationships of 1 year or less, could be counseled to maintain sexual abstinence or use condoms, especially in the third trimester of pregnancy.\textsuperscript{24} Viral suppressive therapy for male partners with genital herpes may also prevent HSV-2 transmission and may be considered.\textsuperscript{25} Future studies to prevent HSV acquisition in pregnancy should focus on these risk reduction strategies to determine their feasibility and efficacy.

Whether routine serologic testing for pregnant women and their partners should be performed was not the focus of this investigation of risk factors for HSV acquisition in pregnancy. However, the risk reduction estimates were based on a cohort known to be at risk for HSV acquisition by serologic screening, which may not be routinely performed in pregnancy. Therefore, we attempted to define demographic and clinical characteristics that could predict maternal HSV susceptibility and exposure status to replace or direct serologic screening to couples at highest risk of serologic discord. This may be more efficient than serologic screening of all pregnant women and their partners. Risk factor profiles were able to identify women with a maximum chance of being HSV-2 seronegative and having an HSV-2 seropositive partner of only 38% and were too complex to be clinically useful. Therefore, demographic and clinical factors were not a viable surrogate for serologic screening of the couple. This finding is an important step toward recognizing that serologic screening may be needed to determine which women are at risk for HSV.
acquisition in pregnancy. Further research should investigate the clinical and economic impact of HSV serologic screening in pregnancy to prevent maternal and neonatal HSV infection.

References


Dioxin-like activity and maternal thyroid hormone levels in second trimester maternal serum

Warren G. Foster, PhD, Alison C. Holloway, PhD, Claude L. Hughes Jr, MD, PhD

Reproductive Biology Division, Department of Obstetrics and Gynecology, McMaster University, Health Sciences Centre, Hamilton, Ontario, Canada; Department of Medical and Scientific Services, Quintiles Inc, Research Triangle Park, NC; Department of Biology, East Carolina University, Greenville, NC

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KEY WORDS
Dioxins
Polychlorinated biphenyls
Chemically activated luciferase expression
Pregnancy
Thyroid

Objective: Developmental exposure to dioxin-like compounds has been associated with cognitive and motor impairments in children. These toxicants have been shown to be thyroid toxicants in animal studies. Therefore, the objective of this study was to quantify the overall dioxin-like activity in maternal serum and determine the association between dioxin-like activity and thyroid hormone levels.

Study design: Cross-sectional examination of serum from pregnant women (n = 150) attending a prenatal diagnosis clinic between January 2002 and December 2003.

Results: Serum dioxin-like activity was measured in 145 of 150 (96.7%) maternal serum samples. The mean (± SEM) serum lipid-adjusted dioxin-like activity was 0.34 ± 0.01 pg/g. Multiple regression analysis failed to demonstrate a relationship between maternal serum dioxin-like activity and serum thyroid hormone levels.

Conclusion: Dioxin-like activity is quantifiable in an overwhelming majority of second-trimester maternal serum samples but there was no relationship between dioxin-like activity and thyroid hormone levels in our study population.

Prenatal exposure to dioxins and compounds with dioxin-like activity, including polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzodioxins (PCDDs), has been associated with cognitive and motor impairments postnatally. These neurologic defects include cognitive and psychomotor developmental delays, visual recognition memory impairment, lower verbal and pictorial memory, and delays in verbal comprehension. Although children are exposed to dioxin and dioxin-like compounds both in utero and during lactation, the adverse effects of these compounds on neurodevelopment appear to be linked specifically to exposure during fetal life. Although attenuation of the adverse effects of developmental exposure to PCBs and dioxins by
breast feeding and a supportive home environment cannot be overlooked, measurement of in utero exposure to dioxin-like compounds is critical to our understanding of potential neurotoxic effects of these environmental exposures. Furthermore, it is critical to determine the mechanism(s) underlying the adverse effects of dioxins during fetal development.

In human populations, dysregulation of maternal thyroid function has been associated with motor and cognitive disorders in the offspring. Moreover, animal studies have demonstrated that dioxins can interfere with thyroid function, and altered thyroid function in humans exposed to dioxins has been documented. Moreover, the epidemiologic evidence suggests that adverse effects of dioxins on thyroid function could occur at background exposure levels. Because fetal thyroid hormone production and secretion is not well established until after 20 weeks of gestation in humans, alterations in maternal thyroid hormone status by environmental toxicants during the first and second trimesters could have significant implications for fetal neurodevelopment. However, to date, there are no studies in human populations that have assessed the interaction between dioxin exposure and maternal thyroid hormone status during this stage of pregnancy. Furthermore, dioxin and dioxin-like compounds (PCBs, PCDFs, and PCDDs) are present in the environment as complex mixtures of congeners that vary in their metabolism and toxicity. Although residue levels of several PCB and dioxin congeners have been documented in human maternal serum, breast milk, umbilical cord blood, and amniotic fluid, the measurement of PCB-, PCDF-, and PCDD-specific congeners is very expensive and time consuming and does not necessarily reflect the overall activity of these mixtures in biologic samples. Therefore, alternative methods of determining PCB, PCDF, and PCDD exposure have been developed. Several studies have measured dioxin-like activity in biologic media with the use of hepatoma (H4L1.1c4) cells transfected with an aryl hydrocarbon receptor (AhR)-activated firefly enzyme gene for the enzyme luciferase. This assay exploits the observation that the majority of the toxic effects of PCDD, PCDF, and dioxin-like PCBs are thought to be mediated through activation of the AhR ligand-activated transcription factor. The assay determines the total dioxin-like toxic equivalence (TEQ) in biologic samples and has been validated for use in human serum.

We propose that results from this assay will provide a cost-effective measure of the overall dioxin-like activity present in maternal serum and an indication of the overall potential biologic stimulation received by AhR-expressing tissues. Because the prenatal period appears to be the most sensitive developmental window with respect to adverse neurodevelopmental effects of dioxin and dioxin-like compounds, the objective of the present study was (1) to quantify the dioxin-like activity in second-trimester maternal serum and (2) to determine whether there is a relationship between dioxin-like activity and maternal thyroid hormone status.

**Material and methods**

**Study subjects**

The current study was approved and conducted in accordance with the McMaster University Research Ethics Board. Study participants were recruited from 310 successive pregnant women attending a prenatal diagnosis clinic at McMaster University Medical Centre between January 2002 and December 2003. McMaster University Medical Centre serves a mixed rural and urban population from South Western Ontario. From the initial cohort of 310 women, 150 pregnant women undergoing a second-trimester amniocentesis for advanced maternal age or maternal anxiety agreed to enter the study. Of the patients not included in the study, 43 of 310 (13.9%) met at least 1 exclusion criterion and 21 of 310 (6.8%) refused to participate (Table I). Exclusion criteria included women without a sufficient command of English, or with a history of illicit drug use, daily alcohol use during the pregnancy, any health condition requiring medical intervention (eg, gestational diabetes, preeclampsia), or prior history of endocrine disease, including thyroid disease, were excluded from the study. At entrance into the study all study participants completed informed consent, demographics, and obstetric history questionnaires at the clinic with the assistance of a research nurse. On the day of their amniocentesis, 2 blood samples (10 mL) were collected in the hospital clinic from all study subjects using standardized procedures for serum collection. Briefly, blood was collected in glass vacutainer tubes, samples were allowed to clot overnight at 4°C, serum was aliquoted for thyroid hormone assay, and a second aliquot collected into pre-cleaned glass vials and frozen at −20°C until required for analysis of dioxin-like activity.

**Measurement of serum dioxin-like activity**

Second-trimester maternal serum dioxin-like activity was determined by using the dioxin responsive-chemically activated luciferase expression (DR-CALUX) assay (Bioclassification Systems, Amsterdam, The Netherlands). Maternal serum was tested for the presence of dioxin-like compounds with the use of the DR-CALUX assay according to procedures developed at Bioclassification Systems in Amsterdam. Briefly, aliquots of 3.0 mL of maternal serum were extracted by using n-hexane:diethyl ether (97:3) and passed through a silica column containing concentrated H2SO4 (33%) to remove acid-labile matrix components. The cleaned extracts were evaporated and redissolved in 8 μL DMSO and dioxin-like activity...
Circulating levels of thyroid-stimulating hormone (TSH) and thyroxine (T4) were measured with the use of commercially available RIA kits (ICN Pharmaceuticals, Costa Mesa, CA). The limit of detection for TSH was 0.04 μIU/mL and the intra-assay coefficient of variation was 5.2% and for T4 the limit of detection was 0.76 μg/dL and the intra-assay coefficient of variation was less than 9%. All samples were analyzed on the same day in a single assay and thus no interassay variation was calculated.

Patients were grouped into hypothyroid, euthyroid, and hyperthyroid categories, on the basis of clinically significant thyroid hormone levels as defined by the assay kits used for their analyses. The TSH group ranges were as follows: hyperthyroid, 0.00 μIU/mL to 0.29 μIU/mL; euthyroid, 0.30 μIU/mL to 6.50 μIU/mL; and hypothyroid more than 6.50 μIU/mL. The T4 expected ranges were as follows: hypothyroid, 0.00 μg/dL; euthyroid, 5.0 μg/dL to 11.49 μg/dL; and hyperthyroid, 11.5 μg/dL to 19.5 μg/dL.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Details of patient enrollment into the study</th>
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<td>Category</td>
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<td>Number of patients meeting inclusion criteria</td>
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<td>Number of patients consenting to the study</td>
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<td>Meet at least 1 of the exclusion criteria</td>
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<td>Refused to participate</td>
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<tr>
<td>Cancelled amniocentesis procedure</td>
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<td>Unable to provide timely entry questionnaires</td>
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<td>Unable to contact the patient</td>
<td>20</td>
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<tr>
<td>Total</td>
<td>133</td>
</tr>
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</table>

| Number of patients meeting inclusion criteria | 177 | 57.1 |
| Number of patients meeting | 150 | 48.4 |
| Reasons for nonentry into study | | |
| Meet at least 1 of the exclusion criteria | 43 | 13.9 |
| Refused to participate | 21 | 6.8 |
| Cancelled amniocentesis procedure | 4 | 1.3 |
| Unable to provide timely entry questionnaires | 45 | 14.5 |
| Unable to contact the patient | 20 | 6.5 |
| Total | 133 | 42.9 |

Statistical methods

Descriptive statistics were completed for all outcome variables measured. Data were compared by t test and multiple linear regression analysis (SPSS Inc, Chicago IL) to determine the presence and magnitude of between group differences in dioxin-like activity comparing previously defined groups (hypothyroid, euthyroid, and hyperthyroid) on the basis of age, parity, body mass index (BMI), duration of breast feeding in previous pregnancies, and number of cigarettes smoked/day. Data that failed tests for normality and equal variance (serum dioxin-like activity) were normalized by log transformation. Data with a P < .05 were considered statistically significant.

Results

Patient characteristics

The mean age of women enrolled in this study was 38.0 ± 0.2 years (range 34-44 years) with a median age of 38 years (Table II). The study population was primarily white 130 of 150 (86.7%), Hispanic 6 of 150 (4.0%), or Middle Eastern 9 of 150 (6.0%). Study subjects reported on average 2.9 ± 0.1 previous pregnancies with a range of the current pregnancy being their first through to the sixth for 2 women. Three women experienced a failed pregnancy and 17 of 147 (11.6%) women delivered preterm (<37 weeks). Of the study subjects, 87 of 150 (58%) women reported that they had previously breast fed their newborn infants and the duration of breast feeding ranged from 0.5 to 64 months with a mean length of breast feeding of 14.2 ± 1.4 months per child. The socioeconomic status of our study population was assessed from education and income levels that revealed that 122 of 150 (81.3%) women had postsecondary school training and 120 of 150 (80%) women had a family income greater than $40,000.

Dioxin-like activity

Of the 150 serum samples analyzed, there were only 5 samples for which levels were nondetectable. The mean (±SE) lipid-adjusted serum CALUX-TEQ level was 0.34 ± 0.01 pg/g serum lipids, median of 0.27 pg/g, and ranged from 0.15 to 0.73 pg/g serum lipids. The CALUX-TEQ level measured in the second trimester serum samples from women who subsequently had a preterm delivery was nonsignificantly higher than in those with term deliveries (0.35 ± 0.04 vs 0.31 ± 0.01 pg/g serum lipids, respectively). Multiple regression
The objective of the current study was to quantify dioxin-like activity in second-trimester maternal serum of women with background exposure to PCBs, PCDFs, and PCDDs. Dioxin-like activity was quantified in 145 population of pregnant women, 109 of 150 (72.7%) women reported that they were nonsmokers, whereas 25 of 150 (16.7%) women reported that they were daily cigarette smokers. The mean number of cigarettes smoked per day was 13.8 ± 1.5 with a minimum of 3 and a maximum of 25 cigarettes smoked per day. The median number of cigarettes smoked per day was 12.0. Dioxin-like activity in smokers versus nonsmokers was 0.30 ± 0.02 versus 0.31 ± 0.02 pg/g, respectively.

**Thyroid function**

Of 150 subjects for which second trimester serum samples were obtained, 131 (87.3%) were euthyroid, 6 (4%) were hypothyroid, 12 (8%) were subclinically hypothyroid, and 1 (0.4%) was hyperthyroid. No statistically significant relationship was found between dioxin-like activity in the serum and circulating levels of TSH or T₄ (Figure). Subjects were grouped according to quartiles on the basis of serum CALUX-TEQ level. Although serum CALUX-TEQ results covered a narrow range, with the highest activity level being just 4.9 times greater than the lowest, serum lipid-adjusted dioxin-like activity levels by percentile group were significantly different between the highest and lowest quartile (P = .001). Comparison between quartiles revealed that there are significant differences (P < .05) in serum dioxin-like activity across the groups. However, no differences were found in circulating TSH and T₄ levels when compared across the highest and lowest quartiles.

**Comment**

The objective of the current study was to quantify dioxin-like activity in second-trimester maternal serum of women with background exposure to PCBs, PCDFs, and PCDDs.
of 150 (96.7%) of the second-trimester maternal serum samples examined. Although dioxin-like activity was detected in an overwhelming majority of the study subjects, the level of dioxin-like activity detected was low compared with prior studies that used traditional analytical methods5,8,25,32,40,41 and a recent study that used the CALUX assay.36 No relationship between serum dioxin-like activity and maternal age, BMI, number of previous pregnancies, duration of breast feeding with previous children, diet, or number of cigarettes smoked could be demonstrated. Furthermore, there was no relationship between serum dioxin-like activity and circulating thyroid hormone levels. Our results therefore demonstrate that overall dioxin-like activity is quantifiable in the vast majority of pregnant women in our Canadian cohort and suggest that background levels of dioxin-like chemicals present in maternal serum are too low to be associated with changes in maternal thyroid function.

In the current study, dioxin-like activity was measured in 96.7% of the study subjects and the CALUX-TEQ values ranged from 0.15 to 0.73 pg/g (ppt) of serum lipid. The CALUX-TEQ levels measured in this study indicate that there is low activity relative to the concentrations of PCBs, PCDFs, and dioxins measured in maternal serum and cord blood in previous studies1,8 by using traditional analytical methods. For example, maternal serum PCBs and PCDFs levels in excess of 25 ppb were documented in the Taiwanese cohort,1 whereas PCB and dioxin levels in maternal plasma and cord blood from The Netherlands were 2.2 and 0.45 ppb, respectively.8 Slightly higher concentrations of PCBs have been documented in fish eaters in the Michigan cohort compared with nonfish eaters, 6.1 ppb versus 4.1 ppb, respectively.3 The lower levels of dioxin-like activity documented in the current study may be the result of different analytical methods. Whereas prior studies have carried out congener-specific analyses and summed PCBs and dioxins to arrive at a TEQ value,1,3,8 we and others have quantified dioxin-like activity using a gene reporter assay.36 The DR-CALUX assay provides a composite measure of the activity of all chemicals present in the serum that act through the AhR and thus provides different but equally important information for population health risk assessment. Despite a similar analytical approach, our results are also lower than the CALUX-TEQ measured in women residing in Seveso, Italy, where plasma concentrations were 25.4 ppt lipid adjusted and a range of 0 to 127.6 ppt.36 Because of the accidental release of dioxins into the environment, serum dioxin-like activity in the Seveso, Italy, cohort would be expected to be higher than in our study population that is representative of a population with background exposure only.

Previous studies have demonstrated that PCBs and dioxins accumulate with age and levels decline with parity and duration of breast feeding.42 In the current study, pregnant women were recruited from the population of pregnant women undergoing a second-trimester amniocentesis for advanced maternal age or maternal anxiety. The women making up our study population were close in age and covered only a 10-year span ranging from 34 to 44 years. Although our study population is not broadly representative of the general population of all pregnant women, the subset of pregnant women participating in this study represent the age-range of a substantial portion of pregnant women as more women postpone childbearing with a consequent increase in the proportion of births (29% in 1986 and 45% in 1999) now occurring among women older than 30 years.43 Similarly the proportion of first births in women under the age of 24 years has steadily declined from 46% to 24% between 1971 and 1999, whereas the proportion

Figure The relationship between maternal second trimester (A) thyroid stimulating hormone and (B) total serum thyroxin (T4) and dioxin-like activity was assessed in pregnant women (n = 150) attending a prenatal diagnosis clinic at McMaster University Medical Centre. Data were compared by multiple regression analysis controlling for maternal age, parity, cigarette smoking, and history of breast feeding.
of first births in women above the age of 25 has increased for all age groups. Furthermore, compared with younger gravid women, our study population would be expected to be at increased risk for higher body burdens of persistent environmental toxicants and thus potential adverse health outcomes. Therefore, if anything, our study design would be expected to bias our results in favor of finding an association between exposure and effects in this study population. However, there was no effect of age, maternal BMI, parity, or duration of breast feeding on the dioxin-like activity measured in these second-trimester maternal serum samples. We interpret these results to indicate that background levels of dioxin-like chemicals are low in women in this region of Canada. Furthermore, we speculate that lifestyle, age, and family planning and breast feeding practices in our study population are too similar to permit differences in exposure to these environmental toxicants to be detectable.

PCBs, PCDFs, and PCDDs are lipophilic compounds, and thus exposure to these environmental toxicants are primarily through the diet with levels measured in fast food being higher than in fresh food. Similarly, dioxin-like compounds such as benzo(a)pyrene are also present in cigarette smoke and thus maternal diet and smoking habits were assessed in this study. In this study no relationship between serum dioxin-like activity and diet could be demonstrated. Although all but 4 study subjects reported consuming fast food meals, the number of fast food meals consumed on a monthly basis was less than 1 per week. Moreover, in this study, few study subjects reported consuming Great Lakes fish and the number of Great Lakes fish meals consumed per month was also low. Thus, although the diet is the principal route of exposure to PCBs and dioxins, the subjects in this study did not consume appreciable amounts of foods thought to be high in these contaminants. In addition, the percentage of women reporting to be daily cigarette smokers is consistent with a recent survey. However, the amount smoked may be too low to significantly increase the concentration of dioxin-like chemicals and thus their activity in maternal serum. We further speculate that trace levels of dioxin-like chemicals are so widespread in the environment and the diet that background levels in the population will be very similar.

Although conflicting reports have appeared in the literature, PCB and dioxin exposure has been associated with increased serum levels of TSH and decreased T4 in several animal studies and thus may provide a mechanism for dioxin-like chemical-induced neurotoxicity. However, in the current study we were unable to find any relationship between maternal serum dioxin-like activity and circulating levels of either TSH. Our results are in contrast with those from children in the Dutch cohort but are in agreement with umbilical cord blood samples from the North Carolina cohort.

Divergent results can be explained by the greater exposures documented in the Dutch cohort compared with those of the current study. Discrepant results may also be a function of using different sampling paradigms such as umbilical cord blood versus second-trimester maternal serum as in our cohort. However, our results are in agreement with an earlier study in which infant plasma in the second week after birth was analyzed.

Our report is important because pregnant women may present for prenatal care with previously undiagnosed clinical hypothyroidism or with subclinical hypothyroidism, in which maternal thyrotopin levels are above a statistically defined reference range while maternal thyroxine levels are within the reference range. Subclinical maternal hypothyroidism has been reported to occur in 2.3% of pregnancies. Although appropriate clinical management of subclinical hypothyroidism in pregnancy remains controversial, accurate determination of maternal thyroid function will clearly be increasingly important for both researchers and clinicians.

In summary, in this study we found that the vast majority of women studied had measurable levels of dioxin-like activity in their second-trimester serum. Background levels of dioxin-like activity measured in the current study could not be associated with maternal age, BMI, parity, duration of breast feeding associated with previous births, and cigarette smoking. Moreover, maternal diet did not provide insight into the sources of the background levels of dioxin-like activity documented in this study. Hence, we conclude that background levels of dioxin-like activity are low in our Canadian population and are not associated with adverse effects on maternal thyroid function.

Acknowledgments

We gratefully acknowledge to time, patience, and effort of the study subjects for agreeing to participate in this study and the recruitment expertise of our study nurse Ms Mary Louis Beecroft. We also acknowledge the assistance of undergraduate students Ms Catherine MacPherson and Mr Zain Kassam for data entry and statistical analyses.

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Damage to ovarian reserve associated with laparoscopic excision of endometriomas: A quantitative rather than a qualitative injury

Guido Ragni, MD, Edgardo Somigliana, MD,* Francesca Benedetti, MD, Alessio Paffoni, BS, Walter Vegetti, MD, Liliana Restelli, BS, Pier Giorgio Crosignani, MD

Infertility Unit, Policlinico, Mangiagalli and Regina Elena Hospital; Università Degli Studi di Milano, Milan, Italy

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KEY WORDS
Endometrioma
Laparoscopy
Ovarian reserve
Enucleation

Objective: Retrospective studies suggest that laparoscopic excision of endometriomas is associated with a reduced responsiveness to ovarian hyperstimulation. In this study, we prospectively evaluated ovarian response to hyperstimulation in women selected for in vitro fertilization and intracytoplasmic sperm injection cycles who previously underwent laparoscopic enucleation of a monolateral endometrioma.

Study design: Operated and contralateral intact ovaries of the same patient were compared in terms of number of follicles, number of oocytes retrieved, fertilization rate, and rate of high-quality embryos.

Results: Thirty-eight subjects were included. A reduced number of dominant follicles, oocytes, embryos, and high-quality embryos was observed in the operated gonad. The mean percentage of reduction was 60% (95% confidence interval 38-81%), 53% (95% confidence interval 30-75%), 55% (95% confidence interval 28-81%), and 52% (95% confidence interval 17-87%), respectively. Fertilization rate and rate of good-quality embryos were similar.

Conclusion: Laparoscopic excision of endometriomas is associated with a quantitative but not a qualitative damage to ovarian reserve.

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Endometriotic ovarian cysts are found in 17% to 44% of patients with endometriosis.1 Several therapeutic modalities have been proposed for this form of the disease. Overall, it is well known that medical therapy and/or ultrasound-guided aspiration are inadequate. There is a general consensus that operative laparoscopy should be considered the first-line treatment in symptomatic women with endometriotic ovarian cysts.2,3 From a technical point of view, excision rather than ablation of the cyst is generally recommended because the former has been associated with a higher pregnancy rate and a lower recurrence rate.1,3,4 The safety of this technique in terms of damage to ovarian reserve has, however, been
questioned.\textsuperscript{5,6} Of note, a vast body of evidence supports the view that endometriomas result from a progressive invagination of ovarian cortex after adhesion to the pelvic peritoneum caused by ectopic implantation of endometrial fragments regurgitated through the tubes.\textsuperscript{5,7} The excision of the so-called cyst wall implies the removal of ovarian tissue, with potential reduction in follicular reserve.

The potential deleterious effects to ovarian reserve associated with excision of endometriotic ovarian cysts have been poorly investigated in the past. There are at least 2 reasons to explain the little attention paid to this topic. First, evaluation of ovarian reserve remains an elusive task of reproductive medicine. Because ovarian function cannot be measured directly, ovarian response to gonadotropin hyperstimulation is currently considered the most appropriate surrogate measurement for ovarian reserve. The use of serum dosages (follicle-stimulating hormone [FSH], inhibin B, 17β-estradiol, FSH/luteinizing hormone ratio, antimüllerian hormone) and/or ultrasound variables (ovarian volume, antral follicle count, ovarian stromal blood flow) may be of help but are still considered less informative.\textsuperscript{8} Second, in most cases, only 1 gonad is involved.\textsuperscript{7,9} The contralateral intact ovary does usually supply to the reduced function of the affected gonad.\textsuperscript{10} For this reason, we believe that the observation that endometriomas has a limited, if any, effect on in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcome cannot be used to infer that ovarian reserve is not injured.\textsuperscript{11-14}

An interesting study design that can overcome these difficulties is represented by the selective evaluation of the responsiveness to hyperstimulation during IVF-ICSI cycles of operated and unoperated ovaries in women who previously underwent monolateral excision of endometriomas. The study group is represented by operated gonads, whereas the control group corresponds to the contralateral intact gonads of the same patient. To the best of our knowledge, this study design has been retrospectively used by 4 independent authors\textsuperscript{15-18} with the specific aim to investigate the effects of laparoscopic cystectomy. These studies consistently documented that the number of dominant follicles and retrieved oocytes is reduced in the operated ovaries. Unfortunately, oocytes quality was not evaluated because IVF-ICSI procedures after oocyte retrieval are generally performed without taking into consideration the ovary of origin.

To eliminate the inherent biases of the retrospective model of these studies and to give insights with regard to the quality of the retrieved oocytes, we designed a prospective study enrolling women selected for IVF-ICSI cycles who previously underwent monolateral laparoscopic excision of an endometrioma. The primary aim of the study was to compare affected and contralateral intact ovaries in terms of number of follicles, number of oocytes retrieved, and fertilization rate.

**Material and methods**

Patients referring to the Infertility Unit of the “Policlinico, Mangiagalli and Regina Elena” Hospital and selected for IVF or ICSI between November 2002 and February 2004 were prospectively evaluated for study entry. Inclusion criteria were as follows: (1) previous laparoscopic enucleation of an ovarian endometriotic monolateral cyst, (2) age less than 40 years at the time of ovarian stimulation, and (3) availability of a detailed description of the surgical intervention. Subjects were included regardless of the ratio of resected endometrioma volume to the whole ovary volume. Exclusion criteria were as follows: (1) enucleation of more than 1 cyst, (2) subsequent intervention(s) for other ovarian cyst(s) in the same or the contralateral ovary, (3) presence of ovarian cyst(s) at the time of ovarian stimulation, and (4) canceled cycle because of low or hyperresponse to ovarian hyperstimulation. Information with regard to surgical technique, dimension, and histology of the cyst were obtained from surgical, echographic, and pathological evidence. Patients were enrolled only for their first oocyte retrieval cycle performed during the study period. Approval for the study was obtained by the local institutional review board, and all patients gave informed consent.

A transvaginal ultrasound aimed to assess ovarian volume and to exclude the presence of ovarian cysts was performed within day 3 of the menstrual cycle of the cycle preceding ovarian hyperstimulation. Ovarian volume was calculated as $4/3 \pi (\text{diameter}/2)^3$, in which the diameter was taken as the mean of the height, width, and depth of the ovary. Two different types of pharmacological regimens were used: the long protocol with daily 0.1 mg gonadotropin-releasing hormone agonist (Triptorelin, Decapeptyl, Ipsen Pharma, Pavia, Italy) and a protocol using daily 0.25 mg GnRH antagonist (Cetrorelix 0.25 mg daily, Cetrotide, Serono Laboratories, Inc, Rome, Italy). Protocol of stimulation and dosage of recombinant FSH prescribed was decided based on age, hormonal tests, ultrasound characteristics of the ovaries, and results from previous pharmacological ovarian hyperstimulation cycles. In all cases, follicular growth was monitored by serial transvaginal ultrasound and serum levels of 17β-estradiol. Ovulation was triggered administering 5000 IU of human chorionic gonadotropin (hCG) (Profasi, Serono Laboratories) when 2 or more leading follicles had mean diameter larger than 18 mm. The day of hCG administration, a careful transvaginal ultrasound was performed to record number and diameter of all follicles with a mean diameter larger than 10 mm. Diameter of follicles was calculated as the mean of 3 perpendicular diameters. Transvaginal oocyte retrieval was performed 36 hours after hCG administration. All follicles with a mean diameter larger than 10 mm were aspirated.
Oocytes were evaluated using an inverted T200 microscope (Nikon, Tokyo, Japan). They were cultured and treated alone in every step of the assisted reproduction procedure to evaluate characteristics of morphology, fertilization, and development and successively correlate them with the ovary of origin. Morphological evaluation was performed as previously reported. High-quality embryos were defined as embryos types 1 and 2 according to the grading scheme proposed by Veeck. Briefly, grade 1 embryos have blastomeres of equal size and no cytoplasmic fragmentation, whereas grade 2 embryos have blastomeres of equal size and minor cytoplasmic fragmentation (10% or less of embryo surface). Embryos were evaluated separately by 2 of the authors (A.P. and L.R.) who were masked to the ovary of origin. If discordant evaluations were given, the 2 biologists were asked to re-evaluate together the case to give a final judgment. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac 4 weeks after embryo transfer.

Physicians performing echographic evaluations and oocytes retrieval and biologists performing assisted reproduction procedures were masked to the side of previous surgery. Analysis of the data was performed using the Statistics Package for Social Sciences (SPSS, Chicago, IL). Data are expressed as mean ± SD. Paired Student t test was used to investigate differences between operated and contralateral ovaries. Differences were always confirmed using nonparametric Wilcoxon rank test for paired data. This test was also employed to compare fertilization rate and rate of good-quality embryos. McNemar’s test was used to compare qualitative data. A binomial distribution model was employed to calculate SD of percentages. P < .05 was considered statistically significant.

## Results

A total of 38 patients fulfilled the inclusion and exclusion criteria. Characteristics of patients and cycles are shown in Table I. As illustrated in Figure 1, a reduced number of dominant follicles, oocytes, embryos, and high-quality embryos in the operated and contralateral intact ovaries. Healthy gonads are represented in white and affected ovaries are represented in black. All four variables were found to be significantly different. *P = .005; **P < .001.

![Figure 1](image-url)
reduction was 60% (95% confidence interval [CI] 38% to 81%), 53% (95% CI 30% to 75%), 55% (95% CI 28% to 81%) and 52% (95% CI 17% to 87%), respectively. Follicles 11 mm to 15 mm were also reduced in the operated ovary, although this reduction was not statistically significant (2.3 vs. 1.5 in the control and affected gonads respectively, \( P = .08 \)). Basal ovarian volume of the unoperated and operated ovaries was similar (8.5 vs. 8.5 cm\(^3\), respectively, \( P = .99 \)). A higher percentage of patients with no dominant follicles, no oocytes, no embryos, and no high-quality embryos was observed in the operated ovary (Table II).

Analyses were repeated, taking into consideration the diameter of the excised cyst. Specifically, patients were divided into 2 groups; diameter 3 cm or less (n = 15) versus diameter larger than 3 cm (n = 17). The diameter of the excised cyst could not be reliably assessed in 6 cases because of discordance between ultrasonographic and/or surgical and/or pathological evidence extracted from the patients’ chart. Results from this analysis are shown in Table III.

Overall, number of retrieved oocytes in the control and operated ovary were 192 and 91, respectively. Biological outcome of these oocytes according to the ovary of origin is illustrated in Figure 2. Fertilization rate of oocytes retrieved from intact and operated ovaries was similar (55% and 53%, respectively, \( P = .70 \)). Rate of good-quality embryos was also comparable (39% and 40%, respectively, \( P = 1.00 \)). Oocytes could be obtained from both gonads in 26 patients. In these patients, fertilization rate and rate of good-quality embryos per patient were also analyzed. The median fertilization rate in the intact and operated ovaries was 61% (interquartile range 50% to 83%) and 55% (interquartile range 33% to 76%), respectively (\( P = .50 \)). The rate of good-quality embryos was 47% (interquartile range 9% to 51%) and 33% (interquartile range 0% to 75%), respectively (\( P = .99 \)).

**Comment**

In this prospective study, we have confirmed previous retrospective evidence suggesting that laparoscopic cystectomy for endometrioma is associated with a reduced responsiveness to ovarian hyperstimulation. Conversely, fertilization rate and rate of high-quality embryos were not affected by previous surgery, thus indicating that the damage is quantitative rather than qualitative.

Some limits of the present study have to be considered. First, we have included only patients who were selected for IVF-ICSI cycles. Thus, inferences of the present results on the entire population of women operated for endometrioma should be drawn with caution. It cannot be excluded that women requiring IVF-ICSI procedures may represent a subgroup of patients who may have been particularly damaged. A second limit of the study is represented by the outcomes chosen to assess oocyte quality. Although fertilization rate and rate of high-grade embryos are frequently used in this context, the best option would have been to evaluate...
implantation and pregnancy development. However, this outcome could not be assessed in this study because patients generally received more than 1 embryo. The present study has documented a reduction in number of dominant follicles, oocytes retrieved, and embryos obtained of about 50%. The entity of this reduction is similar to that observed in our previous retrospective study but probably slightly higher than the one reported in the other 3 studies on this topic. The inclusion in our studies of all operated women regardless of the unit of surgery may at least in part explain this finding. Indeed, it has been claimed that surgical expertise may be of value because an accurate surgical technique may reduce the entity of damage. Of note, studies on this topic have generally been performed by eminent surgical groups. On the other hand, the inclusion of all patients in our studies may better mirror worldwide clinical reality.

The observation that the quality of oocytes retrieved is unaffected is comforting but not reassuring. Indeed, it should be noted that no embryos were obtained in the operated ovary in 40% of patients. Whereas this reduction may be supplied by the contralateral gonad in women with monolateral disease such as those included in our study, patients with bilateral ovarian disease may be at significant risk of failure. Although endometriomas are monolateral in the majority of cases, both gonads are affected in 19% to 28% of patients. To the best of our knowledge, there are no studies specifically investigating IVF-ICSI outcome in women operated for bilateral endometriomas. The observation that the entity of damage may at least in part depend on the size of the excised endometrioma is another interesting, although not surprising, finding of the present study. Reduction in dominant follicles, oocytes retrieved, and embryos seems to be more pronounced in operated ovaries in which larger cysts were excised. The sample size recruited in this study is, however, insufficient to draw firm conclusions on this topic. In this context, we believe that it is of utmost interest noting that a statistically significant damage could be documented also in patients undergoing excision of small endometriomas (diameter 3 cm or less).

The causes of the reduced ovarian reserve in operated ovaries have been poorly investigated. At present there are no definitive data to clarify whether the damage is related to the surgical procedure and/or to the previous presence of the cyst. Indeed, it cannot be excluded that the cyst may per se damage the surrounding ovarian tissue. Using pathological sections of the ovarian cortex surrounding ovarian endometriomas, Maneschi et al found a reduced number of follicles antecedent to surgery, suggesting that the disease per se may damage the ovary. Notwithstanding the entity of the injury related to the presence of the cyst, it is well known that surgery may also damage ovarian reserve. A potential deleterious mechanism is the accidental removal of a consistent amount of ovarian tissue during cystectomy. In a recent histological study performed on pathological specimens, Muzii et al observed the presence of healthy ovarian tissue adjacent to the cyst wall in 14 of 26 endometriomas (54%), compared with only 1 case of 16 nonendometriotic benign ovarian cysts (6%) (P = .002).

The presence of recognizable ovarian tissue adjacent to the wall of enucleated endometriotic cysts also has been documented in a substantial number of subjects by Huchisuga and Kawarabayashi. In the present study, basal ovarian volume of the ovaries was extremely similar, thus suggesting that the accidental removal of a consistent amount of ovarian tissue is not the most relevant insult involved. This finding is surprising, considering that this study also supports the presence of a quantitative defect. Considering the observed reduction in the number of oocytes retrieved, one may have expected to find a reduction in basal ovarian volume as well. This contradiction is difficult to explain. In this context, it has to be noted that a reduction in basal volume was documented in 2 previous studies investigating ovarian volume in patients operated for monolateral endometriomas. There are at least 2 possible reasons to explain discrepancies with our present data. First, it cannot be excluded that a type II error may have played a role in the present study. A quite larger sample size was recruited in the study from Exacoustos et al. Second, the study design was different. Whereas ovarian volume was established within day 8 and day 10 of the
menstrual cycle in our previous retrospective study and in the study from Exacoustos et al, this variable was herein assessed within day 3, thus prior to follicular development. Considering that on one hand ovarian volume may be influenced by follicular growth and that on the other hand a higher ovulation rate in the unoperated gonad has been observed, previously reported differences might merely document a difference in ovarian function rather than a difference in the amount of ovarian tissue.

A further mechanism that may be responsible for the reduced ovarian reserve is represented by the damage that may be inflicted on the ovarian stroma and vascularization by both surgery-related local inflammation and electrosurgical coagulation during hemostasis. Adverse changes in ovarian artery blood flow have been reported following laparoscopic stripping. Future studies should focus on the impact that surgical variables may have in the determinism of the injury to better clarify the causes of the damage. Unfortunately, surgical variables were herein collected in a retrospective manner, thus limiting the validity of their use for this specific aim.

If a surgical-mediated damage will be confirmed, it might be hypothesized that the detrimental effect may be influenced by the excision technique used. Drainage of the endometrioma content and successive laser-vaporization or coagulation of the internal layer of the cyst represents an alternative approach that may be more tissue sparing. To the best of our knowledge, there is only 1 retrospective study investigating responsiveness to ovarian hyperstimulation in the operated and unoperated ovaries in patients treated with this specific surgical technique. No difference in terms of dominant follicles and number of oocytes retrieved was observed in 87 cycles performed in 39 patients. Observation needs further confirmation prior to the conclusion that this technique would be more preferable in women selected for an IVF-ICSI cycle who are found to have ovarian endometriosis.

Overall, the present study supports the following conclusions: (1) laparoscopic excision of endometriomas is associated with a significant damage to responsiveness to gonadotrophin; this injury may be of particular relevance in women undergoing bilateral excision of endometriomas; (2) dimension of the cyst may influence the entity of damage, albeit an injury also could be documented for small cysts; and (3) fertilization rate and rate of high-quality embryos are not influenced by previous excision of endometriomas.

References


CLINICAL OPINION

To the point: Medical education reviews—Dealing with student difficulties in the clinical setting

Patricia J. Hicks, MD,a Susan M. Cox, MD,a,* Eve L. Espey, MD,b Alice R. Goepfert, MD,c Jessica L. Bienstock, MD,d Sonya S. Erickson, MD,e Maya M. Hammoud, MD,f Nadine T. Katz, MD,g Paul M. Krueger, DO,h James J. Neutens, PhD,i Edward Peskin, MD,j Elizabeth E. Puscheck, MDk

University of Texas Southwestern Medical Center,a Dallas, TX; University of New Mexico,b Albuquerque, NM; University of Alabama at Birmingham,c Birmingham, AL; Johns Hopkins University,d Baltimore, MD; University of Colorado,e Denver, CO; University of Michigan,f Ann Arbor, MI; Albert Einstein College of Medicine,g Bronx, NY; UMDNJ-SOM,h Stratford, NJ; University of Tennessee-Knoxville,i Knoxville, TN; University of Massachusetts,j Worcester, MA; Wayne State University,k Detroit, MI

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KEY WORDS
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Professionalism
Undergraduate medical education

Learners with cognitive and behavioral difficulties are particularly challenging in the clinical setting. Cognitive difficulties in the clinical realm may relate to knowledge deficits and/or weak problem-solving skills. Behavioral difficulties resulting from attitudinal or motivational problems may manifest themselves as specific unprofessional acts either committed or omitted in the course of caring for patients as well as in unprofessional behavior. A disproportionate amount of time and energy can be expended addressing the needs of such students. This paper reviews several types of difficulties encountered by educators and suggests strategies for preventing, assessing, and working effectively with challenging students in the clinical setting. Specific attention is directed to impaired students.

Learners may demonstrate cognitive difficulties such as a weak knowledge base, underdeveloped clinical skills, poor problem-solving ability, or difficulty organizing information. Behavioral difficulties can include poor motivation, a negative attitude, an overconfident attitude (ie, arrogance), and an inability to work with colleagues in the context of an integrated health care team. While most students are interested in and capable of learning, a disproportionate amount of a teacher’s time and energy can be expended in addressing the needs of difficult learners. This paper reviews several types of student difficulties, including substance abuse and...
mental illness, and suggests assessment, intervention, and prevention strategies.

Types of learner difficulties

Two publications\(^3\,^4\) on problem students cite 5 common types of difficulties. The student: 1) cannot focus or prioritize what is important; 2) displays a poor fund of knowledge; 3) is overeager; 4) is excessively shy and nonassertive; and 5) does not integrate knowledge well. Table I illustrates the relative frequency of commonly identified student difficulties, and the relative difficulty of managing each of these issues can be related to the following specific causes of problems.

Cognitive problems

Knowledge or skills deficits are often more easily identified than behavioral issues. Importantly, faculty may be more comfortable dealing with knowledge deficits than other problems. The underpinning of diagnostic reasoning is retrieval of stored knowledge. The learner who has not mastered the required knowledge base is at a disadvantage. Cognitive deficiencies may be caused by learning disability,\(^5\) diagnostic reasoning deficiencies and/or inability to integrate knowledge,\(^6\) and immature development of critical thinking.\(^7\) Further, if the learner cannot think in the abstract, he or she will have difficulty applying concepts from one clinical scenario to another.\(^8\)

Behavioral/professionalism problems

Learners may show a poor behavioral attitude toward the curriculum or teachers by demonstrating disrespect with flippant, arrogant, and other disruptive behaviors. Alternatively, a poor attitude toward learning may be manifested by tardiness, absences, lack of enthusiasm or commitment, and poor motivation. These problems may derive from a mismatch between the values and expectations of the learner and those of the teacher, or from impairment caused by substance abuse or mental illness. Professionalism problems are a broad category of noncognitive performance problems that compromise attributes such as honesty, integrity, responsibility, and communications skills. Performance characteristics of students showing a lack of professionalism are listed in Table II.\(^9\,\,11\) In assessing these negative attributes and responsiveness to criticism, many teachers feel judgmental or ill at ease. Many also feel that their role as an educator is to address the knowledge base, and that addressing the behavioral issues is someone else’s responsibility. Most faculty are uncomfortable with direct feedback to the learner regarding deficits in knowledge or behavior; faculty development can help in these situations. In addition, most teachers are not trained in assessing, evaluating, and remediating problems in professionalism or behavior issues. Until teachers hold themselves accountable for the professional development of the learner, assessment, feedback, and directed remediation regarding professionalism will be postponed and the development of the learner will be suboptimal. The top 10 examples of unprofessional behavior are listed in Table III.

Substance abuse

Impairment caused by substance abuse can be particularly difficult to diagnose and may be perceived simply as behavioral problems. Chemical dependency is the leading cause of physician impairment, with a lifetime prevalence approaching 10% to 15%. Medical students and residents experience alcoholism at a rate similar to that of the general population. Gender differences are small in rates of problematic drinking. Some studies have shown that medical students and residents may have a lower rate of nonalcoholic substance abuse compared with the general population,\(^12\) but other studies report a higher rate,\(^13\) more in line with the higher rate in practicing physicians, whose abuse of benzodiazepines and opiates is facilitated by self-prescribing.

Learner behaviors consistent with impairment caused by substance abuse are not precise. These can include

<table>
<thead>
<tr>
<th>Table I</th>
<th>Types of problems with average frequency and degree of difficulty encountered to manage or fix “the problem”</th>
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</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Frequently encountered and difficult to manage</td>
</tr>
<tr>
<td>Bright</td>
<td>with poor interpersonal skills</td>
</tr>
<tr>
<td>Excessively shy, nonassertive</td>
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<tr>
<td>Type 2</td>
<td>Frequently encountered and less difficult to manage</td>
</tr>
<tr>
<td>Poor integration skills</td>
<td></td>
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<tr>
<td>Overeager</td>
<td></td>
</tr>
<tr>
<td>Cannot focus on what is important</td>
<td></td>
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<tr>
<td>Disorganized</td>
<td></td>
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<tr>
<td>Disinterested</td>
<td></td>
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<tr>
<td>A poor fund of knowledge</td>
<td></td>
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<tr>
<td>Type 3</td>
<td>Not frequently encountered and difficult to manage</td>
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<tr>
<td>Cannot be trusted</td>
<td></td>
</tr>
<tr>
<td>A psychiatric problem</td>
<td></td>
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<tr>
<td>A substance abuse problem</td>
<td></td>
</tr>
<tr>
<td>“Con artist” (manipulative)</td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td>Not frequently encountered and less difficult to manage</td>
</tr>
<tr>
<td>Hostile</td>
<td></td>
</tr>
<tr>
<td>Rude</td>
<td></td>
</tr>
<tr>
<td>Too casual and informal</td>
<td></td>
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<tr>
<td>Avoids work</td>
<td></td>
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<tr>
<td>Does not measure up intellectually</td>
<td></td>
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<tr>
<td>Avoids patient contact</td>
<td></td>
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<tr>
<td>Does not show up</td>
<td></td>
</tr>
<tr>
<td>Challenges everything</td>
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<tr>
<td>“All thumbs”</td>
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</table>

Adapted from Hunt et al,\(^3\) Tinesk and Buchanan,\(^4\) and Metheny WP and Carlile.\(^19\)

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poor appearance (grooming, dress), slurred speech, erratic work behavior, tardiness, memory lapses, inappropriate medical care, inappropriate language, and other risk-taking behavior, including prescribing of controlled substances. In addition, diagnosis of substance abuse carries significant social and professional ramifications. For this reason, physician-teachers are often hesitant to identify behavior as potential substance abuse, despite their understanding of the serious consequences for the student and for patient safety. Predictive factors of physician alcohol-related problems include a family history of alcoholism, narcissistic personality style, a perception of low parental warmth in childhood, and particular stressors in the learner environment. Unfortunately, stress is often an integral part of the training process for medical students and residents. Therefore, maintaining abstinence will require ongoing treatment and monitoring.

### Mental illness

Mental illness may cause physician impairment that threatens patient safety, but at a much lower rate than substance abuse. Depression, anxiety, and other psychiatric disorders not diagnosed or not under adequate control often manifest or are exacerbated during the learner’s clinical experiences when multiple stressors are applied in novel situations. A greater awareness and understanding of attention deficit and hyperactivity disorder (ADHD) has resulted in more adults receiving this diagnosis later in life. ADHD may also impact the students’ ability to function effectively and efficiently. Learners with personality disorders find it difficult to change and will need to develop insight into their problem and how it affects others. They can learn how to modify some of their behaviors but their personality disorder will not change. When aware of such issues, then modifications of stressors can be made before problems occur for the learner. However, recognition of such problems requires training and vigilance. Because the signs of such impairments are similar, and in fact can predispose an individual to alcohol abuse, the initial approach with evaluation should include screening for anxiety and depression. These screening procedures fall outside of the realm of the teacher and should include a referral to student health or other appropriate support services.

### Work load and stress problems

Large workloads and multitasking are reported as a routine part of medical training. These sources of stress may diminish with reduced work hours, but other common sources of stress, such as financial, marital, pregnancy/child care issues, or marginal academic status may cause the learner to develop problems in keeping up with the curriculum. On the other hand, the reduced work hours may also increase the need to be more efficient and result in increased stress. High performance expectations may cause considerable distress, including anxiety, somatization, and depression.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Behaviors indicating lack of learner professionalism in the clinical setting</th>
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<tbody>
<tr>
<td>Unaddressed professional responsibility</td>
<td>Lack of awareness/effort towards self-improvement and adaptability</td>
</tr>
<tr>
<td>Learner needs continual reminders regarding responsibilities</td>
<td>Learner is defensive/resistant to advice/criticism</td>
</tr>
<tr>
<td>Learner cannot be relied upon to complete tasks</td>
<td>Learner is unwilling to consider/change in behavior</td>
</tr>
<tr>
<td>Learner misrepresents or falsifies actions and/or information</td>
<td>Learner is abusive or critical during times of stress</td>
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<tr>
<td></td>
<td>Learner demonstrates arrogance</td>
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<td></td>
<td>Learner does not acknowledge self as cause of failure, error</td>
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</table>

<table>
<thead>
<tr>
<th>Table III</th>
<th>Top 10 examples of unprofessional behavior</th>
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</thead>
<tbody>
<tr>
<td>Dishonesty—intellectual and personal</td>
<td></td>
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<tr>
<td>Arrogance and disrespectfulness</td>
<td></td>
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<tr>
<td>Prejudices</td>
<td></td>
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<tr>
<td>Negative or abrasive interactions with colleagues</td>
<td></td>
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<tr>
<td>Lack of accountability for administrative oversights and medical errors</td>
<td></td>
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<tr>
<td>Fiscal irresponsibility</td>
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<tr>
<td>No or lack of commitment to life long learning</td>
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<tr>
<td>Lack of due diligence—ie, carelessness, laziness, and not following through</td>
<td></td>
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<tr>
<td>Personal excesses—ie, substance abuse, gambling, and reckless behavior</td>
<td></td>
</tr>
<tr>
<td>Sexual misconduct</td>
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</tbody>
</table>

Adapted from Duff.
Impact of learner difficulties

Students exhibiting difficulties of any type can have significant consequences at multiple levels in the education system. These include the individual, the teachers, and the profession and society in general.

Impact on learner

Learners may or may not have insight into their learning difficulties. Students may place blame on others, deny the problem exists, or lack insight into the consequences of their deficiencies or behaviors. Some learners are aware of their problems yet may be unable to identify a cause or develop a solution without assistance. Due to the unpleasantness of direct confrontations, teachers are often reluctant to engage students despite obvious problematic cognitive deficiencies or inappropriate behaviors. Ironically, teachers may inadvertently reinforce problematic behaviors if they do not give timely feedback with specific strategies for improvement.

Impact on teacher

Teachers may become discouraged when dealing with certain problem students because, in general, they feel more comfortable addressing knowledge gaps and deficits in critical reasoning than in addressing behavioral problems. Most faculty and clinicians have not been trained to identify or help resolve problems with substance abuse or mental illness. Dealing with students who have these complicated problems may be overwhelming.

Impact on the institution, the profession, and society

Learners with difficulties have a profound impact on our institutions and on society. Knowledge gaps will have impact on the quality of patient care. Unprofessional behaviors in medical school are associated with future problems, including subsequent disciplinary action by state medical boards. Patient safety is affected by disruptive actions. In addition, poor physician-patient relationships are associated with a higher malpractice rate. Helping to identify and modify difficulties during medical education before problems become established and cause harm is an important responsibility of medical school faculty.

Identification and assessment of problem students

Identifying problem students can often be challenging. In general, teachers are more experienced at identifying cognitive deficits than identifying problem behaviors. Their contacts with learners may be episodic or superficial, so they may lack the depth of contact required to identify problems. Some clerkship directors or program directors receive negative input from faculty who have directly observed the problems but have not themselves addressed the problems with the learner, and it is much more difficult for someone who has not witnessed the problem behaviors to effectively confront the learner. Further, some teachers may be concerned about seeming judgmental towards a student. Teachers must be reinforced in identifying problem behaviors so they do not see the learner as the problem, but rather the unprofessional actions or specific behaviors as the problem. The remediation also is then directed at the problem behaviors and not the learner personally.

Sometimes the learner’s peer group may be more astute at identifying problem behaviors than their teachers. These peer-learners may focus on teamwork and work ethic and may more readily identify students with deficiencies in these areas. Identification of problems by peers and others in a 360-degree evaluation can be an effective tool in identifying this type of learner difficulty. It is important that the peers feel comfortable with disclosing such information in order for this evaluation process to be effective. Otherwise, the peers may not disclose either.

Evaluations of students often constitute part of the problem in identifying difficulties. A recent study showed that faculty were sometimes unwilling to record negative comments about students. Both faculty and residents were concerned about inadequate guidelines for handling problem students, a lack of information on problem students before the start of the rotation and failing to act on negative evaluations. This issue is a two-way problem: on one hand it is helpful to have information regarding potential problem students, confidentially given prior to the onset of a rotation and on the other hand, this information may inappropriately label the student as “bad” and the student is on an uphill battle from the start. Because clinical rotations are short, teachers may default to simply passing on a problem student to the next set of teachers to avoid the inconvenience and awkwardness of a confrontation. Additionally, faculty are reluctant to provide negative comments for fear they will receive poor evaluations from the students. Evaluation of students is best accomplished by assessment at multiple levels.

Teacher assessment

Narratives are written from faculty and resident comments. Mid-clerkship comments and end-of-rotation formative and summative evaluations are used in most programs. These evaluations typically cover 2 areas: knowledge base (through the use of MCQ examinations) and clinical skills (often through use of a checklist). Only recently has the assessment of non-cognitive attributes
such as professionalism and interpersonal communication skills been discussed. If assessed at present, it is usually through the use of clinical evaluation forms, a method that is not valid unless large numbers of forms are utilized. More appropriate assessment tools include 360 degree evaluations for professionalism and standardized patient encounters for interpersonal communication. Assessment of these competencies is now required in residency training and extension to undergraduate medical education would enhance this evaluation continuum. Appropriate feedback of student professionalism can support critical development in the learner. More faculty development programs may be needed to give the faculty appropriate level of training so that effective assessments, remediation and evaluations can be performed in this area.

Self-assessment

Self-assessment during medical school may have merit in measuring noncognitive abilities associated with clinical performance and prompting further learning and professional development. When first-year medical students conducted self-evaluations, they were more critical of their performance than the faculty who evaluated them. Again, training and a safe environment are needed for students to truthfully and critically evaluate their performance. Many students who perceive that their self-assessment may impact their grade will merely state that they are doing fine. In addition, the questions for the self-assessment need to be detailed and specific instead of general and open ended. Further development of such self-assessments during medical training would allow for reflection and demonstrate whether students had insight into their own problem behaviors.

Peer assessment

Peer evaluation of medical students can be very helpful in giving feedback on trends and perceptions of performance as well as behavioral problems. Medical students were particularly astute at identifying those individuals who were not displaying acceptable professional behaviors. However, these students displayed less ability to judge their peers’ cognitive ability. This form of evaluation may be a useful tool to provide learners insight into how others see their actions.

Patient/family/care team assessment

Checklists of observed behaviors completed by patients, families, and care team members (receptionists, medical assistants, nurses) can augment teacher assessment of professionalism. The ideal tool for such assessment is the 360-degree evaluation. This tool is a mechanism for evaluating performance based on feedback from everyone with whom the individual comes in contact—supervisors, coworkers, partners, subordinates, the general public.

Objective assessment

Objective assessments include multiple choice examinations, written essays, or by means of an oral examinations. Although such assessments are easy to score and may evaluate learner knowledge and content of professionalism, they may not accurately assess likelihood of desired behaviors in the clinical setting. The use of objective standardized clinical examination (OSCE), rated audio or videotape, and directed/scored observations with real patients are some of the mechanisms used to address competency assessment in the learner. Validity and reliability of such tools, as well as available resources, will likely dictate the management of competence in professionalism and its components.

Primary prevention

Curriculum design

A well-designed and progressive curriculum allows the learner to grow in stages and is built on prerequisite material. Design of the curriculum should provide that no one step is too large or skips over fundamental (physiologic) reasoning. The learning objectives and the evaluation methods need to be clearly stated at the outset. Clear expectations are critical!

Vigilance and feedback

Vigilance is very important in the early stages of the learner’s progress. Targeted feedback is critical for learners in their early stages of development. If a learner has academic difficulty in the curriculum, a mechanism to help that student during the rotation or course and follow his/her progress in the future may help avoid further difficulties.

Previous identification

High-risk individuals can be identified from previous poor performance or poor precourse test scores. While the exchange of information from one set of instructors to the next is controversial, this approach may decrease the time required to identify a problem, allowing for earlier recognition and more efficient implementation of a solution.

Clerkship/rotation design

Strategies to prevent difficult teacher-learner interactions begin with clear communication of expectations for learning and performance. Clear objectives stating
expectations for performance should be shared with all students. A detailed orientation for the learner is critical, with stated and written expectations about logistics, such as arrival time, dress code, and format for documentation and presentation in the clinical setting. All learners should be made comfortable in reporting difficulties of any nature, with assurances of a nonpunitive response. Individual learner’s expectations should be discussed. A midrotation discussion should be scheduled to discuss learning on the rotation. If the learner is having any difficulties, this interim feedback session can be helpful in creating a path for optimal completion of the learner’s clinical experience. It is best to address problems as soon as one is aware of the problem (if it is identified early), and not to wait for the midrotation feedback session whenever possible. The LCME requires that students be informed of their poor performance and be given an opportunity for remediation before giving a failing grade.

Systems support

Most institutions have programs that provide support for stress reduction, financial assistance, supervision, and risk control, as well as tools for effective communication. These programs should be designed to be used effectively and their availability reviewed with learners.

Interventions

Education leaders in the institution may be helpful with this process. Never forget to get help from the institution and to document everything!

Physicians use the SOAP process daily with their patients; Langlois and Thach,28 documented the usefulness of this process for student intervention. They recommend using the following sequential steps. First, investigate the student with the following framework to confirm a problem: Subjective—use experience and opinion to gain an individualized impression of the student’s difficulty; Objective—document specific examples of the problem; Assessment—diagnose the problem; Plan—develop and implement a plan to address the problem, and not a personal attack on the learner. This approach allows for the specific, constructive feedback to the learner, as well as a plan for correction of problem or remediation, reviewed with the student. Often a call to the dean of student affairs or the like may be able to direct you to resources with which you may not be familiar.

Intervention for cognitive problems

Students with cognitive deficiencies should be provided with appropriate support and offered extra tutoring or additional clinical experiences. Students who fail to perform well on objective examinations can be provided tools for studying and/or test-taking strategies. Repeated deficiencies in performance might prompt testing the student for learning disabilities that might be hindering their performance. Timely feedback in the clinical setting is extremely important for early intervention and avoidance of problem deterioration.

Intervention for behavioral/professional issues

Designing an approach to remediate deficiencies in professionalism must be focused on changing student behaviors, not on changing underlying attitudes or motivating factors. Changing behavior requires adaptation. Prochaska and DiClemente’s model of behavior change,29 originally designed for changing patient behavior, can be useful in changing learner behavior in a clinical setting. In the precontemplative stage, the learner’s self-awareness and reflection are minimal. The learner does not realize he or she has a problem, and does not understand the need for change. The learner often has no insight into how he or she is perceived. The student must be made aware of the problem by frank objective examples of the offending actions. The learner is asked to walk through the possible outcomes and consequences of such unacceptable actions. Multiple examples from various environments are helpful in making the student understand the problem. The most common defensive mechanism is to blame others or the system for the events/actions or to deny that a problem exists. When the learner becomes aware that he/she has a problem behavior, the process can move to the contemplative stage. At this stage, the learner may not have enough insight and experience to develop strategies to correct the problem. The determination stage occurs when the learner both recognizes the problem beyond a single example (he/she sees the problem abstractly) and knows that change is needed. Once this stage is reached, the learner can develop strategies to correct the problem. Involving the learner in developing strategies to correct the problem allows the learner to embrace the solution and keeps everyone on the same team: the learner and the teacher want the learner to succeed. This approach tends to be more effective than a paternalistic approach. Behavioral change will require continuous involvement of both a faculty mentor and the learner. Often, specified and frequent meeting times are needed to follow-up on these remediations. Tools that are useful in this process include a daily log of specific desirable actions in checklist format and a behavioral contract that establishes boundaries and limits of tolerance to breaks in the agreement. Continuity of the faculty mentor is helpful to establish trust and consistency of approach. Decisions about sharing performance difficulties with upcoming faculty must be made on an individual basis. Such information could
be helpful in allowing faculty to help the student or could bias their view of such learners. The student may experience relapses and disappointments, but consistency should be maintained. The learner will understand and better adhere to the plan if the learner and mentor acknowledge the difficulty of such change while underscoring the need for that change. Documentation with learner signature on frequent evaluations is mandatory to minimize liability and maximize the remediation process with difficult behaviors.

**Intervention for impairment caused by substance abuse**

Physicians are more likely than the general population to respond to alcohol and drug addiction programs. Their success in quitting may be related to the direct consequences of loss of hospital privileges and state licensure review without treatment adherence. Intervention is best achieved with a combined approach of confrontation and concern. When behavior consistent with impairment is present, the institutional policy must call for a review by an addiction specialist. Referral for evaluation is usually made by a committee at the institution institutional level that is either directly aware of a student’s addiction or is addressing behavior concerns that may be related to addiction. Strict documentation, broad faculty involvement, and adherence to due process are critical for the success of such referrals and programs. Students diagnosed with addiction that undergo appropriate treatment may be required to be monitored throughout the remainder of medical school and beyond.

**Legal concerns**

The threat of being sued is an ever-present worry in addressing learners with difficulties. Adverse academic actions are held to a different standard than that of civil disciplinary actions, and courts will generally uphold academic actions that are well documented and that are in the interests of the institution and society as long as they are not arbitrary and capricious. The documentation will need to follow the LCME recommendations, which clearly state that the student needs to be made aware of the problem and have the opportunity for remediation; each of these steps need to be documented and kept on file.

**Fair and equitable treatment**

Generally, courts will not intervene in faculty decisions regarding academic cases, provided that the faculty members used professional judgment, reviewed the entire record of performance, and there is no evidence of arbitrary and capricious actions on the part of the faculty or institution. Documentation of all interventions, including student understanding and acceptance, is key.

**Due process**

Each institution must have a detailed due process policy that outlines the student’s hearing and appeal rights and the steps that must be taken by both the student and institution when an adverse action is initiated. Adequate documentation of adherence to the policy is helpful in upholding institutional decisions that adversely affect a student, underscoring the importance of escalation within the institution to get appropriate guidance and support with handling these types of problems.

**Conclusion**

Teachers are natural advocates for their learners and should charge themselves with developing each learner irrespective of learner difficulties. The clinical setting, with its focus on patient care and safety, has natural tension between needs of the patient and those of the learner. Thus, the learner who has significant difficulties that may affect his or her ability to deliver safe and compassionate care can be very challenging to the teacher. A primary preventative approach of good orientation with full communication of expectations, coupled with curricular prerequisites encouraging personal development regarding behavior and self-awareness, should be early in the educational progression of the developing physician. If problems do arise, early detection and intervention are important to avoid reinforcement of problems with the learner or patient.

**References**

REVIEW ARTICLE

Etiology and prevention of stillbirth

Ruth C. Fretts, MD, MPH*

Harvard Vanguard Medical Associates, Wellesley, MA

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Objective: This is a systematic review of the literature on the causes of stillbirth and clinical opinion regarding strategies for its prevention.

Study design: We reviewed the causes of stillbirth by performing a Medline search limited to articles in English published in core clinical journals from January 1, 1995, to January 1, 2005. Articles before this date were included if they added historical information relevant to the topic. A total of 1445 articles obtained, 113 were the basis of this review and chosen based on the criterion that stillbirth or fetal death was central to the article.

Results: Fifteen risk factors for stillbirths were identified and the prevalence of these conditions and associated risks are presented. The most prevalent risk factors for stillbirth are prepregnancy obesity, socioeconomic factors, and advanced maternal age. Biologic markers associated with increased stillbirth risk are also reviewed, and strategies for its prevention identified.

Conclusion: Identification of risk factors for stillbirth assists the clinician in performing a risk assessment for each patient. Unexplained stillbirths and stillbirths related to growth restriction are the 2 categories of death that contribute the most to late fetal losses. Late pregnancy is associated with an increasing risk of stillbirth, and clinicians should have a low threshold to evaluate fetal growth. The value of antepartum testing is related to the underlying risk of stillbirth and, although the strategy of antepartum testing in patients with increased risk will decrease the risk of late fetal loss, it is of necessity associated with higher intervention rates.

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Methods

A Medline search was used with the MeSh terms “etiology,” “causality,” “pregnancy outcome,” “fetal death,” “stillbirth,” as was limited to human subjects, English articles with abstracts in core clinical journals from January 1, 1995, to January 1, 2005, identified 1445 papers. Articles were chosen if they had sufficient statistical power to address the risk factor of interest and were performed in developed countries. A total of 113 were identified with this search and an additional 9 were cited for their historical information.

Scope of the problem

Although stillbirth is infrequent, it occurs 10 times more often than sudden infant death. In the United States, stillbirth accounts for a large proportion of all perinatal losses, although its causes remain incompletely understood. In developing nations, preterm births and stillbirths are grossly underreported, thus making international comparisons difficult. Even in developed nations, there is considerable variability in the threshold
for reporting stillbirth. These include differences in either the length of gestation or the birth weight. The World Health Organization (WHO) classification of stillbirth is defined as fetal loss in pregnancies beyond 20 weeks of gestation, or, if the gestational age is not known, a birth weight of 500 g or more, which corresponds to 22 weeks of gestation in a normally developing fetus.

In the United States during 2002, there were approximately 26,000 stillbirths, a rate of 6.4/1,000 total births. There also were about 28,000 infant deaths (equaling a rate of 7.0/1,000 live births), and 19,000 neonatal deaths (4.7/1,000 live births). Black women have more than twice the rate of stillbirth of white women and, although some of this increased risk can be attributed both to access to, and quality of, medical care, other factors probably play a role as well. Within the United States, there is no national program of review for these losses. Death certificates are filled out by the delivering clinician typically before autopsy and other data relevant to the stillbirth evaluation are available. Also, there is no international consensus on the classification of perinatal loss.

Since the 1950s, there has been a decline in rate of stillbirth, but it has not declined to the same extent as the neonatal death rate (Figure 1). Indeed, recent data from the United Kingdom show that there has been a slight increase in the stillbirth rate, related perhaps to the growing number of pregnancies in older women, as well as to increased numbers of multiple pregnancies, due in large part to an increase in assisted reproduction techniques.

In large databases, fetal death is stratified by gestational age into early losses (ie, 20-28 weeks) and late fetal death (29 weeks or more; Figure 2). Presumably, this approach was used initially to divide those pregnancies that might be salvageable (ie, late losses), from very early term losses, the majority of which would not be salvageable. Recent advances in neonatal care make this distinction somewhat arbitrary, but the causes of fetal death do vary according to gestational age. The prevention of early fetal losses, in which a large proportion is related to infection, has been the most difficult to impact to date. Ideally, of course, stillbirths deserve the same systematic evaluation as sudden infant deaths. If an obvious cause of death is not found, then by exclusion the stillbirth is usually considered “unexplained.” Only when fetal deaths are reported according to the specific causes of fetal demise can appropriate strategies be designed to reduce these losses.

### Causes of stillbirth

One of the largest and most comprehensive analyses of the causes of fetal death has been compiled and reported with the use of a Canadian database maintained at McGill University. This analysis evaluated 709 stillbirths among 88,651 births with a 97% autopsy rate. This study was able to track changes in the specific causes of stillbirth over 3 decades (Figure 3). Since the 1960s, when the database was created, the greatest reductions in stillbirth occurred when strategies were developed to intervene in specific causes of fetal demise. Since the introduction of Rh immune prophylaxis, for example, there has been a 95% reduction in stillbirths because of Rh isoimmunization. Stillbirths during labor (intrapartum asphyxia) also decreased by 95% after the introduction of intrapartum monitoring (Figure 3). Currently, these causes of stillbirth account for less than 1 fetal death per 10,000 births. Higher rates of intrapartum asphyxia in fetuses weighing more than 2.5 kg suggests deficiencies in obstetric quality of care. Interestingly, in the McGill experience throughout the 30-year study period, there was a low rate of stillbirths among women who had preeclampsia or diabetes (ie, less than 2/10,000), due in large part to aggressive management of these conditions.

Among other causes of stillbirth, the small-for-gestational-age (SGA) (ie, <2.4th percentile) fetus had an incidence of stillbirth of 46.8 per 1000, whereas the appropriate-for-gestational-age fetus had a rate of 4.0 per 1000 (odds ratio [OR] = 11.8; 95% CI 8.1-17.1). The identification and appropriate management of the growth-restricted fetus remains a significant opportunity for stillbirth prevention. Indeed, although 25% of
stillbirths that occurred in women carrying a SGA fetus had known risk factors such as maternal hypertension, most pregnancies that ended in stillbirth in nonanomalous growth-restricted fetuses had not been identified as having a problem with fetal growth.

Between 24 and 27 weeks of gestation, the most common causes of stillbirth were related to infection (19%), abruption (14%), or significant lethal anomalies (14%), and 21% were “unexplained.” As noted previously, stillbirths related to infection occur most frequently in fetuses weighing less than 1000 g. The stillbirth rates due to infection, like that of preterm birth, have been quite resistant to change despite the availability and wide use of antibiotics. A fetal death that is unexplained by fetal, placental, maternal, or obstetric factors is the most frequent type of fetal demise, representing between 25% and 60% of all fetal deaths. It is also one of obstetrics’ most distressing outcomes, because preventative effective strategies have not yet been identified, in large part because unexplained fetal demise is, by definition, a diagnosis of exclusion and depends on the rigorousness of the stillbirth assessment.

In the first comprehensive analysis of a single large database, Yudkin et al evaluated the timing of fetal demise in 40,635 deliveries in Oxford, England, from 1978 to 1985, in all gestations of 28 weeks or greater. In their examination of 63 unexplained fetal deaths (ie, 43% of all fetal deaths) in this cohort, they found that the risk of unexplained fetal demise more than doubled in pregnancies of greater than 40 weeks of gestation. In the largest study of unexplained stillbirth to date, Huang...
et al.\textsuperscript{14} described a number of apparent risk factors for unexplained stillbirth in a cohort of women from 1978 to 1996. These risk factors included advanced maternal age (ie, 40 years or older, OR = 3.7, 95% CI 1.3-10.6), low educational attainment (OR = 2.5, 95% CI 1.1-5.5), alterations in fetal growth (ie, between the 2.4-10.0 percentile OR = 2.8, 95% CI 1.5-5.2), infants larger than the 87th percentile (OR = 2.4, 95% CI 1.3-4.4), primiparity (OR = 1.9, 95% CI 1.1-3.1), parity 3 or greater (OR = 2.4, 95% CI 1.0-5.7), and the presence of cord loops (OR = 1.7, 95% CI 1.0-2.97).

Froen et al.\textsuperscript{15} using a large data set from Norway, reported findings similar to those of Huang et al.\textsuperscript{14} although with slightly higher risk estimates for advanced maternal age (ie, 35 years or older, OR = 5.1, 95% CI 1.3-19.7), low educational attainment (OR = 3.7, 95% CI 1.5-9.8), prepregnancy obesity, and a body mass index (BMI) of greater than 25 (OR = 2.4, 95% CI 1.1-5.3). Smoking is also associated with the unexplained growth-restricted stillbirth\textsuperscript{18,19} but appeared not to be associated with stillbirths among appropriate-for-gestational age fetuses.\textsuperscript{14} With respect to the timing of unexplained fetal deaths, these studies and others have consistently shown increased losses late in pregnancy, with the rate rising significantly after 37 to 39 weeks of gestation.\textsuperscript{13-15} In addition, Fretts and Usher,\textsuperscript{10} using the McGill Obstetrical Neonatal Database, found that this increase was more pronounced in older women (Figure 4).\textsuperscript{20}

### Common risk factors for stillbirth

#### Race and socioeconomic factors

Nationally, black women consistently have had approximately twice the risk of stillbirth of white women, although typically these rates are not adjusted for differences in obstetric and socioeconomic factors. In Massachusetts in 2002, for example, the household income for black families was significantly lower than that of white families, and black women are less likely to receive adequate prenatal care, less likely to have completed a high school education, and more likely to have received publicly funded prenatal care.\textsuperscript{21} Black mothers who have had a stillbirth were also less likely than white mothers to have sought obstetric care in the first 3 months of pregnancy.\textsuperscript{22}

Even when evaluating only women who had received adequate prenatal care, Vintzileos et al.\textsuperscript{7} found that, in the United States, black women still had twice the risk of stillbirth when compared with white women. The excess of stillbirth was attributed to higher rates of diabetes, hypertension, placental abruption, and premature rupture of membranes.\textsuperscript{7} Given that black women are a relatively high-risk group for stillbirth, increasing access to prenatal care, and the identification and management of those medical and socioeconomic risk factors that contribute to stillbirth obviously will be important.

#### Advanced maternal age

Advanced maternal age remains an independent risk factor for stillbirth, even after accounting for medical conditions that are more likely to occur in older women, such as multiple gestation, hypertension, diabetes, previous abortion, and abruptio placenta, all of which are associated with higher rates of stillbirth. Older women are also more likely to have preterm births, and growth-restricted infants.\textsuperscript{18,19} Historically, women 35 years or older also have had an increased risk of stillbirth related anomalies.\textsuperscript{20} Nevertheless, with the introduction of prenatal diagnostic testing and the availability of elective abortion, where these services are available, there has been a significant reduction in this cause of perinatal demise.\textsuperscript{30} Indeed, longitudinal databases that track anomalies show a transfer of fetal deaths from after 20 weeks to elective terminations before 20 weeks.\textsuperscript{31} After the introduction of routine prenatal diagnosis in the McGill population, for example, women 35 years or older had fewer stillbirths related to lethal anomalies, declining to that observed in younger counterparts. In recent years in this population, the only type of stillbirth

<table>
<thead>
<tr>
<th>Table I</th>
<th>Most frequent types of stillbirth according to gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-27 weeks</td>
<td>28-36 weeks</td>
</tr>
<tr>
<td>Infection (19%)</td>
<td>Unexplained (26%)</td>
</tr>
<tr>
<td>Abruptio placenta (14%)</td>
<td>Fetal malnutrition (19%)</td>
</tr>
<tr>
<td>Anomalies (14%)</td>
<td>Abruptio placenta (18%)</td>
</tr>
</tbody>
</table>

Fetal malnutrition was defined as an otherwise unexplained fetus weighing less than the 2.4%, anomalies were only considered a cause of death if they were potentially lethal. The unexplained stillbirth was diagnosed when other causes of death were eliminated with the use of a comprehensive evaluation that included autopsy in 97% of cases. Adapted from Fretts et al.\textsuperscript{10} and Fretts and Usher.\textsuperscript{20}

![Figure 4](image-url) Reprinted with permission. Fretts RC, Usher RH. Fetal death in women in the older reproductive age group. Contemporary Reviews in Obstetrics and Gynecology 1997;9:173-9.

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1926 Fretts
that was statistically more common in older women was the “unexplained” category of fetal demise, and these were likely to occur late in pregnancy.20

Obesity

The prevalence of maternal obesity is increasing steadily and is associated with an increased risk of fetal macrosomia and perinatal mortality.32-36 The reasons for this association are speculated to be due to behavioral, socioeconomic, as well as obstetric factors. Obese women are more likely to smoke and to have pregnancies complicated by gestational diabetes and preeclampsia.37 However, even when controlling for these factors, an elevated BMI remains a significant risk factor for stillbirth.33,36 and the association appears to increase as the gestation advances. A number of mechanisms for the increased risk seen in obese women have been postulated. Thinner women may be better able to perceive decreased fetal movements. Maternal obesity is also associated with hyperlipidemia,38 which may contribute to increased endothelial dysfunction, platelet aggregation, as well as to clinically significant atherosclerosis. Sleep studies of pregnant women have shown that obese women spend more time snoring (32% vs 1%; P < .001), have more apnea-hypoxia events (1.7 vs 0.2/h; P < .05), and have more episodes of oxygen desaturation (5.3 vs 0.3/h; P < .005) than nonobese pregnant women.39 Snoring has also been associated with pregnancy-induced hypertension and fetal growth restriction.40 Indeed, in addition to advanced maternal age and low socioeconomic status, as discussed previously, the most prevalent risk factor for stillbirth is prepregnancy obesity.

Thrombophilias

Our understanding of the relationship between inherited abnormalities of blood clotting and stillbirth is seriously deficient, in that there have been no large population-based studies that have evaluated this association.41-44 The relationship between late fetal death and thrombophilia is more consistent than with early fetal losses,45 although the odds ratio ranges from as low as 1.8 to estimates as high as 12.46-50 A meta-analysis of smaller studies suggested that the presence of thrombophilias does increase the risk of stillbirth (OR = 3.6; 95% CI 1.4-9.4), with the analysis of specific defects limited by power.41 Martinelli et al41 found the prevalence of mutations either in factor V or prothrombin to be 16% in those pregnancies that ended in an unexplained loss, compared with 6% of normal pregnancies,41 although the value of placental disease to discriminate unexplained losses with and without a diagnosis of thrombophilia is in question. The authors found that 24% of the placentas were normal, whereas the remaining 76% showed intravascular thrombi, decidual vasculopathy, and ischemic necrosis with villous infarctions. The placentas were abnormal in 7 of 9 (78%) women with a mutation and in 40 of 53 (75%) stillbirths without a mutation so that the presence of a known mutation did not correlate with a specific placental histologic or biochemical abnormality. In another small study of 22 women with at least 1 unexplained loss, 4 of 9 placentas showed extensive infarcts in women who had documented thrombophilia, whereas none of the 8 without thrombophilia exhibited similar pathologic findings.47

Systemic lupus erythematous

Systemic lupus erythematous (SLE) complicates less than 1% of pregnancies but the risk of stillbirth in this population is disproportionately high, especially in women with preexisting renal disease.52 Hypertension, preeclampsia, and fetal growth restriction are common in these patients.53-55 Even when pregnancy is conceived during a relatively quiescent period in terms of disease activity, stillbirth can complicate up to 3% to 8% of pregnancies.53-55 The presence of a lupus anticoagulant has been reported to significantly increase the risk of a fetal loss after 20 weeks of gestation. The optimum management of patients with SLE is uncertain, but the use of heparin and aspirin was associated with an improved outcome in 1 small series.45

Medical risk factors

Hypertension and diabetes are 2 of the most common medical conditions to complicate pregnancy (7%-10% and 3%-5%, respectively).23,52,56-59 Historically, both of these conditions have been shown to be responsible for a significant proportion of fetal deaths. However, optimal management, including counseling, preconceptual care, and close medical management of these conditions, has been shown to reduce the risk for perinatal death to a level only marginally elevated over that of the general population.50 Management of patients remains a challenge, however, because of the increased risks of abruptio placenta, of intrauterine growth restriction, and of superimposed preeclampsia, which often necessitates early delivery.37,58,60 Other important medical conditions associated with an increased risk of stillbirth are listed in Table II.52

Infection and immunologic exposure

A significant proportion of perinatal morbidity and mortality is related to infection, which often leads to delivery of a premature liveborn or stillborn infant. Despite the adoption of a strategy to reduce the risk of perinatal infection caused by group B streptococci, there has been little change in the risk of fetal death caused by infection because most of these deaths occur preterm.10,61 Although there are some pathogens that are probable causes of stillbirth, such as parvovirus 19,
cytomegalovirus, toxoplasmosis, and listeria, there are others that may be associated with an increase in risk, but the evidence for which remains inconclusive. For example, colonization with *Ureaplasma urealyticum*[^1], *Mycoplasma hominis*[^2], and group B streptococci has all been associated with an increased risk of stillbirth, despite colonization with these pathogens is also common among healthy women. In recent reports, Refuerzo et al. and Blackwell et al. found that women who had had an unexplained stillbirth, without any evidence of obvious infection, had a higher number of “memory T cells” (CD45RO) than “naive T cells” (CD45RA) when compared with live-born controls. Although this finding suggests that, despite the absence of any overt evidence of clinically significant infection, these women had had prior exposure to infectious agents. Froen et al.[^4] found, in an epidemiologic study of unexplained stillbirths, that bacteruria or symptomatic urinary tract infections during pregnancy were associated with a reduced risk of fetal death, a finding not fully explained by treatment with antibiotics. The role of the immune system has lately become a subject of considerable interest in perinatal birth injury. There is evidence that elevated inflammatory processes are associated with an increase in the risk of adverse outcomes in the premature neonate. Infected infants, both premature and term, were shown to exhibit a significant increase in interleukin 6 production, with C-reactive protein (CRP) increasing rapidly at the onset of infection and remaining elevated until the infection was cleared. Animal data suggest that the combination of subclinical infection and a fetal inflammatory response can both cause abnormalities of gas exchange that result in fetal hypoxia and decreased survival.

**Infertility**

Because women who choose to delay their childbearing are also more likely to have a history of infertility and to conceive with the aid of reproductive technologies, it is important to evaluate the effect of infertility and infertility treatment on the risk of fetal death. Patients treated with advanced reproductive technologies experience excess perinatal mortality. Although the frequency of multiple gestations is responsible for a

### Table II: Estimates of maternal risk factors and risk of stillbirth

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Estimated rate of stillbirth</th>
<th>OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnancies</td>
<td></td>
<td>6.4/1000</td>
<td>1.0</td>
</tr>
<tr>
<td>Low-risk pregnancies</td>
<td>80%</td>
<td>4.0-5.5/1000</td>
<td>0.86</td>
</tr>
<tr>
<td>Hypertensive disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>6%-10%</td>
<td>6-25/1000</td>
<td>1.5-2.7</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>5.8%-7.7%</td>
<td>9-51/1000</td>
<td>1.2-4.0</td>
</tr>
<tr>
<td>Severe</td>
<td>1.3%-3.3%</td>
<td>12-29/1000</td>
<td>1.8-4.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated with diet</td>
<td>2.5%-5%</td>
<td>6-10/1000</td>
<td>1.2-2.2</td>
</tr>
<tr>
<td>Treated with insulin</td>
<td>2.4%</td>
<td>6-35/1000</td>
<td>1.7-7.0</td>
</tr>
<tr>
<td>SLE</td>
<td>&lt;1%</td>
<td>40-150/1000</td>
<td>6-20</td>
</tr>
<tr>
<td>Renal disease</td>
<td>&lt;1%</td>
<td>15-200/1000</td>
<td>2.2-30</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>0.2%-2%</td>
<td>12-20/1000</td>
<td>2.2-3.0</td>
</tr>
<tr>
<td>Thrombophilia</td>
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<td>1.8-4.4</td>
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<td>10-15/1000</td>
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<tr>
<td>Obesity (prepregnancy)</td>
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<tr>
<td>BMI &gt; 30</td>
<td>20%</td>
<td>13-18/1000</td>
<td>2.1-2.8</td>
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<tr>
<td>Low educational attainment (&lt; 12 y vs. 12 y+)</td>
<td>30%</td>
<td>10-13/1000</td>
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<tr>
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<tr>
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<tr>
<td>Multiple gestation</td>
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<td>12/1000</td>
<td>1.0-2.8</td>
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<td>Twins</td>
<td>2.7%</td>
<td>34/1000</td>
<td>2.8-3.7</td>
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<tr>
<td>Triplets</td>
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* OR of the factor present compared to the risk factor absent. Some estimates of medical conditions and stillbirth risk from Simpson. Other risk estimates from references 24,25,29,33,34,35,38,55,58,68.
significant portion of this excess mortality, it also appears that women who undergo either in vitro fertilization (IVF) or ovarian stimulation and have a singleton gestation, also have a statistically increased risk of prematurity, low birth weight, and SGA fetuses. There have been no studies that have evaluated whether infertility itself is associated with an increase in unexplained fetal death. Nevertheless, many physicians who care for infertile patients perceive these pregnancies to be at “high risk” for adverse maternal and fetal outcomes.

Multiple gestations

Over the past 2 decades, the rate of pregnancies with twins has more than doubled, the rate of triplets has increased 6-fold, and the number of quadruplets has increased by 12-fold. With this increase in the number of multiple gestations, there has been a measurable increase in prenatal mortality and morbidity in industrialized countries. The main reason for this increase is the use of reproductive technologies and the associated increase in maternal age. It has been estimated that a strategy of lowering the transfer rate to 2 embryos during IVF could reduce the perinatal mortality rate by 45% in the case of limiting a triplet to twins, or 74% when limiting the quintuplet pregnancies to twins. The optimal duration of an otherwise uncomplicated pregnancy is shorter for multiple gestations. Kahn et al found, for example, that it was safer for a twin pregnancy to be delivered than undelivered at 39 weeks, and for triplets who remain undelivered at 36 weeks, an elective delivery at this time minimized adverse fetal outcomes.

Biologic markers of increased risk of stillbirth

Hemoconcentration

Froen et al from Norway have demonstrated that women with hemoconcentration, defined as the lowest hemoglobin measured during pregnancy greater than 13.0 g/dL, is associated with a 9-fold increase in the risk of unexplained fetal death. Stephansson et al, using a Swedish database, found that both an initial elevated hemoglobin and the failure of significant hemodilution over the course of the pregnancy, increased the risk of stillbirth by 2-fold, even when women with preeclampsia and eclampsia were excluded. Plasma volume expansion and lowered hemoglobin concentration are normal physiologic responses to pregnancy. Plasma volume expansion appears to be important for fetal growth and failure of sufficient hemodilution is associated with an increased risk of stillbirth, even if the fetus is not growth restricted. Stephansson et al suggest that those patients with high initial hemoglobin concentrations should be considered at high risk for adverse obstetric outcomes.

Amniotic and serum markers

Pregnancy-associated plasma protein A (PAPP-A) is a maternal serum marker used in combination with other tests to detect an increased risk of chromosomal abnormalities; it also appears to be of help in detecting, in the second trimester, pregnancies that might be at an increased risk for an adverse outcome. Smith et al assessed adverse perinatal outcomes among the 8839 patients recruited into a multicenter study. Patients with serum markers in the lowest fifth percentile were found to have an increased risk of premature delivery (OR = 2.9, 95% CI 1.6-5.5), preeclampsia (OR = 2.3, 95% CI 1.6-3.3), and stillbirth (OR = 3.6, 95% CI 1.2-11.0). In growth-restricted fetuses, the maternal serum alpha-fetoprotein was not particularly helpful in identifying pregnancies that would later go on to an adverse perinatal outcome, but a combination of factors, an elevated HCG and a low unconjugated estriol, was 67% sensitive and 70% specific in predicting a composite “adverse perinatal outcome” metric, which included perinatal death and neonatal morbidity.

Amniotic fluid abnormalities also have been found to be associated with fetal demise. Florio et al performed a case control study of women undergoing amniocentesis for routine reasons, in which 12 patients with a stillbirth all had elevated levels of S100B (a marker of brain damage in both adult and pediatric patients, but which is not specific for cerebral damage), but the 746 healthy controls did not. At least in this dataset, this test was perfect in predicting fetal death, a very rare finding in medicine, although these data will need to be replicated. The mechanisms linking most abnormal maternal serum and amniotic markers with adverse fetal outcomes are not known, but further study is required before recommendations for specific clinical applications can be considered.

Prevention strategies

The data available for cost-effective stillbirth prevention are limited. The remaining aspect of this review represents the author’s opinion based on the limited data available. In the absence of a prior obstetric history, the patient’s risk for stillbirth is related to her underlying health and lifestyle. Globally, one of the largest modifiable risk factors is smoking, as it is obviously tied to the pathophysiology of many diseases. Additional medical risk factors, as discussed previously, significantly impact both maternal and child health as well, and appropriate medical care for these conditions and preconception counseling can have a significant impact.
on outcome. The provider should perform a risk assessment for each individual patient and give realistic estimates of anticipated obstetric outcomes. Screening for hypertension and diabetes is essential to prevent poor pregnancy outcomes, but a number of other factors should be included in any risk assessment, including advanced maternal age, prepregnancy obesity, infertility, low educational attainment as a marker of lower socioeconomic status, and black race. Although the black race may be a proxy for socioeconomic factors, it is helpful to remember that black women 35 years or older have a risk of stillbirth 4 to 5 times higher than the national average and therefore deserve the same vigilance afforded to other groups at high risk for stillbirth.

A moderate proportion of stillbirths related to congenital anomalies could be reduced with preconceptual counseling and testing, adequate prenatal care, and prenatal diagnostic testing, with elective terminations for affected pregnancies. During pregnancy, patients with medical conditions need to be closely monitored to optimize their treatment and fitness for pregnancy and ensure fetal well-being.

In terms of reducing potentially preventable stillbirths, the Confidential Inquiry into Stillbirths and Infant Death (CISID) of Northern Ireland found that the failure to adequately diagnose and manage fetal growth restriction was the most common error, followed by failure to recognize additional maternal medical risk factors. Given that deaths of intrauterine growth-restricted fetuses represent 1 of the most common types of stillbirths, a significant opportunity remains to improve outcomes. Assessment of fetal growth by ultrasound should be considered in at-risk patients. A customized growth chart more readily identifies the growth-restricted fetus, and reduces "false alarms" in the constitutionally small fetus. Ideally, serial ultrasound reports should be reported together so that the history of intrauterine growth over time can be more readily appreciated. The threshold to perform an ultrasound in the obese patient should be low because fetal growth is often difficult to estimate clinically.

In women who have had a previous pregnancy, a previous preterm delivery, previous obstetric complication, delivery of a growth-restricted fetus, or a stillborn fetus, these events significantly increase their risk for adverse events in future pregnancies. There is some evidence, for example, that a previous cesarean section at term might reduce placental function and therefore increase the risk of a late antepartum unexplained stillbirth. Nevertheless, this association should be confirmed by other groups before it is considered an important risk factor.

Given all of the potential factors that influence the risk of stillbirth, it would be helpful to have an interactive model that would estimate the risk of a fetal demise in a manner similar to that used by physicians who care for patients with cardiovascular risk factors, who have a wealth of information to estimate the risk of myocardial infarction and death. A risk analysis should guide management policies and provide an evidenced-based approach to alter the threshold at which antepartum testing and early delivery is considered. Until such evidence-based guidelines exist, the obstetric care provider must decide on the appropriate type of vigilance, and decide when expectant care increases the risk to the ongoing pregnancy to a degree that warrants intervention for delivery.

Fortunately, for the majority of obstetric patients who are low risk, the incidence of a late stillbirth is a relatively low (1-2/1000). Still, there is a role for vigilance in these pregnancies. In a reanalysis of the results of a fetal movement counting study initially published by Grant et al, Froen has appropriately reigned the interest in fetal kick counting. Even low-risk pregnancies with decreased fetal movement are known to have a higher risk of fetal distress in labor, for being growth restricted, and for having an increased frequency of stillbirth.

The risk of stillbirth in late pregnancies has been appreciated by many authors, as discussed previously. Antepartum surveillance with judicious delivery of fetuses with poor fetal testing has been shown to improve outcomes in pregnancies with growth-restricted fetuses. Antepartum testing is also widely used in patients perceived to be at increased risk for fetal death, with the use of the testing related to the underlying risk of stillbirth. Antepartum testing was also widely used in women who have had a previous pregnancy, a previous preterm delivery, previous obstetric complication, delivery of a growth-restricted fetus, or a stillborn fetus, these events significantly increase their risk for adverse events in future pregnancies.

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marginally. In the initial study by Fretts et al on the risks and benefits of antepartum testing late in pregnancy for older women, they constructed a sensitivity analysis that applies to any condition associated with an increased risk of late stillbirth. Three strategies were compared: no testing, testing after the 36th week with induction for a positive test, and no testing with induction at 41 weeks. The number of fetal deaths averted and the number of tests, inductions, and additional cesarean deliveries per fetal death averted were calculated assuming antepartum testing to be 70% sensitive and 90% specific. The results for OR 1.0 to 5.0 are presented in Table III.

Although a strategy of antepartum testing is predicted to be most successful in reducing the number of unexplained stillbirths, it was also associated with the highest induction rate. For nulliparous women of advanced maternal age, predicted to have an OR of 3.3 over younger women, the number of additional cesarean deliveries performed for unsuccessful inductions was only 14 per fetal death averted. The model also estimated that it would take approximately 863 antepartum tests and 71 additional inductions to prevent 1 unexplained fetal death. The diagnosis has been associated with an increased risk of anxiety years after the loss, when compared with women whose labors were induced within 6 hours. The expectant management of a stillbirth therefore should be discouraged, in addition to the fact that delayed delivery is also associated with increased maternal risks of consumptive coagulopathy. The availability of prostaglandins, in particular misoprostol, has made induction of stillbirth safer and more efficient in women without a previous cesarean delivery. For now, oxytocin will remain the main method of induction for women with a previous cesarean delivery.

After delivery, the parents and other family members should have the opportunity to spend as much time as needed with the deceased infant. Even in the scenario of obvious maceration of the infant, after initial anxiety, parents often find something to connect them to the infant. A recent study has questioned whether holding a stillborn child might increase the risk of later anxiety, this finding has not been duplicated to date.

Management of stillbirth

The diagnosis of a singleton stillbirth must be confirmed with an ultrasound examination of the fetal heart. Most hospitals have instituted a program to help bereaved parents cope with their loss and follow good practice guidelines, which include the opportunity to see and hold their infant and obtain tokens of remembrance. A worksheet for both parents and providers help to streamline the management of these losses and can facilitate the optimal investigation for determining the cause of death. Delayed delivery after 24 hours of the diagnosis has been associated with an increased risk of anxiety years after the loss, when compared with women whose labors were induced within 6 hours. The expectant management of a stillbirth therefore should be discouraged, in addition to the fact that delayed delivery is also associated with increased maternal risks of consumptive coagulopathy. The availability of prostaglandins, in particular misoprostol, has made induction of stillbirth safer and more efficient in women without a previous cesarean delivery. For now, oxytocin will remain the main method of induction for women with a previous cesarean delivery.

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One important aspect of a woman’s care after a stillbirth is an appropriate and comprehensive stillbirth assessment. It is unfortunate that the United States has 1 of the lowest rates of obtaining a comprehensive stillbirth assessment when compared with other developed countries. This may be in part due to an increased level of anxiety over litigation in the United States, but it may also reflect the absence of a nationally coordinated program to evaluate these deaths. Notwithstanding, there are centers within the United States that can serve as role models for a comprehensive approach to stillbirth such those at the University of Southern California and the Wisconsin Stillbirth Service Program. Incerti et al have demonstrated that, within the context of developing a cost-effective stillbirth assessment program, the single most important test to determine the cause of a stillbirth is the autopsy, followed by an evaluation of the placenta. For some parents, a limited fetal evaluation will be more acceptable than a complete autopsy, and this option should be explored if a complete autopsy is not acceptable. An external

<table>
<thead>
<tr>
<th>Table III</th>
<th>Unexplained stillbirth risks and outcomes of weekly antepartum testing initiated at the 37th week of gestation</th>
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<tr>
<td>Outcome*</td>
<td>OR for unexplained stillbirth</td>
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<td>Fetal deaths per 1000 with antepartum testing</td>
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<td>Fetal deaths averted</td>
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<td>Tests per pregnancy</td>
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<tr>
<td>Inductions per fetal death averted</td>
<td>233</td>
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<tr>
<td>Cesarean deliveries per fetal death averted</td>
<td>44</td>
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* Outcomes from week 37 of gestation through week 41.
1 Unexplained fetal deaths averted per 1000 pregnancies compared to no testing.
physical examination and radiologic testing performed by the perinatal pathologist, with or without sampling fetal tissues in situ, can provide significant information. Although an autopsy is optimal, a postmortem magnetic resonance image (MRI) can provide useful additional information, although typically MRI staff are not used to receiving these requests. 117

A genetic analysis of chromosomes will reveal abnormalities in between 5% and 10% of stillbirths. 113 After a stillbirth, the highest yield for obtaining fluid for cytogenetic analysis will be at the time of amniocentesis at the time of the diagnosis of the stillbirth, but this has not been the usual practice at most centers of care within the United States. If amniotic fluid is unavailable, a sample of fetal blood, skin, or fascia lata will be best sources of tissue for culture. The use of a cytogenetic evaluation decreases with the duration of time that the infant has been dead, so reserving placental tissue for fluorescence in situ hybridization (FISH) in a buffered saline solution is an alternative method of determining whether the infant had a common chromosomal abnormality. 118,119

With the use of a protocol of autopsy, evaluation of the cord/placenta and membranes, and laboratory tests of fasting glucose, a Kleihauer-Betke test, urine toxicology and hemoglobin A1c in selected cases, and a thrombophilia workup in normally formed infants, Incerti et al 113 were able to attribute a primary cause of death in 72% of cases of stillbirth, leaving only 28% as “unexplained.” Notably absent in their protocol was the recommendation of obtaining TORCH titers, (i.e., cytomegalovirus, toxoplasmosis, herpes simplex virus, and rubella) because these titers, in and of themselves, almost never aid in the diagnosis of a congenital infection in the absence of autopsy and placental findings of infection. Incerti et al 110 found no significant association between antinuclear antibodies and stillbirth in the evaluation of 286 unexplained stillbirths. Parvovirus 19 is most commonly associated with a fetal death in the setting of nonimmune hydrops, but parvovirus 19 DNA can also be found in the placenta and fetus even in the nonhydropic infant. 121,122

The value of a comprehensive stillbirth assessment cannot be underestimated, because the results are relevant to assess the risk of recurrence, the development of prenatal diagnostic recommendations for subsequent pregnancies. Pauli’s group at the Wisconsin Stillbirth Service, a model state-wide program for the prevention of stillbirth, estimated that in 2001, the real cost of a stillbirth assessment was approximately $1450 US or approximately $12 per cared-for pregnancy, and influenced subsequent perinatal care in 51% of cases. 112 After studying 1631 stillbirths, the most significant consequence of this analysis was the change in the risk estimate of recurrence or stillbirth in 42% of cases. Other consequences were a change in the recommendations with respect to prenatal diagnosis in 22.2% and preconceptual management in 10.9% of subsequent pregnancies.

Summary

Clinicians need to be able to assess each patient’s risk for adverse outcomes, including stillbirth, and to have a low threshold to evaluate fetal growth in at-risk pregnancies. As reviewed previously, late pregnancy is also associated with progressively increasing risk of stillbirth, and although the strategy of antepartum testing in patients with increased risk will decrease the risk of late fetal loss, it is of necessity also associated with higher intervention rates.

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The direct cost of stress urinary incontinence among women in a Medicaid population

Kraig S. Kinchen, MD, MSc, a,* Stacey Long, MS, b Stella Chang, MPH, b Tammy K. Girts, PharmD, MS, c Barbara Pantos, RN, MS a

Outcomes Research, Eli Lilly and Company, Indianapolis, IN; a Medstat, Inc, Hampden, ME, and Washington, DC; Health Economics, Boehringer Ingelheim, Ridgefield, CT

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Objective: To describe health care utilization and costs for women diagnosed with stress urinary incontinence in a Medicaid population.

Study design: We utilized a pooled database of claims for women enrolled in Medicaid in 1 of 3 states. Health care utilization and costs were compared for 12 months before and 12 months after a woman’s urinary incontinence diagnosis. Additional analyses utilized data from a fourth state.

Results: Of 13,672 women with diagnosed stress urinary incontinence, average urinary incontinence–related costs were approximately $800 in the 12-month study period, less than 0.1% of total Medicaid spending. Thirteen percent of women underwent a surgery for stress urinary incontinence in the study period, with sling procedures performed most commonly.

Conclusion: Although population prevalence estimates of any stress urinary incontinence symptoms often are high, diagnosis and health care utilization in the Medicaid population is low. Overall costs of stress urinary incontinence treatment in Medicaid currently are minimal. Further efforts to understand the appropriate detection, diagnosis, and treatment of women with stress urinary incontinence are needed.

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Urinary incontinence (UI) is experienced disproportionately by women and can have a substantial impact on the lives of women with significant symptoms.1-3 For women who are burdened by incontinence symptoms, UI may have an impact on their lives through avoidance and limitation of activities and social interaction.4 For example, among middle-aged women with significant incontinence symptoms, incontinence was cited as 1 reason for not participating in physical activities such as sports.5 Additionally, UI may affect women negatively in the workplace through restriction of activities and the necessity of adopting a variety of coping behaviors.6,7

Although estimates of the prevalence of any incontinence symptoms among women may be high, most women with incontinence have never talked with a physician about their symptoms.8 For those women with bothersome symptoms who do seek care, health...
care utilization and resultant direct medical costs depend on the type of incontinence symptoms that a woman experiences. Urge incontinence, the involuntary leakage of urine preceded or accompanied by urgency, is managed mainly with behavioral approaches such as bladder retraining or prompted voiding and anticholinergic medications. On the other hand, stress incontinence, the involuntary leakage of urine with effort, physical exertion, coughing, and sneezing, is treated primarily with conservative therapy, such as pelvic floor muscle training, devices such as pessaries and/or surgical interventions. Older adults may adopt self-care practices including changes to their environment or alterations in their behavior to deal with incontinence.

In a recent analysis of incontinence studies, stress symptoms were the most common type of incontinence symptoms among women (49% stress symptoms only, 22% urge symptoms only, 29% stress and urge symptoms). In light of the high prevalence of stress incontinence, we examined health care utilization among women with a diagnosis of stress urinary incontinence (SUI). Although UI often is perceived as a natural part of the aging process, women with SUI may be affected throughout adulthood. The prevalence of stress symptoms peaks among women in their 40s. Although two previous studies of SUI health care utilization and costs have focused primarily on commercially insured populations, the present study focuses on women enrolled in Medicaid. As with some other medical conditions, it is possible that utilization patterns of women in need of health care for SUI may be affected by insurance status. Given the predominantly female population served by Medicaid, it is important to address SUI-related utilization and associated costs in this population. Furthermore, focus on incontinence among Medicaid recipients is important to examine in light of the disproportionate burden states must bear related to nursing home care and hospitalization, which may follow a diagnosis of incontinence.

Understanding such utilization patterns and costs is important to clinicians caring for women with Medicaid as well as to health care administrators, particularly because state Medicaid agencies continue to face the challenge of providing access to health care while under increasing budgetary constraints.

Material and methods

Data source

This retrospective analysis utilized data derived from a multistate Medicaid claims database (MarketScan Medicaid, Medstat, Inc.). The database contains the inpatient, outpatient, outpatient prescription drug, and long-term care claims of approximately 8 million Medicaid recipients covered under both fee-for-service and capitated health plans. No personally identifiable information is available in the database (ie, names, social security numbers, medical record numbers, addresses, birth dates); however, persons can be tracked longitudinally using encrypted identification numbers. Medstat’s contracts with the state Medicaid agencies that provide these data for research purposes preclude release of the states’ identities.

The core analysis for this study relied on claims for services incurred from January 1, 1999, through December 31, 2002, in 3 states; additional analyses incorporated data from 1 additional state during the year 2002. Data for prior years from the fourth state were not available to incorporate into the core analyses. The 2002 data were used to provide a snapshot of the budgetary impact of UI-related service use for Medicaid agencies during that year among 4 states.

Study population criteria

Although the present analysis focused on women with a diagnosis of SUI, we first identified an overall study population consisting of females with at least 1 claim containing a primary or secondary diagnosis consistent with stress UI (International Classification of Diseases, version 9 [ICD-9] 625.6 or 599.82 or 599.81) or mixed UI (ICD-9 788.33) or urge UI (ICD-9 788.31) or UI not otherwise specified (UI NOS; ICD-9 788.30) between January 1, 2000, and December 31, 2001.

Women were required to have a 12-month “clean” period free of any stress, urge, mixed, or other UI diagnoses prior to the initially observed claim with a UI diagnosis and at least 12 months’ follow-up data after the initial UI diagnosis. We refer to the 12-month clean period as the preperiod, the 12-month follow-up period as the study period, and the date of the initial UI diagnosis meeting these criteria as the index date.

Patients were classified in 1 of 4 cohorts for the analysis: stress, urge, mixed, or UI not otherwise specified (NOS). The classification was based on the type of UI diagnosed on the index date. Patients with both a stress and urge diagnosis on the index date were classified as mixed. A considerable proportion of patients were first diagnosed with UI NOS and subsequently received a diagnosis of stress, urge, or mixed UI. We theorized that a primary care physician might have assigned this diagnosis before referral to a specialist who diagnosed the specific type of UI, although we were unable to confirm this assumption. Patients with UI NOS on the index date but having a subsequent diagnosis of stress, urge, or mixed diagnosis prior to any UI-related surgery were reclassified according to the more specific subsequent diagnosis; the index date, however, was left intact. For example, we categorized women in our analysis as women with diagnosed stress incontinence if they had both a stress incontinence diagnosis and a UI NOS diagnosis.
We primarily were interested in the treatment and utilization patterns of women diagnosed with stress incontinence. Because the treatment strategies differ for different types of urinary incontinence, we believed it important not to combine all forms of incontinence together in this analysis. The alternative strategy of reporting separate results on analyses of each type of UI would be too much information for the scope of 1 paper.

Outcome measures and covariates

The primary objective of this retrospective claims-based analysis was to assess the overall and UI-specific annual healthcare resource utilization and costs among newly diagnosed SUI patients. We compared utilization and costs in the years before and after the initial UI diagnosis. Annual utilization was summarized for each patient in the preperiod and study period and categorized by the type of service: inpatient, emergency department, outpatient services, and outpatient pharmaceutical prescriptions. To the extent possible, outpatient services were further identified as being delivered by a specialist. The associated costs for these service categories, as well as total costs, were computed. Expenditures documented in the database included the total gross payment to a provider for specific services before application of deductibles, copayments, and coordination of benefits but after applying pricing guidelines such as fee schedules and discounts. Expenditures for services delivered in 1999 through 2001 were inflated to 2002 equivalents using changes in the medical component of the consumer price index between these years and 2002. UI-related health care costs refer to claims for which UI (stress, urge, mixed, UI NOS) is a primary diagnosis.

Rates of incontinence-related surgical interventions (Appendix) and complications within 30 days of the surgeries were investigated. Complications included bleeding (hemorrhage, hematoma, acute anemia, transfusion), surgical injury to the bladder or urethra, genitourinary complications, infection (sepsis, urinary tract infection, postoperative fever, genital infection), wound complications (seroma, dehiscence, wound infection), pulmonary complications (acute respiratory distress syndrome or pneumonia), cardiovascular complications (pulmonary embolism, congestive heart failure, myocardial infarction, postoperative thromboembolic disease), cerebrovascular complications, and anesthetic complications. Among women who had a surgery for incontinence, the proportion that also had a surgical procedure for prolapse was examined.

Women were considered to have had an additional procedure for prolapse if they had a diagnosis for prolapse and had a prolapse procedure (Appendix) coded in the claims database within 30 days of an incontinence procedure. UI-related pharmaceutical utilization also was assessed and included anticholinergic medications (eg, oxybutynin, oxybutynin XL, tolterodine, hyoscyamine, flavoxate, propanthaline, dicyclomine) as well as imipramine and estrogens (if estrogen or imipramine was newly initiated after the initial UI diagnosis and filled within 30 days of a UI-related medical service).

Other clinical characteristics assessed in the study population included comorbidities, including hypertension; irritable bowel syndrome; cancer; diabetes; and depression. Indicator variables for the presence of other comorbid urinary diagnoses in the preperiod or study period claims history also were created, including patients with diagnoses for functional bladder disorders (596.5x), urethral instability (599.83), genital prolapse (618.xx), urinary frequency (788.41), bladder disorders not elsewhere classified (596.8) or not otherwise specified (596.9), and other UI (788.39). To assess the impact of these comorbid urinary-related conditions on study results, a sensitivity analysis was conducted in which results for women with no comorbid urinary diagnoses were compared with the cohort of women in which comorbid conditions were allowed to be present. Demographic variables available for the study population include age, race, state (blinded), plan type, reason for Medicaid eligibility, and dual Medicare eligibility.

Statistical analysis

Descriptive data on demographics, comorbidity, treatment, and summary level utilization and costs were stratified by surgical and pharmaceutical interventions. To assess statistical differences between cohorts, non-parametric Wilcoxon rank sum tests were used for utilization and expenditure statistics because of the nonnormal distribution of these types of data. Wilcoxon signed rank sum tests were used to compare paired preperiod and postperiod utilization and costs within each cohort. \( \chi^2 \) tests were used to determine whether differences in proportions varied across groups.

Descriptive analyses revealed differences in demographic and health care resource utilization by type of UI among patients receiving surgical treatment for UI and patients with comorbid UI-related conditions. To quantify differences in costs between these groups, adjusting for potentially confounding factors, we estimated a series of multivariate models to determine the mean regression adjusted annual total costs for UI patients based on type of UI and surgical and comorbidity status. Additionally, UI-related costs also were predicted. Separate models were estimated for the full UI population and the subset with stress UI. All multivariate analyses were conducted using models with fixed variables based on a priori hypotheses. Specifically, dependent variables in the model are total costs and total UI-related costs. Covariates in the model included age (years), state (A, B, or C), race, Charlson Comorbidity Index score in the preperiod, any use of
long-term care services in the preperiod, presence of specific comorbidities, and use of UI-related pharmaceuticals. Specific comorbidities included irritable bowel syndrome, cancer, hypertension, depression, and common UI-related conditions (urinary tract infection, genital prolapse, functional bladder disorder, and urinary frequency). The models were also estimated among the cohort of women with SUI but no comorbid UI-related illness. These models included the indicator variables for UI-related comorbidities (with the exception of urinary tract infections).

Ordinary least squares (OLS) models with log transformation, exponential conditional mean (ECM) models, and 2-part models were considered for the functional form of the multivariate models. Because patients had zero total costs in the 12 months following UI diagnosis, 2-part models and OLS models with log transformation are indistinguishable. To examine the appropriateness of OLS versus ECM, the data were assessed for homoscedasticity and kurtosis. On confirmation that the log scale residuals were both heteroscedastic and heavily tailed, the performance of ECM and OLS with heteroscedastic retransformation was examined using Schwartz criterion and Akaike information criterion. Both tests favored ECM over OLS with log transformation. ECM regression is a generalized linear model with a log link function; its use avoids many of the pitfalls of retransformation. The model produced parameter estimates similar to those found in an OLS regression model; however, because the exponential model is nonlinear, the estimated regression coefficients do not equal the marginal or incremental effect of a 1-unit change in the covariate of interest on the conditional mean. Parameter estimates from the models were used to compute marginal effects for each of the covariates in the models.

To assess the impact of UI on Medicaid agencies annually, we examined 2002 data for 4 state Medicaid agencies. For each state, the proportion of female recipients with a diagnosis of UI during the year as well as the proportion of the state's budget spent on UI-related services (primary diagnosis of UI) was quantified.

Descriptive analyses were conducted using SAS (version 8.0, Cary, NC), and multivariate analyses were conducted using STATA software (version 7, College Station, TX).

**Results**

A total of 48,160 women had claims consistent with a diagnosis of UI. Of these, 28.4% had an initial diagnosis of stress incontinence (N = 13,672), 6% urge incontinence (N = 2890), and 5% mixed incontinence (N = 2484). Another 60.4% had only a general UI diagnosis (UI NOS, N = 29,114) for which the specific type of incontinence was not provided. In Table I, we provide information on characteristics of women with an initial SUI diagnosis. In terms of insurance status, approximately one third of women with SUI also were dually eligible for Medicare. Forty percent of women with SUI also had a more general UI diagnosis at some point in the study period. Thirteen percent had a diagnosis of depression in the study period. Almost one quarter had diabetes and 43% had hypertension. Between 48% and 56% of women in each of the 4 states were under the age of 40 years (data not shown).

Table II presents pharmacotherapy utilization for the SUI population that may have been related to treatment of UI symptoms (although none of these medications are indicated for the treatment of SUI). Approximately 20% received an anticholinergic medication in the preperiod, and 33% in the study period. When we excluded patients with any other UI-related comorbidities, for which anticholinergic use might have been indicated, use was only slightly lower (17% in the preperiod and 29% in the study period).

Among patients with an SUI diagnosis, 1791 (13.1%) underwent surgery for SUI in the study period (Table III). Sling procedures were the most commonly performed surgery. Among surgical patients, 141 (7.9%) had a claim for a prolapse procedure coded within 30 days of the surgery for incontinence. Coded complications were relatively infrequent (1% bleeding complications; 2% infections, <1% genitourinary complications, <2%

<table>
<thead>
<tr>
<th>Table I</th>
<th>Characteristics of Women with a Diagnosis of SUI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean, N</td>
</tr>
<tr>
<td>Age, yr</td>
<td>56.1</td>
</tr>
<tr>
<td>Medicare eligible</td>
<td>4929</td>
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<tr>
<td>Insurance plan type</td>
<td></td>
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<td>Fee for service</td>
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<tr>
<td>Managed care</td>
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<tr>
<td>Missing</td>
<td>203</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<tr>
<td>White</td>
<td>6883</td>
</tr>
<tr>
<td>African American</td>
<td>1241</td>
</tr>
<tr>
<td>Native American</td>
<td>39</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
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<tr>
<td>Asian/Pacific Islander</td>
<td>945</td>
</tr>
<tr>
<td>Unknown/missing</td>
<td>3189</td>
</tr>
<tr>
<td>Other diagnoses in study period</td>
<td></td>
</tr>
<tr>
<td>Urge UI</td>
<td>442</td>
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<tr>
<td>Mixed UI</td>
<td>480</td>
</tr>
<tr>
<td>UI NOS</td>
<td>5565</td>
</tr>
<tr>
<td>Functional disorders of the bladder</td>
<td>714</td>
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<tr>
<td>Bladder disorder NEC</td>
<td>206</td>
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<tr>
<td>Bladder Disorder NOS</td>
<td>69</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3769</td>
</tr>
<tr>
<td>Genital prolapse</td>
<td>2679</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>621</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5817</td>
</tr>
<tr>
<td>Depression</td>
<td>1888</td>
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<tr>
<td>Diabetes</td>
<td>3161</td>
</tr>
</tbody>
</table>

NEC, Not elsewhere classified.
wound complications, 0.1% pulmonary embolism). An additional 315 patients had a code for an incontinence-related surgery, but no UI-related diagnosis was coded on the claim. If we include these patients, approximately 15% of all patients with an SUI diagnosis potentially had surgery in the study period.

In Table IV, we present utilization and costs for SUI patients with and without a UI-related surgery in the study period. For each type of incontinence, we present all utilization as well as the subset of utilization for which incontinence was listed as the primary diagnosis. Overall, when comparing the 1-year period before the incontinence diagnosis to the 1-year period after the diagnosis, total health care costs increased 53%, from $8423 in the preperiod to $12,878 in the study period (P < .001) for those with a surgery in the study period. By comparison, for those without a surgery, average costs increased 3%, from $11,211 to $11,561 (P < .001). Regarding UI-specific costs in the study period, the mean costs for the surgical group was $3258, compared with $424 (P < .001) for the nonsurgical group.

We conducted multivariate analysis to determine adjusted overall and UI-specific costs for women with SUI (Figure). Women with any type of UI were included for comparison. Increasing age, white race (compared with other races), higher Charlson Comorbidity Index scores, preperiod functional bladder disorder, preperiod hypertension and depression, and long-term care utilization in the preperiod were associated with higher overall costs in the SUI population (all, P < .001). Increasing age, white race, UI-related comorbidities in the preperiod (specifically UTI and prolapse), and UI-related medication use in the preperiod were associated with higher UI-related costs (all, P < .05). There also was variation, albeit inconsistent, in overall and SUI costs because of geographic location (state). After adjusting for confounding characteristics, those with a surgical procedure in the study period had greater overall and UI-specific costs than those without surgical procedures.

For the 4 states included in the analysis of 2002 Medicaid costs, approximately 1% or less of the female population had a diagnosis of SUI during the year. The percentage of total Medicaid spending accounted for by all health care utilization for these patients was less than 1% for 3 states and 3% for 1 state. Total proportion of Medicaid spending for care delivered to SUI patients was disproportionately higher than the proportion of patients with the condition (approximately 2 times). Average total spending accounted for by UI-related care for the SUI patients was less than 0.1% of total Medicaid spending.

The analysis focused only on women with a coded SUI diagnosis, although some of these women with SUI may also have had a UI NOS diagnosis during the study period. With our primary focus on stress incontinence, we did not include in our main analyses women who had a UI NOS diagnosis but who never had a diagnosis of SUI in the study period. We recognize that a large proportion of women with a UI diagnosis had a non-specific UI NOS diagnosis without being given a diagnosis of a specific type of UI in the study period. To address the possibility that we may have underestimated SUI utilization by not including these women, we performed sensitivity analyses and reviewed their utilization. Only 83 (0.29%) of women with only a UI NOS diagnosis underwent surgery for UI. A total of 20% had anticholinergic use in the study period.

Average preperiod and study period total costs were $14,690 and $15,359, whereas average study period UI-related costs were $368.93. Of note, when compared with the women with a coded SUI diagnosis, a greater proportion of patients with a UI NOS diagnosis were under age 40 years (33% of UI NOS patients versus

---

**Table II**  Incontinence-related pharmaceutical use (N = 13,672)

<table>
<thead>
<tr>
<th></th>
<th>Preperiod</th>
<th></th>
<th>Study period</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>1051</td>
<td>7.7</td>
<td>1463</td>
<td>10.7</td>
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<tr>
<td>Oxybutynin XL</td>
<td>551</td>
<td>4.0</td>
<td>1269</td>
<td>9.3</td>
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<tr>
<td>Tolterodine</td>
<td>1118</td>
<td>8.2</td>
<td>2072</td>
<td>15.2</td>
</tr>
<tr>
<td>Anticholinergic, other</td>
<td>429</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>35</td>
<td>0.3</td>
<td>429</td>
<td>3.1</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>165</td>
<td>1.2</td>
<td>35</td>
<td>0.3</td>
</tr>
<tr>
<td>Hyoscyamine</td>
<td>39</td>
<td>0.3</td>
<td>165</td>
<td>1.2</td>
</tr>
<tr>
<td>Propantheline</td>
<td></td>
<td></td>
<td>39</td>
<td>0.3</td>
</tr>
<tr>
<td>Any anticholinergic use</td>
<td>4484</td>
<td>32.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen*</td>
<td>1598</td>
<td>11.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine*</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
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* No prescription in the preperiod and at least 1 prescription within 30 days of a UI diagnosis.

**Table III**  Urinary incontinence-related surgery in the year following initial SUI diagnosis

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sling procedures</td>
<td>874</td>
<td>6.39</td>
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<tr>
<td>Retropubic suspensions</td>
<td>496</td>
<td>3.63</td>
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<tr>
<td>Needle procedures/transvaginal suspensions</td>
<td>152</td>
<td>1.11</td>
</tr>
<tr>
<td>Anterior repair</td>
<td>567</td>
<td>4.15</td>
</tr>
<tr>
<td>Collagen implant</td>
<td>148</td>
<td>1.08</td>
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<tr>
<td>Retropubic/transvaginal suspensions Overlap</td>
<td>28</td>
<td>0.20</td>
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<tr>
<td>Other UI procedures</td>
<td>159</td>
<td>1.16</td>
</tr>
<tr>
<td>Other, laparoscopic</td>
<td>39</td>
<td>0.29</td>
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</table>

* No prescription in the preperiod and at least 1 prescription within 30 days of a UI diagnosis.
16% of SUI patients), and a greater percentage of these women were age 70 years and older (33% of UI NOS patients versus 23% of SUI patients).

**Comment**

We examined utilization and costs for UI treatment among women with a coded diagnosis of SUI in a Medicaid database, and we report several main findings. First, a relatively small portion of women had a new diagnosis of SUI in the 12-month study period. Second, among the women with Medicaid and a coded diagnosis of SUI, 13% of women underwent surgery for incontinence in the study period. Third, average total health care costs did not increase greatly between the 12 months before and the 12 months after the SUI diagnosis. Average UI-related costs for women with a coded diagnosis of SUI increased by an average of approximately $800, accounting for less than 0.1% of total Medicaid spending. Finally, almost one third of women with an SUI diagnosis (and without a coded diagnosis of a UI-related comorbidity) had a prescription for an anticholinergic medication in the study period, although these medications are not indicated for SUI treatment.

Among women with at least 2 years’ enrollment in Medicaid, only a very small percentage of women had a new diagnosis of UI in general or SUI in particular during the study period. This finding is not inconsistent with results for a larger female population. An analysis of year 2000 data from the National Ambulatory Medical Care Survey found that the number of physician outpatient visits for which UI was given as any reason for the visit was only 1845 per 100,000.21 Similarly, low levels of coded diagnoses and utilization have been noted in other claims-based studies of SUI.15,16

It is important to recognize that our results reflect only the findings from our study period. We do not know, for example, the overall prevalence of treatment seeking for SUI in this population because we have no information on treatment seeking by these women prior to the study period. Furthermore, because almost half of the women in our Medicaid sample are under the age of 40 years, our Medicaid sample does not represent the

<table>
<thead>
<tr>
<th>All diagnoses</th>
<th>Women without surgery (N = 11,881)</th>
<th>Women with surgery (N = 1791)</th>
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<tbody>
<tr>
<td></td>
<td>With any use, %</td>
<td>Mean expenditure, $ (SD)</td>
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<tr>
<td>Inpatient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preperiod</td>
<td>14.3</td>
<td>1088 (7073)</td>
</tr>
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<td>Study period</td>
<td>16.9</td>
<td>1179 (7424)</td>
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<tr>
<td>Long-term care</td>
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<td>Preperiod</td>
<td>2.5</td>
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<tr>
<td>Study period</td>
<td>3.5</td>
<td>748 (5415)</td>
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<tr>
<td>ER</td>
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<td>Preperiod</td>
<td>34.9</td>
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<td>77 (318)</td>
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<td>Preperiod</td>
<td>99.3</td>
<td>6385 (9829)</td>
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<td>Study period</td>
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<td>6423 (10419)</td>
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<td>Outpatient pharmaceutical</td>
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<td>3190 (3811)</td>
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<td>3134 (3722)</td>
</tr>
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<td>Total</td>
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<tr>
<td>Preperiod</td>
<td>11211 (15197)</td>
<td>6943</td>
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<tr>
<td>Study period</td>
<td>11561 (16252)</td>
<td>6844</td>
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<table>
<thead>
<tr>
<th>UI-related (primary diagnosis) in study period</th>
<th>Women without surgery (N = 11,881)</th>
<th>Women with surgery (N = 1791)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td></td>
<td></td>
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<tr>
<td>Preperiod</td>
<td>0.7</td>
<td>6 (140)</td>
</tr>
<tr>
<td>Study period</td>
<td>1.6</td>
<td>1 (7)</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
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<tr>
<td>Preperiod</td>
<td>98.8</td>
<td>351 (1331)</td>
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<tr>
<td>Anticholinergic prescriptions</td>
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<tr>
<td>Preperiod</td>
<td>18.7</td>
<td>32 (129)</td>
</tr>
<tr>
<td>Study period</td>
<td>31.4</td>
<td>66 (202)</td>
</tr>
<tr>
<td>Total study period</td>
<td>424 (1360)</td>
<td>135</td>
</tr>
</tbody>
</table>

*ER, Emergency room.*
burden of SUI in the general population, in which SUI peaks in women in their 40s.

From previous studies, we do know, however, that a large percentage of women with UI symptoms have never talked to a physician about incontinence and that a number of factors play a role in explaining treatment-seeking behavior.22 Nygaard and colleagues21 pointed out that although surveys may report incontinence prevalence rates of up to 50% of women, a review of surveys shows that approximately 7% to 10% have more frequent and more severe incontinence symptoms. Women with greater frequency and bother of symptoms, for example, are more likely to have ever sought treatment.22 However, Burgio and colleagues23 and others found that even among middle-age women with daily symptoms of incontinence, only 54% had ever talked with a physician. Thus, in addition to frequency and bother, the lack of treatment seeking must involve other factors, including the embarrassment of discussing incontinence with a physician and the perception that incontinence is a natural part of aging.22

Approximately 13% of women with a new, coded SUI diagnosis had a UI-related surgery in the study year. This compares with 28% of women with a new, coded SUI diagnosis in the MarketScan claims database study of patients with commercial health coverage.15 Although the designs of these 2 studies were similar, it is difficult to state conclusively that surgery is more or less likely to occur in a woman with an SUI diagnosis in Medicaid versus a woman in a commercial database without comparing estimates within the same study. We were also unable to determine conclusively whether women with incontinence symptoms in Medicaid are more or less likely than women with commercial insurance to receive a coded SUI diagnosis.

Considering the very small proportion of the Medicaid study sample with a new SUI diagnosis, the percentage of the women in the Medicaid population who underwent surgery for SUI is quite small. These figures are not unexpected in light of the relatively small number of surgeries performed for SUI yearly. On the basis of data from the National Hospital Discharge database, Waetjen et al24 determined that only 135,000 inpatient surgeries for SUI were performed in 1998. Overall, Diokno et al25 estimate that less than 5% of the U.S. community-dwelling female population report having undergone a surgery for UI.

In our sample, mean direct costs for UI-related care were only about $795, although the difference between surgical patients and nonsurgical patients was significant ($3258 versus $424, respectively, P < .001). In the study year, those patients who underwent surgery, on average, had a greater increase in UI-related costs. Differences in health care costs between surgical and nonsurgical patients also were seen in the studies using commercial claims databases.15,16

Finally, among women with a diagnosis of SUI, approximately one third filled at least 1 prescription for an anticholinergic medication in the study period. To our knowledge, there are no published studies demonstrating efficacy of anticholinergic treatment in a study sample of women determined to have SUI. In a claims-based study, it is not possible to determine the precise reasons that a medication was prescribed or whether the prescription was appropriate. Less specific anticholinergic medications (ie, dicyclomine), which accounted for only a small percent of all of the anticholinergic prescriptions, may have been used to treat a nonurologic condition. It also is possible that some of the anticholinergic prescribing was for concomitant urge or overactive bladder symptoms, although even after removing from the analysis women who had comorbid urinary diagnoses, approximately 29% of women still received an anticholinergic prescription. Even among women who underwent surgery for SUI, 42% received an anticholinergic prescription. Another possibility is that, given the lack of a prescription medication indicated for SUI treatment, physicians prescribed anticholinergics in hopes of achieving some clinical benefit. Similar figures were seen among commercially insured women.15

Although the use of Medicaid data from several states represents a strength of this study, there are a number of limitations. First, as with any claims-based analysis, these findings are limited by the well-known problems with claims-based research, including the likely incomplete nature of claims-based data, the lack of medical record data, and the possibility of coding errors. Second, this study represents the Medicaid experiences of only a small number of states, and this could have an impact on the generalizability of our results. Further work might examine this relationship in a larger number of states. It is important to recognize that the degree of overall health care coverage and urinary incontinence treatment coverage may vary by individual state Medicaid plans. Third, in the attempt to determine the costs associated with SUI
care, we focused only on women with a potentially new diagnosis. Analyzing data for women with multiple UI diagnoses over a period of years would provide a more complete picture of resource utilization among women with long-term incontinence symptoms. Fourth, the data set captures only women for whom a physician gave a diagnosis of SU. This likely biases the data set to include women for whom physicians were more likely to offer some form of intervention.

Additionally, by limiting our analysis to women with a coded diagnosis of SU, we potentially underestimate the number of women with stress symptoms who underwent treatment of incontinence because we did not include cost estimates for women with only a UI NOS diagnosis. Finally, utilization and costs were considered to be related to UI only if the claim had a primary diagnosis (not secondary) of urinary incontinence. Although this conservative approach helps to avoid the error of attributing costs to UI that may have been for other purposes, it may underestimate the costs that actually may have been due to UI care.

In conclusion, in this study of women enrolled in Medicaid, a small proportion of enrollees had a new diagnosis of SU specifically or UI overall during the study period. This is reflected in the consistently small proportion of Medicaid spending related to UI.

References


Appendix

Surgical procedures

<table>
<thead>
<tr>
<th>Urinary incontinence procedures</th>
<th>ICD-9</th>
<th>CPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure description</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sting procedures</strong></td>
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<td>57288</td>
</tr>
<tr>
<td><strong>Retropubic suspensions</strong></td>
<td>59.5</td>
<td>51840, 51841</td>
</tr>
<tr>
<td><strong>Needle procedures/ transvaginal Suspensions</strong></td>
<td>51845, 57289</td>
<td></td>
</tr>
<tr>
<td><strong>Anterior repair</strong></td>
<td>59.3</td>
<td>57220, 57240, 70.50</td>
</tr>
<tr>
<td><strong>Collagen implant</strong></td>
<td>59.72</td>
<td>51715</td>
</tr>
<tr>
<td><strong>Retropubic/transvaginal suspensions overlap</strong></td>
<td>58267</td>
<td></td>
</tr>
<tr>
<td><strong>Other procedures</strong></td>
<td>59.6, 59.71, 59.79</td>
<td>57284, 53445</td>
</tr>
<tr>
<td><strong>Other, laparoscopic</strong></td>
<td>51990, 51992</td>
<td></td>
</tr>
</tbody>
</table>

* The procedure must be accompanied by a primary UI diagnosis on the claim.
<table>
<thead>
<tr>
<th>Prolapse procedures</th>
<th>ICD9</th>
<th>CPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectocele</td>
<td>70.52</td>
<td>57250, 45560</td>
</tr>
<tr>
<td>Uterine suspension</td>
<td>69.22</td>
<td>58400, 58410</td>
</tr>
<tr>
<td>Vaginal suspension and fixation of the vagina</td>
<td>70.77</td>
<td>57280, 57282</td>
</tr>
<tr>
<td>Enterocele surgery and operations of cul-de-sac</td>
<td>70.92</td>
<td>57265, 57268, 57270</td>
</tr>
<tr>
<td>Cystocele and rectocele repair</td>
<td>70.50</td>
<td></td>
</tr>
<tr>
<td>Repair of cystocele only</td>
<td>70.51</td>
<td></td>
</tr>
<tr>
<td>Vaginectomy</td>
<td>70.4</td>
<td>57106, 57107, 57109, 57110, 57111, 57112</td>
</tr>
<tr>
<td>Obliteration of vaginal vault</td>
<td>70.8</td>
<td>57120</td>
</tr>
<tr>
<td>Vaginal hysterectomy</td>
<td>68.5</td>
<td>58260, 58262, 58263, 58270, 58275, 58280, 58290, 58291, 58292, 58293, 58294, 58550, 58552, 58553, 58554</td>
</tr>
<tr>
<td>Subtotal hysterectomy</td>
<td>68.3</td>
<td>58180</td>
</tr>
<tr>
<td>Total hysterectomy</td>
<td>68.4, 68.9</td>
<td>58150, 58200</td>
</tr>
</tbody>
</table>

* The procedure must be accompanied by a diagnosis of prolapse on the claim.
Analysis of knowledge and attitudes of adult groups before and after attending an educational presentation regarding adolescent sexual activity

Patricia J. Sulak, MD,* Sara Herbelin, MS, Alicia L. Kuehl, BS, Thomas J. Kuehl, PhD

Department of Obstetrics and Gynecology, Scott & White Memorial Hospital, Scott, Sherwood and Brindley Foundation, Texas A&M University System Health Science Center College of Medicine, Temple, TX

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KEY WORDS
Sex education
Adolescent sexual health
Teen pregnancy
Adolescents
Sexual activity

Objective: To assess changes in knowledge and attitudes of adult groups before and after attending an educational presentation on adolescent sexual health.

Study design: A diverse group of adults attended the presentations and completed a presurvey and postsurvey containing 10 knowledge questions, 3 opinion questions, and demographics.

Results: Survey forms were completed by 3661 participants before and 3605 participants after 62 educational programs during the 2002 to 2003 school year. Adult participants consisted of school employees, adults attending parent presentations, health care professionals, adults at community presentations, and teachers. Presurveys revealed a significant lack of information by all groups, with health care professionals answering 37.9% and other adults answering 30.2% correct. All groups demonstrated significant ($P = .0005$) improvements in knowledge and a shift in attitude, favoring the delay of sexual activity until at least after high school from 94% before the survey to 98% after the survey ($P < .0001$) and the delay until marriage from 77% to 91.5% ($P < .0001$).

Conclusion: Educating adults on the ramifications of adolescent sexual activity results in significant increases in knowledge and the proportion who think teens should delay sexual activity.

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Sexual activity among adolescents has gained national attention because of its multiple consequences including teen pregnancy, sexually transmitted diseases (STDs), and a huge socioeconomic burden. Unfortunately, adolescents and parents often have inaccurate information with regard to the ramifications of early onset of sexual activity among adolescents and the health risks of multiple sexual partners. Of the 4,021,726 births in the United States in 2002, 10.8% (432,808) were to teenage mothers, 80.2% of whom were not married. It is estimated that families started by teens aged 17 years or less result in costs of 29 billion dollars annually in the United States. Since its peak in 1991, the teen pregnancy rate has declined 30% to its lowest level in 2002.
Interestingly, the only 2 articles published to date in the medical literature analyzing the decline attribute the majority of the decreasing teen pregnancy rate to delaying the onset of sexual debut. Of the estimated 18,900,000 new cases of STDs that occur each year in the United States, approximately half occur in teens and young adults. According to the Centers for Disease Control and Prevention (CDC), this STD epidemic results in additional billions of dollars in evaluation, diagnostic tests, and treatment of the infection and its sequelae. In a 2004 American Journal of Obstetrics and Gynecology review, Genuis and Genuis assessed the current STD pandemic and its consequences, emphasizing delayed sexual debut, partner reduction, and the avoidance of risky sexual behaviors as essential factors in reducing this enormous health burden.

If delaying sexual debut is effective in decreasing teen pregnancy and STDs, then determining who influences sexual activity is crucial. Studies confirm the vital role of parents and other adults in adolescents’ decisions about sexual activity. Results from the Longitudinal Study on Adolescent Health published in JAMA report that parent’s disapproval of adolescents having sex is 1 of the most significant factors in teens delaying sexual activity. In another nationally representative survey of adolescents, conducted by the National Campaign to Prevent Teen Pregnancy, teens say their parents influence their decisions about sex more than friends, siblings, or the media. If adults are most influential in adolescent sexual behavior, programs that educate adults on the ramifications of early onset of sexual activity were developed for a diverse group of adult audiences.

To assist with adolescent sex education, Scott & White Memorial Hospital/Texas A&M Health Sciences Center College of Medicine initiated a sex education program that included not only a curriculum for middle school students (aged 10-14 years) but also seminars for teachers, parents, community organizations, and health care professionals (HCPs). After reviewing the published literature on the problems of adolescent sexual activity, a group of professionals including doctors, attorneys, and educators developed the program. Realizing the documented importance of adults in influencing sexual decisions of adolescents, programs detailing the ramifications of early onset of sexual activity were developed for a diverse group of adult audiences. Knowledge deficiencies by parents and other influential adults may lead to recommendations and guidance not favorable to optimal adolescent health. The aim of this study was to correlate adults’ knowledge concerning adolescent sexual activity and its outcomes with their attitudes regarding adolescent’s initiation of sex as well as what information should be given to adolescents by parents and HCPs. Because adolescents receive information from a variety of adult groups, our program was delivered to a diverse group including teachers, health care professionals, school personnel, parents, and community members. Correlation of knowledge base and attitudes were assessed prior to and after an educational intervention.

Material and methods

To assess knowledge base and opinions, adult groups attending Scott & White adolescent sexual health conferences and presentations during the academic year 2002-2003 primarily in the central Texas area were anonymously surveyed immediately prior to and after a presentation on adolescent sexual health. Although length of time and amount of material presented at the educational venues varied, all groups were postsurveyed after the initial presentation usually lasting 1 to 2 hours. All nonmedical adult groups received a presentation entitled “What Adults Need to Know About Teens and Sex,” whereas medical professionals received a presentation entitled “Adolescent Sexual Health: The Critical Role of Healthcare Professionals.” Information presented included current published medical data on ramifications of adolescent sexual activity including socioeconomic and legal issues. Educational programs were developed under the direction of a board-certified obstetrician-gynecologist and contraceptive researcher (P.J.S.) with program content from the CDC and National Institutes of Health publications/guidelines along with peer-reviewed medical journals. All presentations were given by HCPs (staff physicians, medical students, residents) who had previously attended a Scott & White adolescent sexual health training conference.

The survey included 10 knowledge questions concerning published information on adolescents specifically related to sexual activity. The survey also included 3 opinion questions concerning viewpoints on adolescent sexual activity and information adolescents should receive from parents and doctors. The forms contained the same knowledge and attitude questions, with wording appropriate for the group. Demographic information included age, race, parental status, gender, and marital status. This survey instrument was designed and tested during the prior academic year to establish the unified set of knowledge questions that tested the same factual information in all adult groups and common set of attitude questions and demographic variables.

The adults were divided into 6 distinct groups. Group I included parents attending an optional evening 2-hour presentation prior to implementation of the sex education curriculum in their child’s middle school. Group II was made up of all school employees including administrators; teachers; and ancillary school personnel including janitors, cafeteria workers, and bus drivers attending mandatory 2-hour district-wide presentations. Group III consisted of civic organizations and businesses familiar with the program requesting a presenta-
tion. Group IV was comprised of middle school teachers assigned to implement the curriculum attending a mandatory 2-day training conference. Group V was comprised of HCPs attending a variety of continuing medical education (CME) conferences for primary care providers in which 1 of the many topics included an approximately 60-minute presentation on “Adolescent Sexual Health: The Critical Role of Healthcare Professionals.” This presentation was given by a practicing obstetrician-gynecologist (P.J.S.) who is frequently asked to speak at medical conferences on women’s health issues. Group VI consisted of HCPs attending a 2-day Scott & White CME conference devoted entirely to adolescent sexual health issues. Groups V and VI were composed of primary care HCPs, primarily physicians (obstetrician-gynecologists, family medicine).

Identical, anonymous survey forms were distributed and collected immediately prior to and after the presentation and entered into data files via a scantron device. Comparisons were made between pretest and posttest knowledge scores and attitude questions and further grouped by various demographic characteristics including age, parental and marital status, and HCP.

Data were tabulated into spreadsheets and migrated to Statistica software (StatSoft, Tulsa, OK) for statistical comparisons. Comparisons were made, taking into account the repeated measures aspects of preprogram and postprogram testing and surveying. Proportions were calculated for scores on knowledge exams and for choices of individual attitude questions for each of the courses. These values were analyzed with analysis of variance using general linear methods for repeated measures with post hoc tests. Arcsin transformation was performed when needed to maintain homogenous variance terms for the proportional data.

For postsurvey attitude testing in relationship to parental status, $\chi^2$ methods were used. For all comparisons, a $p<0.05$ was taken as indicating significance. For a final analysis of factors related to attitude choices, multiple logistic regression was performed using dichotomous characteristics (married, parent, female, white non-Hispanic, and younger than 50 years of age) as independent variables and the dichotomous choices of 3 attitude questions. Maximum likelihood $\chi^2$ was used to assess the significance of each of these analysis models and results are reported as ORs with 95% CIs.

## Results

### Demographics

A total of 7266 survey forms were completed by 3661 participants before and 3605 participants after the 62 presentations to 6 distinct adult groups (Table I). The largest number of adult participants was school district employees (group II) at mandatory district-wide presentations, followed by adults attending voluntary parent presentations (group I). As seen in Table I, before-survey and after-survey completion by attendees did not differ ($P = .60$).

### Table I

<table>
<thead>
<tr>
<th>Group</th>
<th>Total number of adults</th>
<th>Number of sessions</th>
<th>Average number surveyed before</th>
<th>Average number surveyed after</th>
<th>Difference (before-after)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Parent groups</td>
<td>1082</td>
<td>26</td>
<td>42 (2 to 176)</td>
<td>39 (2 to 173)</td>
</tr>
<tr>
<td>II</td>
<td>School district employees</td>
<td>1495</td>
<td>9</td>
<td>166 (33 to 711)</td>
<td>172 (32 to 758)</td>
</tr>
<tr>
<td>III</td>
<td>Community groups</td>
<td>364</td>
<td>12</td>
<td>30 (7 to 51)</td>
<td>29 (7 to 46)</td>
</tr>
<tr>
<td>IV</td>
<td>Teacher training programs</td>
<td>214</td>
<td>5</td>
<td>43 (27 to 73)</td>
<td>43 (27 to 73)</td>
</tr>
<tr>
<td>V</td>
<td>HCPs attending CME conferences</td>
<td>393</td>
<td>7</td>
<td>56 (20 to 143)</td>
<td>52 (20 to 144)</td>
</tr>
<tr>
<td>VI</td>
<td>HCPs attending adolescent sexual health conferences</td>
<td>113</td>
<td>3</td>
<td>38 (29 to 47)</td>
<td>35 (32 to 39)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3661</td>
<td>62</td>
<td>3661</td>
<td>3605</td>
</tr>
</tbody>
</table>

Using ANOVA methods for repeated measures, group sizes differed ($P < .01$) among types of groups, whereas the change in the number of participants surveyed before and after each program did not differ ($P = .60$).
The composition of these groups varied with regard to gender, marital status, and parental status (Table II). Adults attending parent presentations (group I) were more likely to be female, married, and parents (P < .05), compared with middle school teachers (group IV) and HCPs attending CME conferences (group V). However, racial mix and age did not differ among the 6 groups.

Knowledge

As seen in Table III, the 506 HCPs (groups V and VI) had a pretest score of 37.9% and posttest score of 87.4% (P < .0001). The 10-item knowledge test was examined for reliability. The Cronbach alpha of 0.84 with low interitem correlation of 0.35 demonstrate that this component of the survey is reliable. The nonmedical adult audiences (groups I-IV) averaged 30.2% correct on the pretest and 75.8% on the posttest. The reliability (0.80 Cronbach alpha and 0.30 interitem correlation) of this modified instrument for lay adults is similar to that for HCPs.

Questions tested knowledge on STDs, teen pregnancy, and legal issues. Despite commonly published medical information and frequent well-publicized press releases, the majority of adults including those with health care backgrounds lacked correct information on important adolescent sexual health issues (Table III). For example, only 38.3% of HCPs (groups V and VI) and 24.1% of the other adult groups (groups I-IV) knew that the teenage pregnancy rate in the United States was decreasing consistently over the last 10 years (question 8) as documented by the National Center for Health Statistics. When asked for which STD had condoms been shown to greatly reduce transmission, only about 1 in 10 knew HIV was the correct answer (question 1), as stated by the National Institutes of Health workshop on condom effectiveness, documenting an estimated 85% reduction in transmission of HIV.

The majority of adults in all groups did not know that 1 in 5 people older than age 12 years in the United States are infected with genital herpes simplex virus type 2 (question 9) and that the majority of infected individuals are unaware they are infected (question 6). When asked what was the STD with the most new cases per year, 64% of HCPs answered human papillomavirus (HPV) correctly, compared with 48.8% of other adult groups (question 2). The majority of HCPs and other

Table II Composition (mean percent with SE) of adult groups and comparison between parent groups and others based on presurvey

<table>
<thead>
<tr>
<th>Groups</th>
<th>Female</th>
<th>Married</th>
<th>White, non-Hispanic</th>
<th>Nonparent</th>
<th>Under age 50 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Parent groups</td>
<td>81 ± 3</td>
<td>88 ± 2</td>
<td>80 ± 3</td>
<td>2 ± 2</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>II School district employees</td>
<td>79 ± 3</td>
<td>79 ± 3*</td>
<td>88 ± 6</td>
<td>20 ± 3*</td>
<td>82 ± 13</td>
</tr>
<tr>
<td>III Community groups</td>
<td>73 ± 4</td>
<td>80 ± 3*</td>
<td>73 ± 5</td>
<td>17 ± 3*</td>
<td>74 ± 4</td>
</tr>
<tr>
<td>IV Teacher training programs</td>
<td>63 ± 6*</td>
<td>73 ± 4*</td>
<td>80 ± 8</td>
<td>27 ± 5*</td>
<td>76 ± 6</td>
</tr>
<tr>
<td>V HCPs attending CME conferences</td>
<td>67 ± 5*</td>
<td>77 ± 4*</td>
<td>81 ± 6</td>
<td>30 ± 4*</td>
<td>80 ± 8</td>
</tr>
<tr>
<td>VI HCPs attending adolescent sexual health conferences</td>
<td>59 ± 8*</td>
<td>91 ± 5</td>
<td>84 ± 10</td>
<td>14 ± 6*</td>
<td>73 ± 5</td>
</tr>
</tbody>
</table>

* Groups that differed from parent groups in composition with P < .05 using Fishers least significant difference post hoc following analysis of variance for comparisons of arcsin transformations of percentages of group composition.

Table III Percent correct answers to the 10 knowledge questions

<table>
<thead>
<tr>
<th>Question topic</th>
<th>Healthcare professionals</th>
<th>Other adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Condoms and STD prevention</td>
<td>11.3±6.9</td>
<td>10.1±4.0</td>
</tr>
<tr>
<td>2. Most common STD</td>
<td>64.0±13.4</td>
<td>48.8±10.4</td>
</tr>
<tr>
<td>3. High school sexual activity rates</td>
<td>31.4±19.1</td>
<td>17.9±11.7</td>
</tr>
<tr>
<td>4. Legal age of consent to have sex</td>
<td>33.8±20.1</td>
<td>32.9±20.1</td>
</tr>
<tr>
<td>5. Age of aggravated sexual assault</td>
<td>6.5±3.5</td>
<td>5.3±3.5</td>
</tr>
<tr>
<td>6. Percent herpes asymptomatic</td>
<td>47.2±5.9</td>
<td>45.0±5.9</td>
</tr>
<tr>
<td>7. Factors that delay teen sex</td>
<td>45.3±5.9</td>
<td>40.4±5.9</td>
</tr>
<tr>
<td>8. Teen pregnancy rate decline</td>
<td>38.3±7.8</td>
<td>24.1±7.8</td>
</tr>
<tr>
<td>9. Percent infected with HSV-2</td>
<td>43.1±7.8</td>
<td>47.2±7.8</td>
</tr>
<tr>
<td>10. HPV usually has no sequelae</td>
<td>58.3±7.8</td>
<td>30.6±7.8</td>
</tr>
<tr>
<td>Average score</td>
<td>37.9±5.9</td>
<td>30.2±5.9</td>
</tr>
</tbody>
</table>

HSV-2, Herpes simplex virus type 2.
adults were not aware that most people infected with HPV have no associated health problems (question 10). When asked about factors associated with teens delaying sexual activity, only 38.3% of HCPs and 24.1% of other adults were aware of the important influence of parents’ viewpoints, school involvement, and pledges to delay sexual activity (question 7). Importantly, only 31.4% of HCPs and 17.9% of the other adult groups were aware that the number of high school students having ever had sexual intercourse has decreased over the last 10 years in the United States (question 3) as documented by CDC surveys. Specifically related to Texas, only 1 in 3 adults knew the legal age to consent to sex in the state is 17 years (question 4), and only about 6% knew that sex with someone 13 years of age or younger is aggravated sexual assault or “statutory rape” (question 5).

Although groups differed in their average scores before and after presentations, Figure 1 demonstrates the significant improvements in knowledge ($P = .0005$). HCPs attending adolescent sexual health conferences (group VI) had a significantly ($P < .02$) higher knowledge score before the programs and were more likely ($P < .001$) to have attended a prior presentation.

Attitudes

The survey forms included 3 standardized opinion questions pertaining to viewpoints on adolescent sexual activity and information. Respondents were asked: “I think teens should: (a) have sex at whatever age they want; (b) wait until after high school to have sex; (c) wait until after college/trade school to have sex; (d) wait until marriage to have sex; or (e) I don’t know.” The vast majority (94%) chose waiting until at least after high school (options b, c, and d), increasing to 98% after the program ($P < .0001$). The majority in all groups indicated that waiting until marriage was the preferred
option prior to the presentation (77.0%) increasing to 91.5% \((P<.0001)\) after the presentation.

There were significant variations among groups with regard to when initiation of sex should occur (Table IV). Although the majority of HCPs attending CME lectures (group V) thought people should wait until marriage, they had the lowest frequency of choosing this response both before (53%) and after (76%) the program. On the opposite end of the spectrum, HCPs attending training conferences specifically on adolescent sexual health (group VI) were most likely to support the attitude of delaying sex until marriage both before and after attending the program. Characteristics of adults who favored delaying sexual activity until marriage included being a parent (odds ratio [OR] 2.2, confidence interval [CI] 1.4-3.3.). Group V had the highest percentage of nonparents, which may have been related to attitude choice. Marital status, gender, race, and age were not significant factors. As demonstrated in Table I, attendance did not change significantly before and after the programs so the change in attitude, as with the change in knowledge, appears related to the information acquired during the educational program.

Adults were also asked, “If a 14-year-old goes to the doctor, the doctor should: (a) not ask about sex; (b) ask about sex, encourage abstinence, and discuss failure rates of birth control; (c) ask about sex and discuss how to practice safe sex; or (d) ask about sex and discuss both abstinence and safe sex.” The majority of respondents chose either b or d, but there was a significant \((P<.0001)\) shift in survey answers. Prior to the program, 36.2% chose option b and 50.2% chose option d. As seen in Figure 2, after the program the majority (72.4%) favored option b when seeing a 14-year-old in the office. This was particularly the case if the adult was married (OR 1.3, CI 1.01-1.7).

Adults were then asked to respond to the question, “A parent today should: (a) discourage teens from having sex before marriage; (b) discourage teens from having sex but discuss safe sex; (c) not have a problem with their teen having sex as long as they use birth control/condoms; (d) not discuss sex with their teens; or (e) I don’t know.” Less than 3% chose either options c, d, or e. Compared with the response before the program, there was a statistically significant \((P<.0001)\) shift after the program from response b to response a. Prior to the program, 58.0% chose response b and 39.3% chose response a. As seen in Figure 3, the majority in all groups (75.4%) after the program favored option a. Group V favored option b more frequently than the other groups, which may have been related to the characteristics of this group of HCPs. Characteristics of adults who favored discouraging sex before marriage included being married (OR 1.4, CI 1.1-1.9) and being a parent (OR 1.5, CI 1.1-1.9). Characteristics of adults who did not favor discouraging sex before marriage included being female (OR 0.7, CI 0.5-0.9) and being younger than 50 years of age (OR 0.7, CI 0.5-0.9).

The results apply to a diverse group of adults, including HCPs, but may not apply to all areas of the United States. Groups differed in whether they were voluntarily attending the educational programs. Groups I (parent presentations), III (community groups), and VI (HCPs attending adolescent sexual health conferences) selected to attend the programs. Groups II (school district employees) and IV (middle school teachers) included 1709 adults (46.7% of the total) who were mandated to attend. Group V (HCPs attending CME conferences) were registrants at women’s health care conferences.

**Comment**

Providing accurate, current information to teens, and those adults who influence them, on the issues of sexual activity is important to impact changes in behavior that can positively affect their lives. Adolescent sexual activity can create a multitude of medical, legal, and socio-economic sequelae not only for the adolescents but also for society as well. Although the CDC has documented through the Youth Risk Behavior Surveillance that the number of high school students engaging in sexual intercourse has declined from 1991 to 2003 (57.4% of
males and 50.8% of females in 1991 to 47% and 45.3%, respectively, in 2003), the overall rate is still high and fraught with medical repercussions. Researchers estimate that approximately 9.1 million STDs annually occur among persons aged 15 to 24 years. Most STDs are asymptomatic, making it difficult to diagnose, treat, and counsel those infected. The problems of STDs in adolescents are well known to obstetricians-gynecologists who deal with the complications including cervical dysplasia, recurrent herpes simplex virus type 2 (HSV-2), and pelvic inflammatory disease often leading to infertility, ectopic pregnancies, and acute/chronic pelvic pain. The 432,808 births to teenagers that occurred in the United States in 2002 are often associated with adverse medical and socioeconomic issues that have an impact on the family, community, and all of society, including welfare dependency, poverty, lack of educational preparedness, and inadequate workforce training.

Considering the health and socioeconomic impact of adolescent sexual activity, it is important to evaluate who and what influence teenage sexual behavior. Our data along with several national surveys give insight into the role of adults who have contact with teens. In December 2003, Zogby International surveyed more than 1000 parents in the United States. When asked what is the best message for programs to send young people in high school, 93% of parents responded that adolescents should be taught to abstain from sexual activity until after high school, after high school and in a potential marriage relationship, or until marriage. In December 2004, the National Campaign to Prevent Teen Pregnancy surveyed more than 1000 parents and 1000 teens on the issues surrounding adolescent sexual activity. In this national survey, 91% of adults and 94% of teens thought it was “somewhat” or “very” important for teens to be given a strong message.

Figure 2  Percent of adults responding after the presentation to the question, “If a 14-year-old goes to the doctor, the doctor should ____.” Choices included: (A) not ask about sexual activity; (B) ask about sexual activity, encourage abstinence, and discuss failure rates of birth control including condoms; (C) ask about sexual activity and discuss how to practice safe sex using condoms; (D) ask about sexual activity and discuss both abstinence and how to practice safe sex using condoms. There were no difference between groups ($P = .93$). Difference between choices are significant ($P < .0001$). There were no interaction between groups and choices ($P = .055$).
from society to not have sex until at least after high school.  

Our results of adults’ opinions on when adolescents should become sexually active are also consistent with those of other surveys. Ninety-four percent of adults taking our presurvey thought teens should at least wait until after high school to have sex, increasing to 98.0% on the postsurvey. This overwhelming common ground message of encouraging adolescents to wait until at least after high school to engage in sexual activity is seen in all groups surveyed, including medical professionals.

Not included in other adult surveys concerning adolescent sexual health, our report documents the lack of knowledge by most adults in many areas of adolescent sexual activity. Even HCPs do not know many important facts with regard to STDs, teen pregnancy, and legal issues. When educated on issues concerning adolescents and sex, all adult groups increased knowledge scores significantly ($P = .0005$). More importantly, there was a statistically significant shift not only in the knowledge scores but also a corresponding shift in attitudes. Adults who listed themselves as parents on the surveys were statistically more likely to favor delaying sexual activity.

We were surprised at the change in attitude in all groups after the presentation. There was a statistically significant shift favoring discussions of abstaining from sexual activity when a doctor encounters a 14-year-old in the office. Similarly, a shift occurred in messages that teens should receive from parents, favoring abstaining from sexual activity. These changes occurred in all groups, despite voluntary or mandatory attendance at the presentations. Variations among groups in attitudes may be related to variation in group characteristics, especially in relation to the percentage of adults who were parents and were married. For example, HCPs in

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**Figure 3**  Percent of adults responding after the presentation to the question, “A parent today should ____.” Choices included: (A) discourage teens from having sex before marriage; (B) discourage teens from having sex but discuss safe-sex measures; (C) not have a problem with their teen having sex as long as they use birth control including condoms; (D) not discuss sex with their teens; (E) I don’t know which choice is best. There were no difference between groups ($P = .48$). Differences between choices are significant ($P < .00001$), and interaction between groups and choices is significant ($P = .0004$).
group V who attended the adolescent sexual activity conference as a CME event least frequently had the attitude that sexual activity should be delayed until marriage and were also least frequently parents, whereas parents in all groups most frequently had the attitude that sexual activity should be delayed until marriage.

Several factors may have influenced the statistically significant difference in opinions seen after the programs. All groups did learn valuable information. Importantly, most adults in attendance, including HCPs, were not aware of the decreasing teen pregnancy rates in the United States over the past 10 years and were not aware of the significant decline in high school students having sexual intercourse as reported by the CDC. Becoming aware of these trends documented by government health care agencies may have altered opinions.

There have been only 2 published reports analyzing the factors responsible for the decreasing teen pregnancy rates in the United States over the past decade. Mohn et al analyzed contraceptive use and sexual activity rates among high school students to assess their degree of influence on the declining pregnancy rates noted from 1991 to 1995. They concluded that 67% of the decline in pregnancy among single teenagers during that interval was secondary to declining rates of vaginal intercourse. Santelli et al from the CDC also evaluated the effect of changes in sexual behaviors among high school students to explain the decline in teen pregnancy rates in the 1990s. They concluded that 53% of the decline in pregnancy rates can be attributed to decreased sexual experience and 47% to improved contraceptive use.

These reports confirm that continuing to encourage a delayed onset of sexual activity can play a major role in reducing the teen pregnancy rate. Although improved hormonal contraceptives have the potential to further the current decline in teen pregnancy, they will provide no reduction in STD acquisition. In an article in this journal, reviewed the serious consequences of current STDs, the limitations of barrier contraception, and the need for HCPs to focus on primary prevention of behaviors predisposing individuals to STD risk.

What is the role of obstetrician-gynecologists in the important issue of adolescent sexual health? First, they can review sex education curricula in their communities for content and accuracy. But to do so, they must have the facts themselves. They can also discuss sexual issues in the office but, more importantly, in the community to adolescents in schools and youth groups and to adult groups. Adolescents need the facts from a knowledgeable medical professional, and parents need the same information along with the knowledge of the important role they play in their child's sexual decisions. As obstetrician-gynecologists dealing with adolescents are well aware, when kids become sexually active, health problems can and often do occur. In our current continuing medical emphasis on risk avoidance and primary prevention of disease in all areas of women's health care, encouraging adolescents to defer the onset of sexual debut can lead to significant health benefits.

Previous studies have documented the important role of adults in the behaviors of adolescents. We have documented the knowledge base and attitudes with regard to adolescent sexual activity of a diverse group of adults who interact with this age group and how an educational intervention can influence changes. We are continuing to develop and research additional adult components to reach a larger group of individuals that have an impact on adolescents. Realizing the vital role of parents and other adults in the lives of adolescents, more evidence-based sex education programs that include programs for adults are needed, thus determining interventions that can positively influence healthy adolescent behaviors.

Acknowledgments

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References


Glycodelin reduces carcinoma-associated gene expression in endometrial adenocarcinoma cells

Hannu Koistinen, DSc,a,* Markku Seppälä, MD,a Balint Nagy, PhD,c Johanna Tapper, MD,b Sakari Knuutila, PhD,c Riitta Koistinen, PhD a,b

Department of Clinical Chemistry, a and Department of Obstetrics and Gynecology, b Helsinki University Central Hospital, Biomedicum; Laboratory of Cytomolecular Genetics, c Haartman Institute, University of Helsinki, and HUSLAB, Helsinki University Central Hospital, Helsinki, Finland

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Objective: Glycodelin is a major secretory glycoprotein of differentiated endometrial epithelium, rarely expressed in proliferative endometrium or endometrial cancer. We aimed to elucidate its role in growth and gene expression of endometrial adenocarcinoma cells, and hypothesized that glycodelin affects cell growth and tumor-associated gene expression.

Study design: Endometrial adenocarcinoma HEC-1B cells were transfected with glycodelin cDNA in both antisense and sense orientations. Cellular morphology, cell proliferation, and gene expression were compared between native and transfected cells.

Results: Compared with native and antisense-transfected carcinoma cells, sense-transfected, glycodelin-producing carcinoma cells showed reduced proliferation, morphologic changes, and altered expression of cancer-related genes. Notably, anti-apoptotic Bcl-X L and MUC1 genes were down-regulated.

Conclusion: Reduction by glycodelin transfection of carcinoma cell proliferation and expression of MUC1 and Bcl-X L is significant because these genes are often overexpressed in human cancers—MUC1 is linked to invasive growth and metastases, and both confer resistance to chemotherapy. These results suggest a novel mechanism whereby malignant growth of endometrial adenocarcinoma cells is regulated.

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* Reprint requests: Hannu Koistinen, PhD, Department of Clinical Chemistry, Helsinki University Central Hospital, Biomedicum Helsinki, P.O. Box 700 (Haartmaninkatu 8), 00029 HUS (Helsinki), Finland.
E-mail: Hannu.K.Koistinen@hus.fi

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adenocarcinoma cells by coculturing them with normal endometrial stromal cells and basement membrane components. At the same time that glycodelin became expressed, the adenocarcinoma cells differentiated to more closely resemble normal endometrial epithelial cells. While these results demonstrate an association of glycodelin with endometrial epithelial differentiation, they do not show whether glycodelin is a cause or a consequence in that process. We addressed this by studying the effects of glycodelin cDNA transfection into another glycodelin-negative endometrial adenocarcinoma cell line, the HEC-1B cells, paying special attention to cell proliferation and carcinoma-related gene expression.

Material and methods

The study was approved by the Institutional Review Board, Department of Obstetrics and Gynecology, University Central Hospital, Helsinki.

Cell culture

The human HEC-1B endometrial adenocarcinoma cell line (HTB-113) was purchased from American Type Culture Collection (Rockville, MD). The cells were cultured on plastic cell culture flasks (Nalge Nunc Int., Naperville, IL) or on glass chamber slides (for immunocytochemistry, Lab Tec Chamber Slides, Nalge Nunc) in RPMI-1640 (HyClone Laboratories, Logan, UT) supplemented with 10% fetal calf serum (HyClone), 100 IU/mL penicillin, 100 µg/mL streptomycin and 2 mmol/L L-glutamine (all from Gibco, Paisley, UK) at 37°C in a humidified atmosphere of 5% CO₂ in air. The cells were also cultured in Matrigel basement membrane matrix (Becton Dickinson, Bedford, MA) using the thick gel method according to manufacturer’s instructions.

Transfection and selection of stable transfectants

The whole protein-encoding region of glycodelin cDNA was cloned to pCR3.1 vector (Eukaryotic TA-cloning kit, Invitrogen, San Diego, CA) in both antisense and sense orientations. Recombinant DNA was extracted (Wizard Minipreps, DNA Purification System, Promega, Madison, WI), purified further using EndoFree Plasmid Kit (Qiagen, Valencia, CA), and sequenced. Glycodelin cDNA (5 µg) was transfected in both antisense and sense orientations using Superfect transfection reagent (Qiagen), and stable glycodelin-expressing cells were selected using genetin (200 µg/mL, Sigma, St Louis, MO). The plasmid vector contained the drug resistance gene that makes genetin selection procedure feasible. The glycodelin-secreting clones were identified by immunofluorometric assay. Seven glycodelin cDNA-transfected HEC-1B cell clones (sense cells) were selected for further investigation. In addition to the wild-type cells, 3 HEC-1B cell clones into which glycodelin was transfected in the antisense orientation (antisense cells) were used as controls.

Cell proliferation assay

Cell proliferation was assessed in plastic cell culture plates using BrdU Cell Proliferation ELISA (Boehringer-Mannheim, Mannheim, Germany). The cells were plated in triplicate at densities from 1000 to 10,000 cells in a 96-well plastic cell culture plate and incubated for 20 hours before adding the BrdU-labeling reagent and incubating for another 3 hours. Seven different sense-transfected and 3 antisense-transfected cell clones and the wild-type HEC-1B cells were tested in 5 experiments.

To evaluate cell proliferation in Matrigel, equal amounts of sense, antisense, and wild-type cells (50,000 cells/200 µL) were grown for 2 weeks and then treated with Matrisperse (Becton Dickinson) to dissolve cells from the gel, and counted. Cell proliferation was also assessed by H³-thymidine (8 µCi/200 µL, Perkin Elmer Life Sciences, Inc, Boston, MA) incorporation assay. Briefly, after 5 hours’ incubation with H³-thymidine, the cells were treated with Matrisperse, washed, and counted in a beta-counter (1216 RackBeta, Wallac, Turku, Finland).

Apoptosis assay

Labeling of DNA strand breaks (TUNEL technology) of Matrigel grown cells was done using In Situ Cell Death Detection Kit (Roche, Indianapolis, IN). Clear staining of the cells was considered as a sign of apoptosis.

Immunocytochemistry

The cells grown on glass chamber slides were fixed with cold acetone-methanol (1/1), and the cells grown in Matrigel for 2 weeks were fixed in formalin and embedded in paraffin. Immunocytochemical staining was carried out using antibodies described below and Vectastain ABC kit (Vector laboratories, Burlingame, CA). The antibodies were chosen to represent known markers of epithelial differentiation and/or prognostic immunohistochemical markers of endometrial cancer. The antibodies included anti-E-cadherin (Zymed Laboratories, San Francisco, CA), anti-β-catenin (Transduction Laboratories, Lexington, Ky), anti-HER-2/neu (also known as c-erbB-2, NCL-L-CB11, Novocastra Laboratories, Newcastle upon Tyne, UK), anti-cytokeratin-8, -19, -20, and -5/6/18 (NCL-CK 8, NCL-CK 19, and NCL-LP 34, respectively, Novocastra Laboratories), anti-Hsp70 (K-20, Santa Cruz Biotechnology, Inc, Santa Cruz, CA), anti-Ki-67 (B56, BD Biosciences/Pharmining, San Diego, CA), anti-p53 (Pab 1801, Santa Cruz Biotechnology, Inc), and anti-vimentin (NCL-VIM-V9, Novocastra Laboratories). Anti-MUC1 clone GP1.4 was from
Novocastra Laboratories. This antibody reacts with the protein core of MUC1 (synonymously known as episialin, epithelial membrane antigen [EMA], CA15-3, or polymorphic epithelial mucin).

Western blotting

Western immunoblotting was performed on Matrisperse-treated cells grown in Matrigel essentially as described. MUC1 and vimentin antibodies were the same as those used for immunocytochemistry. Detection was done using enhanced chemiluminescence (ECL) reagents and Hyperfilm MP (both from Amersham Biosciences, Buckinghamshire, UK). Quantitation from films was performed using InGenius Bio Imaging System (SynGene, Cambridge, UK).

cDNA array

Human 1.2 cDNA array (Clontech, Palo Alto, CA) consisting of 1176 genes was used for the detection of overall gene expression differences between glycolelin sense- and antisense-transfected HEC-1B cells. Labeling of total RNA (5 μg, pooled from 2 sense and 2 antisense clones grown in Matrigel for 1 week) and detection were done according to the manufacturer’s instructions. The hybridization signals were analyzed using AtlasImage 1.0 software (Clontech). The images were normalized using the 9 different housekeeping genes included in the membrane, except for HLAC that was not expressed. Gene expression was considered different between glycolelin sense and antisense cDNA-transfected HEC-1B cells when the signal ratio was >1.5 and the difference between hybridization signal intensities was greater than 3.5 times the median difference of all expressed genes.

Quantitative real-time reverse transcription-polymerase chain reaction

To validate the cDNA array results, quantitative reverse transcription-polymerase chain reaction (RT-PCR) was performed using pooled RNA samples from sense and antisense-transfected HEC-1B cells grown in Matrigel (see Table I for the genes). cDNA was synthesized using 0.5 μg DNAse-I treated total RNA and First Strand cDNA Synthesis kit for RT-PCR (Roche). Gene-specific primers were designed by TIB MOLBIOL (Berlin, Germany), except for MUC1 and vimentin, for which 5′-ATT CCT TGC TGG AAG ATC CC 3′ and 5′-GAC AGA CAG CCA AGG CAA TG 3′, and 5′-AGC GCC TCC TGG AGC A3′ and 5′-TGC TGT TCC TGA ATC TGA GC3′, were used as primers, respectively. The PCRs were performed in the LightCycler thermal cycler (Roche) as described. β-actin was used for normalization of RNA quantity in the samples. PCR reactions with control DNA were used according to manufacturer’s instructions (Roche) for conversion of Ct values to values used for calculations of fold changes.

Results

Glycolelin-transfected clones produced 0.3 to 2.5 μg glycolelin/10⁶ cells/24-hour culture. The control cells did not produce glycolelin.
Glycodelin expression reduces proliferation of carcinoma cells

The glycodelin-transfected carcinoma cells grown in Matrigel showed reduced proliferation compared to the antisense-transfected or wild-type cells (Figure, A). This was not accompanied by changes in apoptosis because 57.3 ± 3.2% of glycodelin antisense-transfected and 54.6 ± 2.9% of sense-transfected cells ($P = .39$) showed clear staining in the in situ TUNEL test. When the cells were grown on plastic, the same degree of proliferation was observed in the sense- and antisense-transfected and wild-type cells.

Glycodelin induces morphologic changes

When the HEC-1B cells were grown in Matrigel, the sense-transfected, glycodelin-producing cells showed clear morphologic changes in all 4 different clones studied, compared to the wild-type or the antisense-transfected cells (2 different clones tested). Whereas the wild-type and antisense-transfected cells formed predominantly glandular structures, the sense-transfected glycodelin-producing cells grew mostly as compact spherical structures without acini (Figure, B). The cells cultured on glass or plastic grew as regular monolayers and showed no differences in morphology between the wild-type cells or those transfected with glycodelin sense or antisense cDNA strands.

Glycodelin transfection affects gene expression

Glycodelin transfection induced changes in markers of epithelial differentiation and immunohistochemical prognostic markers of endometrial cancer. Among the studied proteins, glycodelin transfection (sense strand) was followed by significantly reduced MUC1 and vimentin staining after 2 weeks’ culture in Matrigel, as compared to the wild-type or antisense-transfected cells (Figure). This difference was consistent in all the clones studied (4 sense and 2 antisense clones). Immunostaining of MUC1 was also reduced in the transfected cells grown as a monolayer on glass. Reduced MUC1 expression was confirmed by quantitative RT-PCR and

Figure  (A) Proliferation of glycodelin sense-transfected (S), glycodelin antisense-transfected (AS), and wild-type (wt) HEC-1B cells grown in Matrigel, assessed by 3H-thymidine incorporation. Mean counts per second (cps) + SD of 3 assays with 2 different S clones, 1 AS clone and wild-type cells. Values are expressed as percentage of the wild-type. *$P < .05$ as compared to AS. (B) Effect of glycodelin transfection on HEC-1B cells grown in Matrigel basement membrane matrix. Numbers 2 and 4 depict glycodelin-transfected cells, and numbers 1 and 3 are control cells transfected with glycodelin antisense cDNA. Numbers 1 and 2 illustrate typical results of MUC1 staining, and numbers 3 and 4 show vimentin staining. Positive staining appeared as red/brown color, shown as black in this picture.
by Western immunoblot from Matrigel-grown cells (1.6- and 2-fold decreases, respectively, Table II). In the antisense-transfected cells, vimentin usually covered the entire cell surface, whereas in the glycodelin-producing cells, vimentin staining was markedly reduced and polarized. However, reduced vimentin expression after glycodelin transfection could not be demonstrated by Western blotting or by quantitative RT-PCR (Table II).

The differences in gene expression between glycodelin sense- and antisense-transfected carcinoma cells were further studied by cDNA arrays. Among the 1176 genes studied from the Matrigel-grown HEC-1B cells, 9 genes were up-regulated and 4 were down-regulated in sense-transfected cells, as compared to the antisense-transfected cells (Table I). Importantly, significant down-regulation of the Bcl-X<sub>L</sub> gene expression was observed. Some of the changes identified in the cDNA array were confirmed by quantitative RT-PCR (Table I). Up-regulation of Hsp70 was also confirmed by immunoblotting.

**Comment**

Glycodelin-transfected endometrial carcinoma cells grown in Matrigel showed reduced cell proliferation, unlike the cells grown on plastic. The difference between plastic and Matrigel is accounted for the presence of extracellular matrix components in Matrigel that regulate cell differentiation and strongly influence the ability of cells to respond to soluble mitogens and differentiation factors. Previous studies have shown that Matrigel induces morphologic and functional differentiation in endometrial adenocarcinoma cells, also demonstrated in this study. Matrigel provides a physiologically relevant environment for studies on cell morphology and gene expression. Under these circumstances, the additional effects of glycodelin transfection were studied in Matrigel-cultured carcinoma cells.

Reduction of cell proliferation by tumor suppressor proteins is accompanied by differentiation. In this respect, the changes observed in cell morphology and gene expression after glycodelin transfection concur with the tumor suppressor nature of glycodelin. Those carcinoma cells that did not produce glycodelin contained high levels of MUC1 and formed a gland lumen, whereas glycodelin-transfected carcinoma cells exhibited reduced MUC1 staining and formed more compact spherical structures, rarely maintaining a gland lumen (Figure). It is possible that the differences seen in formation of structures could result from a reduction in the rate and extent of gland formation rather than a difference in their propensity to form glands. MUC1 has anti-adhesive activity, and its expression is related to formation and maintenance of the gland lumen. Therefore, its down-regulation should indicate increased adhesive propensity in glycodelin-transfected carcinoma cells. MUC1 is frequently overexpressed in cancer cells, where it may cover the entire cell surface, possibly facilitating invasive growth and metastasis. In endometrial carcinoma, MUC1 overexpression is held as an independent predictor of recurrent disease, and its low expression is associated with a favorable prognosis. Transgenic overexpression of MUC1 in mouse mammary glands results in decreased apoptosis and mammary gland tumorigenesis. Importantly, MUC1 has been reported to attenuate cisplatin-induced apoptosis, and its knockdown is associated with increased sensitivity to genotoxic drugs in vitro and in vivo. Given the above considerations, reduction of MUC1 expression in glycodelin-transfected cells is significant because it describes a mechanism whereby the down-regulation of MUC1 may take place.

Reduction of vimentin expression in glycodelin-transfected endometrial carcinoma cells was another change observed in this study. This finding is based only on immunocytochemical evidence and is not supported by Western blotting or quantitative RT-PCR. Thus, it is possible that reduced staining in immunocytochemistry reflects change in localization of vimentin rather than change in protein levels. Nevertheless, the observation is of interest because, in carcinoma cells, vimentin has been related to advanced malignant phenotype, increased invasiveness, and metastatic potential. While it does not seem to confer the resistant phenotype itself, vimentin expression has been suggested to constitute a marker of chemoresistance. Increased expression of vimentin has been reported in endometrial adenocarcinoma.

A prerequisite for malignant transformation is deregulated cell propagation and suppressed apoptosis. Bcl-X<sub>L</sub> overexpression has been shown to cause resistance to apoptosis, and higher Bcl-X<sub>L</sub> levels have been reported in endometrial carcinoma. Contrary to the down-regulated Bcl-X<sub>L</sub>, another anti-apoptotic gene, Hsp70, was up-regulated after glycodelin transfection. These opposite changes may explain why no overall changes were seen in the TUNEL test. But because pooled samples were used, providing an average expression level for a number of specimens, the data are not suitable for statistical analysis. Nevertheless, these observations raise legitimate questions about whether

<table>
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<th>Marker</th>
<th>ICC&lt;sup&gt;*&lt;/sup&gt;</th>
<th>RT-PCR</th>
<th>Western</th>
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<tr>
<td>MUC1</td>
<td>Reduced</td>
<td>0.63</td>
<td>0.50</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Reduced</td>
<td>N.S.&lt;sup&gt;1&lt;/sup&gt; (0.82)</td>
<td>N.S.&lt;sup&gt;1&lt;/sup&gt;</td>
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<sup>*</sup> See Figure.  
<sup>1</sup> N.S., expression difference between sense and antisense >0.67.
resistance to apoptosis during chemotherapy would be different between glycodelin-producing and nonproducing cells. Down-regulation of anti-apoptotic Bcl-X<sub>L</sub> is significant because, among a number of anti- or pro-apoptotic genes, only Bcl-X<sub>L</sub> level has been found to correlate with resistance to cell death induced by various chemotherapeutics. Bcl-X<sub>L</sub> action has been implicated as a major component of chemoresistance in cancer cells, and this has been taken as an indication that Bcl-X<sub>L</sub> is the major target to be overcome for effective chemotherapy. It is of interest in this context that chemotherapy-treated patients with glycodelin-expressing serous ovarian carcinoma have longer survival time than those with glycodelin-negative tumors with the same differentiation grade and clinical stage. It may be relevant here that glycodelin is often expressed in the same malignant cells as the progesterone receptor, and glycodelin synthesis is stimulated by progesterone (reviewed in<sup>1</sup>).

It is concluded that glycodelin transfection reduces proliferation of endometrial adenocarcinoma cells, induces morphologic changes, and reduces expression of carcinoma- and chemoresistance-associated genes, such as MUC1 and Bcl-X<sub>L</sub>. Given that progestogens and progesterone antagonists stimulate glycodelin gene expression,<sup>1</sup> the potential of the present results is that they may encourage reappraisal of glycodelin synthesis-stimulating pathways in supporting chemotherapy of malignant tumors, notably those expressing the progesterone receptor.

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References

Neovascularization and mast cells with tryptase activity increase simultaneously with pathologic progression in human endometrial cancer

Domenico Ribatti, MD, a,* Nicoletta Finato, MD, b Enrico Crivellato, MD, c Andrea Marzullo, MD, d Domenica Mangieri, PhD, a Beatrice Nico, PhD, a Angelo Vacca, MD, e Carlo A. Beltrami, MD b

Department of Human Anatomy and Histology, a Department of Pathology, d Department of Internal Medicine and Clinical Oncology, e University of Bari Medical School, Bari, Italy; Department of Medical and Morphological Research, Pathology b and Anatomy c Sections, University of Udine Medical School, Udine, Italy

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Objective: In vitro and in vivo studies have linked mast cell (MC) degranulation and activation with angiogenesis and neovascularization. This assumption is partially supported by the close anatomic association between MC and the vasculature and the recruitment of these cells during tumor growth. The aim of this study was to correlate the extent of angiogenesis with the number of MC expressing tryptase in human endometrial adenocarcinoma.

Study design: Tissues from human endometrial hyperplasia and endometrial adenocarcinoma were investigated immunohistochemically, using 2 murine monoclonal antibodies against the endothelial cell marker CD31 and the MC marker tryptase.

Results: Angiogenesis, measured as microvessel counts, was highly correlated with MC tryptase-positive cell counts and that these parameters increase in agreement with tumor progression.

Conclusion: These results suggest that angiogenesis in endometrial cancer increases with tumor progression and that angiogenic tryptase secreted by host MC cooperate in its induction.

In solid tumor growth, a specific critical turning point is the transition from the avascular to the vascular phase. In human endometrial adenocarcinoma, the neoplastic mass is able to growth indefinitely both in situ and at distant sites (metastasis) in so far as an intrinsic vascular network enables its cells to enter the vascular bed and colonize other organs. Female reproductive tissues are among the few adult tissues in which angiogenesis occurs as a normal process. Uterine malignant tumors, such as endometrial cancer, leiomyosarcoma, and choriocarcinoma, contain newly formed vessels and angiogenesis is associated with high-grade squamous cell carcinoma of the cervix.
previously demonstrated that implants of biopptic fragments from human endometrial carcinoma and, to a lesser degree from endometrial hyperplasia, induced a significantly higher vasoproliferative response in the CAM assay than biopsy samples from patients with uterine prolapse, used as controls.7

Tumor cells are surrounded by an infiltrate of inflammatory cells, such as lymphocytes, neutrophils, macrophages, and mast cells (MC). It is becoming clear that stromal cells cooperate with endothelial and cancer cells in promoting angiogenesis. In particular, infiltrating inflammatory cells secrete a diverse repertoire of growth factors and proteases that enable them to enhance tumor growth by stimulating angiogenesis. These cells communicate by a complex network of intercellular signaling pathways mediated by surface adhesion molecules, cytokines, and their receptors.8 The density of MC is highly correlated with the extent of both normal and pathologic angiogenesis, such as that in chronic inflammatory diseases and tumors.9

Two types of human MC have been described on the basis of the differences in their neutral protease composition, MC T cells, which contain tryptase only, and MC Tc cells, which contain both tryptase and chymase.10 Tryptase positivity reflects the total number of MC, whereas chymase is not present in all MC. Blair et al11 have shown that tryptase released by MC at an angiogenesis site may play an important role in neovascularization. Direct addition of tryptase to microvascular endothelial cells cultured on Matrigel (Collaborative Research, Bedford, MA) caused a pronounced increase of capillary growth, which was suppressed by specific tryptase inhibitors. Moreover, tryptase directly induced endothelial cell proliferation in a dose-dependent fashion. We have previously demonstrated that in multiple myeloma, B-cell non-Hodgkin’s lymphoma, myelodysplastic syndromes, B-cell chronic lymphocytic leukemia, and melanoma, there is a striking association between MC and microvessel counts and both increase in function of malignancy.12–17 Moreover, we have further demonstrated that tumor vascularity and tryptase-positive MC correlate with a poor prognosis in melanoma.18

In this study, we correlate the extent of angiogenesis with the number MC reactive with tryptase in human endometrial adenocarcinoma.

**Materials and methods**

**Tissues samples**

Endometrial tissue specimens were collected from patients (n = 10) who were scheduled to undergo hysterectomy for endometrial hyperplasia and from patients (n = 20) undergoing hysterectomy for endometrial adenocarcinoma stage I (n = 10) and stage III (n = 5 stage IIIA and 5 stage IIIB), without lymph nodes involvement, grouped according to Rose.19 The depth of the myometrial invasion was classified as tumor invasion within the inner half (corresponding to the stage Ia) or the outer half (corresponding to the stage Ib) of the uterine wall. There was significant correlation between stages and depth of invasion. Portion of the tissues were fixed in formalin and embedded in paraffin according to standard procedures. The study was conducted on archived tissue blocks.

**Immunohistochemistry**

Two murine monoclonal antibodies (MAbs) against the endothelial cell marker CD31 (MAb 1A10) and tryptase (MAb AA1, Dako, Glostrup, Denmark) were used. Briefly, 4 µm thick sections were collected on 3-amino-propyl-trietoxysilane–coated slides, deparaffinized by the xylene-ethanol sequence, rehydrated in a graded ethanol scale and in TRIS-buffered saline (TBS, pH 7.6), and incubated overnight at 4°C with MAb 1A10 (1:25 in TBS) and AA1 (1:1500 in TBS), after prior antigen retrieval by enzymatic digestion with Ficin (Sigma, St Louis, MO) for 30 minutes at room temperature for tryptase, and in a pressure cooker for 90 seconds in EDTA buffer, pH 8 for CD31. The immunoreaction was performed with alkaline phosphatase antialkaline phosphatase (APAAP, Dako) and Fast Red as chromogen for tryptase, and with the streptavidin-peroxidase complex (LSAB2, Dako) and 3,3′ diaminobenzidine tetrahydrochloride (Dako) 5% as chromogen for CD31, followed by hematoxylin counterstaining. An unrelated monoclonal immunoglobulin G1 (IgG1) produced by the P3X63Ag8 mouse secretory myeloma replacing the MAb served as negative controls.20

**Microvessel counts**

These were simultaneously assessed without knowledge of the final pathological diagnosis by 2 investigators with a double-headed light microscope (Axioplan II, Zeiss, Oberkochen, Germany). Four to six 200X fields covering almost the whole of each of 4 sections per sample were examined with a 144-intersection point square reticulum (0.78 mm²) inserted in the eyepiece. Care was taken to select microvessels, ie, capillaries and small venules, from all the CD31-stained vessels. They were identified as transversally sectioned tubes with a single layer of endothelial cells, either without or with a thin basement membrane. Each assessment was agreed upon in turn. Microvessels were counted with a planimetric point-count method with slight modifications,12 according to which, only microvessels transversally cut occupying the reticulum points were counted. As the microvessel diameter was smaller than the distance between adjacent points, only 1 transversally sectioned microvessel could occupy a given point. Microvessels
transversally sectioned outside the points and those longitudinally or tangentially sectioned were omitted. Therefore, it was sufficiently certain that a given microvessel was counted only once, even in the presence of several of its section planes. As almost the entire section was analyzed per sample, and as transversally sectioned microvessels hit the intersection points randomly, the method allowed objective counts. Means GSD and medians were determined for each section, sample, and group of samples.

MC counts

MC were counted in six to eight 250X fields, covering almost the whole section, inside a square reticulum (0.25 mm²), and calculated as means GSD and medians for each group of samples.

Statistics

The significance of changes in the counts of microvessels and tryptase-positive MC was assessed with parametric (Fisher test) and nonparametric (Kruskal-Wallis test) analysis of variance, followed by the Duncan, Bonferroni, and Wilcoxon tests to compare groups 2 by 2. Correlations between counts were assessed with Pearson’s (r) coefficient and simple regression analysis. The χ² test was split into the linear and the residual component according to Cochran. Data were computed with the Statistical Analysis Software (SAS, SAS Institute, Cary, NC).

Results

The Table shows the microvessel and tryptase positive MC counts on adjacent tissue sections selected from patients affected from endometrial hyperplasia and endometrial adenocarcinoma stage I and stage III. There are significant differences (χ² = 32.4, df = 3, P < .001; F = 34.4, P < .001) between the 3 subgroups concerning the microvessel density. The microvessel counts showed a significant increase in adenocarcinoma stage I subgroup over endometrial hyperplasia (P < .001), yet another in the adenocarcinoma stage III A over adenocarcinoma stage I (P < .001) and in the adenocarcinoma stage III B over stage IIIA (P < .001). The MC counts were also significantly different between the 4 subgroups (χ² = 36.5 , df = 3, P < .001; F = 38.2, P < .001).

These differences are also shown in the Figure, showing the differences in microvessel and MC density between endometrial hyperplasia and endometrial adenocarcinoma. MC were generally scattered throughout the neoplastic tissue and within the interstitial stroma where they rested near or around the blood capillaries.

In hyperplastic endometrium sparse and occasional tryptase-positive MC were observed in the endometrial stroma admixed with a vascular component composed of small and highly ramified vessels.

Poorly differentiated endometrioid adenocarcinomas showed more numerous small and ramified vessels, mostly in carcinomas of solid type, as compared with well-differentiated endometrioid adenocarcinomas. In cases of endometrioid adenocarcinoma with squamous differentiation (adenoacanthoma and adenosquamous carcinoma), a higher vascular response was observed in the stroma next to the glandular component as compared with areas with squamous differentiation. A similar behaviour was noted for MC that were mostly present in areas with glandular differentiation.

Both counts of microvessel and tryptase-positive MC were significantly correlated with the degree of myometrial invasion. In fact, the percentage of immunoreactive endothelial cells CD31-positive and of MC

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<th>Tissue density of microvessels and tryptase-positive cell population</th>
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<tr>
<td></td>
<td>Endometrial adenocarcinoma*</td>
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<tr>
<td></td>
<td>Endometrial hyperplasia</td>
</tr>
<tr>
<td>Number of Microvessels</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Tryptase-positive mast cells</td>
<td>4 ± 1</td>
</tr>
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* Grouped according to Rose.19
<sup>1</sup> P < .001 vs endometrial hyperplasia.
<sup>2</sup> P < .0001 vs adenocarcinoma stage I and endometrial hyperplasia.

Figure Sections of endometrial biopsy specimens stained with tryptase for mast cells (A, B) and CD 31 for microvessels (C, D) from patients with endometrial hyperplasia (A, C) and with endometrial adenocarcinoma stage III B (B, D). Note the higher density of mast cells and microvessels in the sections of adenocarcinoma. Original magnification: A-D, ×250.
tryptase-positive was significantly associated with the presence of invasion to greater than a half myometrium (P < .001).

Comment

This article shows that angiogenesis in human endometrial carcinoma, measured as microvessel counts, is highly correlated with MC tryptase-positive cell counts and that these parameters increase in agreement with tumor progression.

Angiogenic activity in the endometrium may be the consequence of several factors: (1) mechanical forces associated with increased blood flow; (2) direct or indirect hormone stimulation; and (3) overexpression of angiogenic factors. Concerning the mechanical factors, Greiss and Rose\(^2^1\) showed that estrogens increase uterine blood flow and a strong relationship between increased blood pressure and capillary growth has been found.\(^2^2\) Concerning the direct hormone-induced effects, histologic and ultrastructural studies indicate that endothelial cell division occurs in the rodent’s uterus 24 to 48 hours after estrogen treatment.\(^2^3\) Concerning growth factor regulation of uterine vascular growth, endometrial adenocarcinoma cell lines produce a fibroblast growth factor-2 (FGF-2)-like protein.\(^2^4\) In addition, 17-β estradiol is capable of stimulating the synthesis of this molecule in the same cell lines\(^2^4\) and human recombinant FGF-2 induces cell proliferation and plasminogen activation production in the same cells.\(^2^5\) Guidi et al\(^2^6\) reported that in invasive squamous cervical carcinoma and in high-grade squamous intraepithelial lesions, vascular endothelial growth factor (VEGF) messenger RNA (mRNA) expression and microvessel counts were significantly higher than in low-grade intraepithelial lesions and benign squamous epithelium. Moreover, they demonstrated expression of VEGF and its receptors in endometrial carcinoma.\(^2^7\)

Although it is possible that MC have a wide variety of roles in the female reproductive tract, there is only limited information about the distribution and heterogeneity of these cells in the human uterine tissue. The uterus is characterized by relatively large numbers of MC, and these cells are especially numerous in the inner half of the myometrium.\(^2^8\) The physiologic role of MC in the normal uterus remains incompletely understood. There are some investigators who indicate that MC are more common in the proliferative phase endometrium,\(^2^9\) others reporting that they are more common in the secretory phase endometrium,\(^3^0\) and still others postulate that MC occur with an equal frequency in both phases of the normal menstrual cycle.\(^3^1\)

MC are strikingly associated with angiogenesis in tumors\(^8\) where they are preferentially accumulated in the peripheral areas of the tumor, within the surrounding connective tissue, and rest near or around blood or lymphatic vessels. The fact that MC contribute to the induction of tumor angiogenesis stems from studies on MC-deficient mice, which display slow angiogenesis, and its restoration after local reconstitution of MC.\(^5^2\) MC contain many angiogenic factors and a variety of cytokines, such as transforming growth factor-beta (TGF-β), tumor necrosis factor-α (TNF-α),\(^3^3\) interleukin-8 (IL-8),\(^3^4\) FGF-2,\(^3^5\) and VEGF\(^3^6\) implicated in normal as well as tumor-associated neoangiogenesis.

Tryptase stimulates the proliferation of human vascular endothelial cells, promotes vascular tube formation in culture\(^1^1\) and is likely to play an important role in neovascularization in human tumors, such as B-cell non-Hodgkin’s lymphomas, multiple myeloma, myelodysplastic syndromes, chronic lymphocytic leukemia, and cutaneous melanoma.\(^1^2\) Moreover, in malignant breast lesions the number of MC with tryptase activity was significantly higher than in benign lesions\(^3^7\) and MC derived from human renal tumor tissues contained tryptase.\(^3^8\)

In line with other reports showing a close relationship between increased number of tryptase-positive MC and tumor progression, our data suggest that tryptase-positive MC may contribute, at least partly to the endometrial carcinoma-associated angiogenesis, and that tryptase antagonization could be used as an antiangiogenic approach in the treatment of endometrial carcinoma.

References


Noninvasive prenatal RHD genotyping by real-time polymerase chain reaction using plasma from D-negative pregnant women

Lan Zhou, MD, PhD,a,b,* John A. Thorson, MD, PhD,a Clark Nugent, MD,c Robertson D. Davenport, MD,a Suzanne H. Butch, MA, MT (ASCP) SBB,a W. John Judd, FIBMS, MIBiol,a

Department of Pathology,a University of Michigan Medical School, Ann Arbor, MI; Department of Pathology, Case Western Reserve University,b Cleveland, OH; Department of Obstetrics and Gynecology,c University of Michigan Medical School, Ann Arbor, MI

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KEY WORDS
Prenatal RHD genotyping
Real-time polymerase chain reaction
Fetal DNA in maternal plasma

Objective: Prenatal noninvasive determination of fetal Rh status is an important aid to the management of hemolytic disease of the fetus and newborn. We performed real-time polymerase chain reaction on fetal DNA derived from maternal plasma to determine fetal Rh status.

Study design: Cell-free plasma DNA from 98 D-negative pregnant women was tested for the presence of exons 4, 5, and 10 of RHD. The presence of fetal DNA was confirmed by detection of SRY or biallelic insertion/deletion polymorphisms in the maternal plasma and buffy coat.

Results: Seventy-two D-positive infants and 26 D-negative infants were determined by serologic studies. All 3 RHD exon sequences were detected in 68 of 72 mothers of D-positive infants. The presence of fetal DNA in mothers of D-negative infants was confirmed in all 10 boys and in 14 of 16 girls.

Conclusion: Fetal RHD genotyping in this study correctly predicted fetal Rh status in 92 of 98 (94%) cases.

Because Rh immune globulin (RhIG) has been routinely used in prenatal prophylaxis, the incidence of alloimmunization to the D antigen has been reported to decrease from 13.2% to 0.14%.1 However, hemolytic disease of the fetus and newborn (HDFN) caused by anti-D is still problematic because of inadequate patient care, especially in indigent populations, inadequate dosing for large fetomaterna hemorrhages,2,3 and delays in RhIG administration.4

The prenatal determination of fetal Rh status in a pregnant woman who is Rh-negative (D-negative) and has made anti-D provides valuable information for predicting the risk of HDFN and for subsequent management of the pregnancy. A negative paternal D typing result assures the fetus is not at risk for HDFN. If the father is D-positive, additional testing for the Rh antigens C, c, E, and e may predict a high likelihood of
homozygosity for \textit{RHD}. In such situations, serial peak systolic velocity (PSV) in the fetal middle cerebral artery (MCA) by Doppler flow velocimetry, or serial amniocenteses for the determination of amniotic fluid $\Delta OD_{450}$ are recommended. When the partner is unavailable for testing, paternity is questionable, or the paternal Rh phenotype predicts possible heterozygosity for \textit{RHD}, patients can be monitored noninvasively with MCA Doppler flow velocimetry. Invasive procedures are performed when the MCA PSV is elevated. Alternatively, fetal Rh status can be determined by noninvasive genotyping.

Normally amniocentesis is performed at 15 weeks’ gestation and beyond to determine whether the fetus is antigen positive. Because of the risk of spontaneous miscarriage and alloimmunization associated with invasive procedures, noninvasive approaches to prenatal determination of Rh status have been actively pursued. \textit{RHD} genotyping of free fetal DNA present in maternal plasma by real-time polymerase chain reaction (PCR) is particularly attractive because of the feasibility of large scale screening in the laboratory. Awareness of a D-negative fetus being carried by a D-negative woman also eliminates unnecessary antenatal RhIG prophylaxis.

PCR assays that used primers directed to different \textit{RHD} exons or introns for fetal genotyping have been described. In cases with a male fetus, amplification of the fetal Y chromosome associated \textit{SRY} gene can be used to confirm the presence of fetal DNA in a maternal plasma sample. However, in cases with a female fetus, the possibility of a false-negative result is a concern unless an internal control for the presence of fetal DNA is used. Genotyping by using a combination of \textit{RHD} specific primers, \textit{SRY} specific primers for the detection of the Y chromosome, and analysis of biallelic insertion/deletion polymorphisms (IDP) has been shown to provide satisfactory results at the International Blood Group Reference Laboratory in the United Kingdom. The biallelic IDP system allows the detection of paternal marker alleles in maternal plasma DNA when compared with DNA prepared from the maternal buffy coat. DNA prepared from maternal buffy coat represents exclusively maternal DNA, whereas DNA present in maternal plasma comprises free fetal DNA carrying paternal genetic markers in addition to maternal DNA. The absence of an IDP allele in the maternal buffy coat and the presence of that same allele in the maternal plasma confirms the presence of fetal DNA and therefore fetal \textit{RHD} genotyping results can be reported in such cases with certainty. The clinical application of such testing in a hospital-based transfusion service has not been assessed in the United States. We present data that used real-time PCR to genotype fetal \textit{RHD} from maternal plasma in an academic medical center.

Material and methods

Maternal blood samples

This study was approved by the University of Michigan Institutional Review Board. EDTA blood samples were obtained from D-negative pregnant women (n = 98) who were monitored at the Department of Obstetrics and Gynecology for their prenatal care. These samples were requested for routine prenatal care and sent to the blood bank for ABO and Rh typing and testing for unexpected antibodies. When practical, plasma was separated from red cells by centrifugation ($3000 \times g$, room temperature) immediately after testing. In some cases, plasma was separated up to 48 hours after completion of serologic studies. The plasma samples were recentrifuged at $3000 \times g$, and the supernatants transferred to fresh polypropylene tubes and stored at $-20^\circ C$. Buffy coat from each blood sample was also collected and stored at $-20^\circ C$.

DNA extraction

DNA was extracted from plasma and buffy coat by using the QIAamp Blood Kit (Qiagen, Valencia, CA) according to the manufacturer’s Blood and Body Fluid protocol. Eight hundred microliters of the plasma samples and 200 $\mu$L of buffy coat samples were used per column for DNA extraction. The DNA was eluted in 50 $\mu$L of water and stored at $-20^\circ C$ until further testing.

Real-time PCR

Real-time PCR analysis using the Taqman assay format was performed on an ABI PRISM 7900 instrument (Applied Biosystems, Foster City, CA). TaqMan probes (Applied Biosystems) for \textit{RHD} exon 4 and the \textit{SRY} gene were labeled at the 5’-end with the reporter dye 6-FAM (carboxyfluorescein). Probes for \textit{RHD} exon 5 and exon 10 were labeled at the 5’-end with the fluorochrome dye VIC. All TaqMan probes were labeled at the 3’-end with the quencher dye TAMRA (6 carboxy-tetramethylrhodamine). Primers used for this study targeted the \textit{RHD} gene ( exon 4, exon 5, and exon 10), the \textit{SRY} gene, and 8 biallelic short IDPs. Primers for the \textit{GAPD} gene were used as an internal control for DNA amplification. All primers were purchased from Integrated DNA Technologies (Coralville, Iowa). Five microliters of extracted DNA were amplified in a 25-$\mu$L reaction volume using the TaqMan Universal PCR Mastermix (Applied Biosystems). All probes were used at 100 nmol/L and primer concentrations were 200 nmol/L (\textit{RHD} exon 4, \textit{RHD} exon 10, and \textit{SRY}) or 300 nmol/L (\textit{RHD} exon 5). For real-time PCR detection of the IDP system alleles, primer concentrations were 400 nmol/L and probe concentrations were 200 nmol/L. PCR cycling conditions were 50°C for...
Results

A total of 98 plasma samples were collected from pregnant women who were D-negative by serologic testing: 82 were white women, 7 were black women, and 1 was an Asian woman. The ethnicity of the remaining 9 D-negative women was unknown. Among these, 2 samples were collected at less than 14 weeks’ gestation, 39 were collected at 15 to 28 weeks’ gestation, and 57 were collected at 29 to 42 weeks’ gestation. Fetal DNA was found to be present in the maternal plasma as early as 10 weeks’ gestation.

Serologic studies were conducted on cord blood from newborn infants delivered from the women enrolled in this study. Seventy-two newborn infants were identified as D-positive. Among these, 37 were male and 35 were female. Twenty-six were identified as D-negative, of which 16 were female and 10 were male (Table I).

The concordance of the newborn Rh status determined by serology and fetal genotyping on maternal plasma was analyzed in all 98 patients included in this study. Fetuses were predicted to be D-positive when RHD exon 4, RHD exon 5, and RHD exon 10 signals were obtained. Fetuses were predicted to be D-negative when no RHD signals were obtained. Cases were considered inconclusive when only 1 or 2 of these exon signals were obtained. In twin pregnancies, the pregnancy was considered D-positive if genotyping revealed the presence of RHD. Plasma from women carrying a D-negative fetus (n = 72) gave positive results in 69, 71, and 72 samples using RHD exon 4, 5, and 10 primers, respectively (Table II). Of 72 plasma samples, 68 generated positive results for all 3 RHD exon primers and were predicted to be D-positive. Four plasma samples had negative results with 1 of the RHD exon primers (exon 4 or exon 5) in duplex PCR. The ethnicities of these 4 D-negative women were 3 white and 1 unknown. To increase the sensitivity, these samples were further amplified in a monoplex PCR. The results were confirmed negative and therefore deemed inconclusive. Furthermore, the threshold cycle number for all of these samples was greater than 32, strongly suggesting that the amplification product was of fetal origin and not from maternal DNA with an unusual genotype that may result in a D-negative phenotype.

Among 26 women carrying a D-negative fetus, none were positive with RHD primers and 10 were positive with SRY gene primers in either duplex or monoplex PCR, matching actual fetal sex in male infants at birth. The remaining 16 plasma samples gave negative results with either RHD primers or SRY primers. Biallelic IDP analysis identified a nonmaternal allelic polymorphism in 14 of the plasma samples, whereas 2 samples showed no evidence of fetal DNA (Table II).

Comment

We performed fetal RHD genotyping using maternal plasma from 98 pregnant women at 10 to 42 weeks of gestation. A flow chart summarizing the steps of genotyping assays is shown in the Figure. Our results demonstrated that we were able to predict fetal Rh status in 92 of 98 (94%) cases.

RHD genotyping by real-time PCR was inconclusive in 6% of our samples. The inconclusive results were caused by a lack of PCR amplification of RHD exons 4 or 5 (4/72 cases) or a failure to detect the presence of nonmaternal IDPs in maternal plasma. Discrepancies between serology and genotyping results can be due to several factors. Variant forms of RHD may result in the inability to amplify specific exon regions with the primer sets used in this study. It is known that Rh is the most complex blood group system, with approximately 50 different variants documented. The primers used for this study were designed to distinguish RHD from RH pseudogene (RHDΨ), which accounts for two thirds of
black Rh negatives, or hybrid RHD-CE-D, which arises from replacement of some of the RHD exons (including exons 4 and 5) by the corresponding RHCE exons. The 4 inconclusive cases in our study are unlikely to represent false-positive results because they showed negative genotyping only in exon 4 or 5 and phenotyped as D positive by serology. Further, the high threshold cycle (>32) in these samples strongly argues against the possibility of maternal DNA amplification as a source of a false-positive result. Although 3 of the 4 inconclusive cases were observed in samples collected from white women, the patterns we observed did not match the variant form of a partial D category VI (DVI) that is normally seen in white women (DVI). It is possible that these unusual patterns could arise from variants such as DBT, a partial D associated with the low-incidence antigen Rh32 (exon 4–, exon 5+, exon 10+), or others.
Alternatively, it is possible that our negative results are due to an insufficient amount of fetal DNA present in the PCR assay. The amount of fetal DNA present in maternal serum is variable from pregnancy to pregnancy and from day-to-day throughout the entire pregnancy. A lower concentration of fetal DNA is present in the maternal plasma in the first and second trimester, whereas the concentration increases in the late third trimester. In 4 samples that did not show amplification of RHD exons 4 or 5, 3 were collected during the early second trimester and 1 was collected during the time of delivery. It is unclear whether the negative PCR result in this sample was because the sample was actually collected after the delivery. It is known that fetal DNA in maternal plasma has a half-life of 16 minutes and is not detectable by 2 hours after delivery. In addition, delayed sample processing was associated with increased total free DNA released from maternal cells and a decreased relative proportion of fetal DNA. Although real-time PCR was performed in duplicate, we found no amplification in either replicate for each implicated exon region in all 4 discrepant cases. Further, the threshold cycle numbers observed for the other exon regions were high from these same samples, indicating that amplification was limited by a low quantity of target fetal DNA and a low sensitivity of the implicated primers. Because lower sensitivity is associated with duplex PCR assays due to competition between 2 sets of primers, we confirmed these results in monoplex PCR assays for RHD exon 4 or exon 5.

Decreased sensitivity for SRY gene amplification has also been documented. In our study although several cases showed no amplification of the SRY gene in duplex PCR assays, the presence of male fetal DNA in those cases was subsequently confirmed by monoplex PCR for the SRY gene. For future studies, improved sensitivity could be achieved by increasing the input sample size. In addition, fixing the maternal blood samples with formaldehyde has been shown to increase the relative fetal DNA concentration by inhibiting maternal cell lysis. However, such manipulations of samples will likely have a limited impact on the sensitivity of amplifying fetal DNA and further studies are needed to address this issue.

In 16 cases in which maternal plasma DNA samples were negative for RHD and SRY, we were able to document that fetal DNA was present in 14 cases by demonstrating the presence of paternal IDP markers in the maternal plasma samples. The absence of these markers in 2 of 16 cases is again likely due to the scarcity of fetal DNA; alternatively, the primers used for polymorphic allele detection may not have been able to discriminate paternal markers from maternal markers. Our results are similar to the findings from other studies, indicating inherent limitations associated with the use of the biallelic IDP system. Improved informativity may be achieved by combining the IDP system with short tandem repeat (STR) marker detection. STR markers have been shown to have almost 100% informativity in bone marrow chimerism studies, although the sensitivity is somewhat lower than IDP. Unfortunately, we did not have a sufficient quantity of plasma DNA to test the hypothesis.

Our study demonstrates the feasibility of using real-time PCR on maternal plasma to predict the fetal Rh status in a university hospital-based laboratory. Combined with high throughput automation for DNA extraction and pipetting, fetal genotyping by real-time PCR on maternal plasma provides a rapid and reliable assessment of fetal RHD genotype while avoiding the significant risks of invasive sampling procedures. The cost of such testing by using automated technology will likely be less than the cost of administering RhIG according to Moise. False-negative results still pose a challenge for the wide clinical application of this technique; however, several approaches can be used to increase the accuracy of this technique. Larger input sample size with more fetal DNA will be helpful to enhance the amplification of target sequences. Repeat testing may be required to follow inconclusive cases. In the case of a D-negative fetus, RHD genotyping on paternal blood can be performed to verify that an unusual genotype is not a source of error. Finally, multiple polymorphic genetic markers can be used to confirm the presence of fetal DNA in cases with D-negative female fetuses.

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Simulation of therapy in a model of a nonhydropic and hydropic recipient in twin-twin transfusion syndrome

Jeroen P. H. M. van den Wijngaard, MSc,a Michael G. Ross, MD, MPH,b Jos A. P. van der Sloot, MD, PhD,c Yves Ville, MD,d Martin J. C. van Gemert, PhDa,∗

Laser Center and Department of Obstetrics and Gynecology, Academic Medical Center-University of Amsterdam,a Amsterdam, The Netherlands; Department of Obstetrics and Gynecology, Harbor-UCLA School of Medicine,b Torrance, CA; Department of Cardiology and Intensive Care, Academic Medical Center-University of Amsterdam,c Amsterdam, The Netherlands; Department of Obstetrics and Gynecology, University Paris Ouest Versailles St. Quentin,d Centre Hospitalier Intercommunale Poissy St. Germain, Poissy, France

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KEY WORDS
Twin-twin transfusion syndrome Mathematical model Hydrops Amnioreduction Laser ablation Digoxin

Objective: This study was undertaken to model the sequence of events that occurs after amnioreduction, laser therapy, and digoxin administration in twin-twin transfusion syndrome (TTTS) with and without a hydropic recipient twin.

Study design: We added amnioreduction, laser therapy, and digoxin administration to our mathematical TTTS model and simulated combinations of these therapies.

Results: With a nonhydropic recipient, simulated amnioreduction delays the onset of hydrops. Conversely, with a hydropic recipient, amnioreduction aggravates the degree of hydrops. Furthermore, amnioreduction increases the transplacental fluid flow and may temporarily cause a hydropic donor. Laser therapy terminates the cause of recipient hydrops. Digoxin reduces the degree of recipient hydrops, but increases arteriovenous fetofetal transfusion.

Conclusion: Laser therapy is superior in TTTS with a hydropic recipient, because simulated amnioreduction aggravates the recipient’s cardiovascular status. Digoxin benefits a hydropic recipient but slightly worsens the donor’s condition. Therefore, TTTS presenting with a hydropic recipient prior to fetal viability (~26 weeks) may be best treated with laser therapy, whereas more advanced gestations may be offered digoxin administration plus amnioreduction, to delay the progression of TTTS.

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Twin-twin transfusion syndrome (TTTS) is an abnormally developing imbalance between the fetoplacental circulations of monochorionic donor and recipient twins as a consequence of placental vascular anastomoses. This serious problem is encountered as the oligo-polyhydramnios sequence, often deteriorating to more
severe forms, where development of hydrops in the recipient twin is associated with the highest incidence of adverse pregnancy outcome.\textsuperscript{1,2}

TTTS has a widely variable clinical presentation, which likely is a consequence of a complex and largely inaccessible pathophysiology. This is because human study of the critical fetal parameters that contribute to the course and sequelae of TTTS, and the response to therapy, is presently impossible (eg, fetomniotic fluid flows, fetal blood pressures, net fetofetal transfusion). As a TTTS animal model is lacking, mathematical models of TTTS have been developed as a vital alternative.\textsuperscript{3-6} These models have contributed significantly in identifying the pathophysiologic events that lead to the various presentations of TTTS (eg, oligopolyhydramnios sequence,\textsuperscript{3,5} onset of hydrops\textsuperscript{6}). Recent advances in modeling have aided in predicting both donor and recipient responses to varying therapeutic interventions (ie, amnioreduction, septostomy, laser ablation of vascular anastomoses).\textsuperscript{7,8}

An unexplored but yet important topic in TTTS pathophysiology is whether the therapeutic responses of a hydropic recipient differ from those of a nonhydropic twin. Theoretically, this is to be expected because, with hydrops, the intercompartmental pathways of fluid flows (eg, urine production, transplacental and transvascular flows) are severely disturbed, implying that any therapy affecting these flows may further alter fetal responses. When hydrops presents shortly beyond the period of fetal viability (\textsim\text{26} weeks), the obstetrician is presented with a clinical dilemma: optimal therapy with fetoscopic laser is generally not offered because of a significant risk of losing 1 or both twins within several days, whereas the response to less efficacious therapies (eg, amnioreduction) is unknown. However, amnioreduction procedures, steroid administration for lung maturation, and elective delivery between 28 and 32 weeks, are usually preferred, depending on fetal conditions and response to therapy. The rareness of such late severe cases makes it difficult to identify optimal therapy (eg, by conducting a multicenter clinical trial, randomizing between therapy and delivery). Under these conditions, mathematical TTTS modeling of therapy is an essential first step toward predicting the efficacy of therapeutic interventions in the presence of a hydropic recipient.

Recently, we developed a mathematical model of TTTS that includes a hydropic recipient twin, predicting fetal and amniotic fluid abnormalities in relation to the placental angioarchitecture.\textsuperscript{6} We sought to extend our mathematical model to predict the therapeutic responses of TTTS cases with a nonhydropic versus hydropic recipient to combinations of amnioreduction, laser obliteration of anastomoses, and administration of digoxin.

**Methods**

**Mathematical model of TTTS with a hydropic recipient twin**

The model incorporates 10 differential equations for each twin, coupled by the net fetofetal transfusion of blood volume and blood constituents (ie, colloids, osmoles, and vasoconstrictive peptides). These 20 equations describe the development (growth) of, and the interactions occurring between the following parameters: volumes of fetal arterial and venous blood, interstitial fluid, intracellular fluid and amniotic fluid; colloid osmotic pressures (COP) of fetal blood and interstitial fluid; osmolality of fetal blood and amniotic fluid; and the concentration of vasoconstrictive peptides in the fetal blood, generically referred to as renin-angiotensin-system (RAS) mediators. In this model we emphasize the role of the RAS, although effects of sympathetic stimulation, increasing the cardiac output, have not been taken into account separately. In addition, the model relates fetal cardiac output to varying preload and afterload,\textsuperscript{9} and fetal urine production to mean arterial pressure,\textsuperscript{7} but also to concentrations of blood colloids and RAS mediators. The model has been described in detail elsewhere.\textsuperscript{6}

**Models of therapeutic interventions**

We used an equally shared placenta, and a single uncompensated arteriovenous anastomosis (arteriovenous resistance at 40 weeks is 0.29 mm Hg/mL/24h), also representative of multiple unidirectional and bidirectional arteriovenous anastomoses.\textsuperscript{2,4,7} This angioarchitecture generates a polyhydramniotic recipient at 20 weeks, a stuck (anhydramniotic) donor just before 22 weeks, donor anuria at 22 weeks, and development of hydrops in the recipient at 24.4 weeks.

We simulated the response to 4 therapeutic interventions: (A) total amnioreduction, (B) laser ablation with total amnioreduction, (C) digoxin administration, and (D) digoxin administration with total amnioreduction. We simulated the interventions at 2 different TTTS stages: (1) at onset of a stuck donor twin (22 weeks) and (2) in the presence of a hydropic recipient (26 weeks). We specifically sought to determine whether therapy causes a possible delay in the onset of hydrops in the recipient, and whether the therapeutic responses of a hydropic recipient differs from those of a nonhydropic twin.

Total amnioreduction, performed by Jauniaux et al,\textsuperscript{10} was modeled by removing all amniotic fluid from the recipient sac. We modeled total rather than partial amnioreduction because it produces the maximum fetal response. Laser obliteration of a placental anastomosis was simulated by setting the anastomotic
fetofetal transfusion to zero. The use of digoxin, by oral maternal administration, assuming passive diffusion across the placenta into the fetoplacental circulation, relates to an increased myocardial contractility. We modeled the inotropic effect of digoxin on the heart by increasing the cardiac reserve from 1.1 as previously used to 1.3 times normal preload, and increasing the fetal arterial pressure by 20% at the same cardiac output. In the model, this results in an increased fetal vascular resistance, in agreement with clinical observations. To facilitate normal transplacental flow and incorporate maternal effects of digoxin administration, maternal intervillous pressure was increased by 10%, ie from 40 mm Hg as previously used to 44 mm Hg. Lastly, digoxin is implicated either directly via hemodynamic improvement or indirectly via neurohormonal pathways to attenuate plasma renin activity, angiotensin II, and aldosterone levels. Consequences are an improved cardiovascular status and, in cases of fetofetal transfusion, a reduced concentration of RAS mediators transfused to the recipient twin. In the model we therefore reduced the upregulation of donor excess RAS production, defined as $F_{\text{RAS}}$ in equation M.21 of our previous paper, below 80% of normal arterial pressure as $F_{\text{RAS-Digoxin}} = F_{\text{RAS}} \cdot 0.75 + 0.25$. In addition, normal production of RAS mediators was decreased with 25%, reaching 26 pg/mL instead of the 35 pg/mL as previously used. As a result of these model adaptations, digoxin administration in normal (singleton) fetuses essentially has no influence on clinical outcomes, ie, on cardiac output, urine production, amniotic fluid volume, and transplacental and transvascular flows. This unaltered clinical behavior is in agreement with observations by Eichhorn et al.

We defined polyhydramnios as at least twice the normal singleton amniotic fluid volume, and hydrops in the recipient as an increase in the interstitial fluid volume of at least 18% compared with normal. In the donor, we defined (transient) hydrops caused by intervention as an increase in interstitial fluid volume of at least 18% compared with the level at intervention. We defined the resolution of (transient) donor hydrops as a reduction of the transvascular flow to less than 25% of its maximal increase, because the volumetric definition predicts permanent donor hydrops at normalizing interstitial fluid volumes, eg, after laser therapy, obviously contradicting reality.

### Results

(A1) Total amnioreduction at 22 weeks at the onset of a stuck donor twin

Simulation of total amnioreduction at 22 weeks decreases the amniotic fluid pressure, hence increases the transplacental fluid flow to the donor and recipient twins. The consequential increase in their blood volume and blood pressures increases the donor’s urine production and amniotic fluid volume (Figure 1, A), and subsequently the arteriovenous fetofetal transfusion to the recipient. The latter represents the dominant mechanism compared with increased blood volume and pressures; thus with advancing gestational age, the donor’s blood volume and arterial pressure decrease.
again and its urine production ceases again. The results indicate transient resolution of the donor anhydramnios until 24.9 weeks and of the recipient polyhydramnios until 25.3 weeks (Figure 1, A). The temporarily increased donor arterial pressure after amnioreduction delays the upregulation of donor RAS mediators (Figure 1, B), which delays (but not prevents) onset of hydrops by 1.3 weeks, now developing at 25.7 weeks (Figure 1, C). The strongly increasing severity of hydrops affects the extend of polyhydramnios, here subsequently disappearing at 31 weeks.

(A2) Total amnioreduction at 26 weeks in the presence of a hydropic recipient twin

At 26 weeks, simulation of total amnioreduction shows donor urine production to remain absent, hence, no resolution of the stuck donor occurs (Figure 2, A). Here, the amnioreduction mediated increased donor blood volume and pressures rapidly restores the donor interstitial fluid volume (Figure 2, C), presenting as a temporary donor hydrops between 26.2 and 30.4 weeks, as clinically described by Morine et al. The increased donor arterial pressure in turn strongly decreases the donor production of RAS mediators, occurring around 27 weeks (Figure 2, B), and increases the arteriovenous transfusion to the recipient (not shown). This increasing arteriovenous transfusion temporarily increases the recipient’s interstitial fluid volume (Figure 2, C).
However, the recipient’s interstitial volume subsequently decreases again, as the reduced donor RAS concentration results in less RAS transfused to the recipient. Thus, amnioreduction of TTTS with a hydropic recipient twin provides a slight benefit for the donor at the cost of an aggravated hydrops for the recipient.

(B1) Laser ablation with total amnioreduction at 22 weeks at the onset of a stuck donor twin

Laser therapy before the development of a hydropic recipient results in resolution of the fetofetal transfusion and, hence, the prevention of hydrops (not shown).7

(B2) Laser ablation with total amnioreduction at 26 weeks in the presence of a hydropic recipient twin

These simulations indicate resolution of the stuck donor at 26.5 weeks (Figure 3, A). When the arteriovenous transfusion ceases, the donor blood volume and blood pressures increase, so donor production of RAS mediators decreases rapidly. In addition, RAS mediators are no longer transfused to the recipient twin, hence an important mechanism for recipient hypertension ceases to be functional and recipient blood pressures normalize. Hydrops quickly resolves at 26.4 weeks and interstitial fluid volume is virtually normal at 27.5 weeks (Figure 3, B). Interestingly, our model predicts recipient hydrops resolves faster if laser is combined with less aggressive than total amnioreduction. This is caused by the lesser increase in transplacental flow as a result of smaller amniotic fluid pressure reduction. Because the increased COP of the recipient twin takes time to resolve, the transplacental fluid flow remains increased and the amniotic fluid volume of the recipient after laser therapy remains elevated, however, without reaching levels of polyhydramnios (Figure 3, A). On the basis of the same mechanism as discussed in case A2, amnioreduction causes a temporary hydrops in the donor twin.
between 26.2 and 27.3 weeks (Figure 3, B), clinically described by Gratacos et al.\textsuperscript{18}

**C1) Digoxin administration at 22 weeks at the onset of a stuck donor twin**

Administration of digoxin increases the donor’s arterial pressure. The resulting increase in arteriovenous fetofetal transfusion aggravates the course of TTTS severity for the donor twin and increases polyhydramnios in the recipient (Figure 4, A). Digoxin delays the onset of recipient heart failure and hydrops from 24.4 to 26.9 weeks (Figure 4, B).

**C2) Digoxin administration at 26 weeks in the presence of a hydropic recipient twin**

Administration of digoxin causes an aggravated polyhydramnios (Figure 5, A) caused by the temporary resolution of hydrops from 26.2 until 27.3 weeks (Figure 5, B). The sequence of events is as follows. First, the increased recipient cardiac output occurring at 26 weeks increases its arterial pressure and therefore also its urine production. Thus, the reduced or reversed recipient hydrops at 26 weeks (Figure 5, B) necessarily causes an increased polyhydramnios\textsuperscript{6} (Figure 5, A, upper curve after 26 weeks). On the other hand, an increased urine production implies a reduced volumetric growth of the fetal total body fluid and, as a consequence, ultimately reduced urine production and mitigation of the severity of polyhydramnios, subsequently disappearing at 34.5 weeks (Figure 5, A). Interestingly, digoxin provides no beneficial effect for the donor twin. By increasing the arterial pressure of both twins, and also reducing the recipient’s venous pressure by mitigating its heart failure, digoxin actually increases the arteriovenous fetofetal transfusion to the recipient by about 50\% (not shown).
(D1) Digoxin administration with total amnioreduction at 22 weeks at onset of a stuck donor twin

Combined with total amnioreduction, administration of digoxin causes the donor to become stuck again at an earlier time than with amnioreduction alone (24.1 weeks, Figure 6, A, vs 24.9 weeks, Figure 1, A). However, digoxin somewhat reduces donor RAS production (not shown; predictions are similar as in Figure 1, B), and delays the onset of recipient hydrops from 25.7 (case A1, Figure 1, C) to 27.5 weeks (Figure 6, B).

(D2) Digoxin administration with total amnioreduction at 26 weeks in the presence of a hydropic recipient twin

Digoxin administration plus total amnioreduction increases the fetofetal transfusion approximately 2-fold compared with the untreated case (not shown). In the recipient, similar as with amnioreduction alone (case A2), polyhydramnios does not redevelop (Figure 7, A) and donor production of RAS mediators is decreased (not shown; predictions are similar as in Figure 2, B). As a result of decreased RAS concentrations transfused to the recipient, resolution of recipient hydrops occurs from 26.3 until 28.5 weeks (Figure 7, B). In the donor, the increased transplacental fluid flow caused by amnioreduction causes the loss of fluids, due to increased fetofetal transfusion, to be partly compensated by amnioreduction compared with digoxin therapy alone. This effect is reflected in the donor interstitial fluid volume, producing transient donor hydrops between 26.3 and 28.9 weeks (Figure 7, B).

Comment

With the use of mathematical modeling, we have identified for the first time the sequence of events that likely develops in the donor and hydropic recipient twins of severe TTTS in response to various therapeutic interventions. Without the use of a mathematical model, such results are virtually impossible to obtain in a clinical setting, because TTTS pathophysiology includes intercompartamental fluid flows that are inaccessible to ultrasonography (eg, between vascular, interstitial and amniotic fluid compartments). The therapeutic interventions chosen were total amnioreduction, laser therapy with total amnioreduction, and digoxin administration without and with total amnioreduction. We selected total amnioreduction (ie, removing all amniotic fluid volume from the recipient sac10) rather than partial amnioreduction, to show the maximum fetoplacental fluid responses. We recognize that under clinical conditions therapeutic amnioreduction would retain a volume of recipient amniotic fluid, eg, to prevent cord compression. Simulations indicate this residual volume does not significantly alter our model predictions of fetal responses (not shown).

Simulated amnioreduction in TTTS has a different outcome for nonhydropic versus hydropic recipients. When performed before hydrops, the onset of recipient hydrops is delayed, although at the cost of an increased arteriovenous transfusion. However, with a hydropic recipient, amnioreduction has potential adverse effects because recipient forward heart failure causes the additional excess fluid resulting from the amnioreduction to be driven from the circulation into the interstitium, worsening its hydrops. For the donor, its arterial pressure increases, so urine production may recommence, arteriovenous transfusion increases but production of RAS mediators decreases. In addition, amnioreduction dilutes the blood colloids, causing a reduced blood COP. The combination of increased arterial pressure and reduced COP increases the transvascular flow from circulation to interstitium,6 causing (transient) donor hydrops. Thus, the explanation18 that this phenomenon is a consequence of cardiac overload secondary to relative hypervolemia is not supported by our model.

The model-derived pathophysiology is supported by recent clinical reports of amnioreduction therapy.19-21 Among 23 cases treated with serial amnioreduction, alone or in combination with septostomy, 2 recipients presented with hydrops at the beginning of the study; however, 6 additional became hydropic after amnioreduction.19 Notably, these authors identified fetal hypertension from atrioventricular valve regurgitation in at least 10 of the TTTS recipients. We postulate arterial hypertension was exacerbated by the increased arteriovenous transfusion because of amnioreduction, worsening the recipient cardiovascular status. Similar results of recipient cardiovascular deterioration after amnioreduction have been reported by Simpson et al.20 Furthermore, in 54 TTTS pregnancies, Barrea et al21 indicate that despite (total) amnioreduction, the cardiovascular disease persisted and even progressed in many recipient twins, supporting our postulate that amnioreduction (in the presence of hydrops) does not prevent and may even contribute to deterioration of the recipient cardiovascular status. This implies that less aggressive amnioreduction may be the preferred choice in TTTS presenting with a hydropic recipient after fetal viability.

Laser obliteration of placental anastomoses in TTTS terminates fetofetal transfusion of blood volume and blood constituents, resulting in a quick resolution of recipient hydrops when present. This result may explain the higher recipient survival rates after laser therapy plus amnioreduction than amnioreduction alone.22,23 Our simulations suggest that recipient hydrops resolves faster with less aggressive amnioreduction, a
consequence of a smaller reduction in amniotic fluid pressure, causing a smaller increase in the excess maternal fluid flow.

Digoxin administration in TTTS, only applicable with a hydropic recipient, simulated an improved recipient cardiovascular function, causing an improved or reversed recipient hydrops. Although digoxin may be used alone, amnioreduction may be necessary to prolong the pregnancy, by reducing the uterine size and risk of prematurity. Because digoxin reduces the (hydropic) recipient venous pressure, and amnioreduction increases the donor arterial pressure, digoxin plus amnioreduction will strongly increase the arteriovenous fetofetal transfusion. Thus, digoxin and amnioreduction will temporarily improve, but ultimately only delay the deteriorating effects of arteriovenous fetofetal transfusion on donor and recipient twins. Our simulations (case D2) are comparable to a case described by DeLia et al in which recipient hydrops was treated by maternal administration of digoxin at 26 weeks, resulting in 2 live born fetuses at 34 weeks. Digoxin was also given in a case of triplet TTTS. Tricuspid insufficiency and born fetuses at 34 weeks. Digoxin was also given in a case of triplet TTTS. Tricuspid insufficiency and born fetuses at 34 weeks. Digoxin was also given in a case of triplet TTTS.24

In conclusion, mathematical modeling of therapeutic interventions of TTTS with a hydropic recipient twin indicates several results of potentially clinical relevance. Amnioreduction aggravates the hydropic recipient's cardiovascular function but improves that of the donor. Laser ablation of anastomoses is the optimal therapy for severe TTTS with a hydropic recipient in previable twins. After laser therapy, hydrops ceases faster by less, rather than more aggressive amnioreduction. Finally, administration of digoxin, with or without amnioreduction, may be the optimal therapy in TTTS with a hydropic recipient presenting around fetal viability (about 26 weeks) as laser therapy is generally not performed anymore and delivery may have significant complications of prematurity.

Acknowledgment

We kindly acknowledge communications with Dr Julian E. DeLia, Milwaukee, WI, on the fetal use of digoxin.

References

Risk during pregnancy—Self-report versus medical record

Tay K. McNamara, PhD,a E. John Orav, PhD,a,b Louise Wilkins-Haug, MD, PhD,a,c Grace Chang, MD, MPHa,d,*

Brigham and Women’s Hospital,a Departments of Medicine (Biostatistics),b Obstetrics (Gynecology),c and Psychiatry,äd Harvard Medical School, Boston, MA

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KEY WORDS
Prenatal alcohol use
Alcohol consumption
T-ACE questionnaire

Objective: This study was undertaken to compare the frequencies with which physicians and patients report medical and behavioral risk factors during pregnancy, with particular attention to identification of women at risk for prenatal alcohol use.

Study design: The sample included 278 women, drawn from a randomized trial of T-ACE (alcohol screening questionnaire) positive pregnant women receiving obstetric care. Medical records and participants’ self-reports were available for comparison.

Results: Physicians identified only 10.8% of women recognized as at risk for alcohol consumption by the T-ACE screening measure. In contrast, the physicians’ records were more inclusive for medical risk factors than the participant’s self-reports. Physicians were significantly more likely to correctly identify nonwhite participants as being at risk for prenatal alcohol use (odds ratio = 3.59, P = .026), compared with their white counterparts.

Conclusion: Self-report on the T-ACE questionnaire is more effective than medical records in identifying women at risk for prenatal alcohol use.

Physicians often have difficulty identifying problematic alcohol use, despite its prevalence in medical and other settings.1-7 Because the correct identification of problem drinking in women is even more difficult, physicians and other clinicians working in obstetric practices are particularly challenged.8,9 In laboratory models, prenatal alcohol consumption at levels less than 1 drink per day adversely affects fetal growth and development.10,11 Pregnant women reporting amounts greater than 1.3 drinks per week may actually be drinking at levels consistent with risk for birth defects.12 Possible explanations include underreporting, or the possibility that the mean rate of alcohol consumed actually reflects brief, but heavier episodes of drinking that are averaged out over the course of several days or a week.13

However, because past drinking predicts drinking levels during pregnancy,14 researchers have developed a number of screening instruments to facilitate the identification of alcohol use in the general population and among pregnant women.15 These instruments include the Alcohol Use Disorders Identification Test (AUDIT), the T-ACE questionnaire, the TWEAK questionnaire, and the CAGE questionnaire.16 Although each instrument has strengths and weaknesses,17,18 some research...
has found that the relatively short 4-item T-ACE questionnaire outperforms obstetric staff assessment of alcohol use by pregnant women.19

We reviewed the medical records of women, all of whom screened positive for risk of problem drinking on the T-ACE, and compared the frequencies with which physicians and patients reported medical and behavioral risk factors during pregnancy. Because all the women were alcohol-screen positive, we hypothesized that a high percentage of the women would have been correctly identified in their medical records as being at risk for alcohol use.

Methods

This study draws on a sample of pregnant women drawn from a randomized trial of a single session brief intervention. Study staff recruited the participants attending faculty (30%), resident (8%), and nurse midwife practices (4%). The remainder (58%) of the sample were drawn from e-mail recruitment, Web site recruitment, referrals, or other sources. All the women were screened for risk of problem drinking, using the T-ACE.20 The 4 T-ACE questionnaire items are listed in Table I. The T-ACE is positive with a total of 2 or more points. Two points are assigned if a respondent reports more than 2 drinks to the “tolerance” question. An affirmative response to the “annoyed,” “cut-down,” or “eye-opener” questions is given 1 point each. Women were eligible for the study if they scored 2 or higher on the T-ACE, had consumed alcohol while pregnant in the 3 months before study enrollment, reported gestation less than 28 weeks, intended to carry to term, and agreed to the study terms. The results of the brief intervention are discussed in detail elsewhere.21

This study focuses on baseline information documented in participants’ medical records. More than 90% of the study participants had medical records available, resulting in a sample of 278. There were no systematic differences among the participants with regard to medical record availability by practice site or recruitment method. Computerized and hard copy medical records were abstracted by using a structured form developed by the investigators. Approximately 20% of the records were dually reviewed for quality control and 90% of those records agreed.

The women’s self-reported medical problems were collected at both baseline (approximately 3 months into pregnancy) and follow-up (shortly after delivery). Each woman was asked to list all medical, gynecologic, and obstetric problems in an open-ended format. The potential risk factors were abstracted from the list of conditions reported by the subject.

The sociodemographic characteristics of the women in the sample were similar to those of women in the surrounding area. For instance, the median household income for the ZIP code where the subject resided was $55,361, compared with the Massachusetts median household income of $50,502 during the study time period.22 Participants had a mean age of 31.4 years and a median education of 16 years. Most were European American (80%). Although they were pregnant at the time of study enrollment (median 11.5 weeks’ gestation), less than 20% of the women were abstinent. When they drank, they averaged 1.5 drinks per drinking day. Nearly 30% of the women had 2 or more drinks per drinking day while pregnant.

The SAS statistical package was used to analyze the data (version 8.2, SAS Institute, Cary, NC), and the descriptive results are reported as percentages, along with 95% CIs. To test for agreement between physicians and patients, McNemar’s tests were used with a Bonferroni corrected level of alpha for comparisons (P < .002) of 22 risk factors. In addition, logistic regression was used to identify maternal characteristics that predicted greater accuracy in the medical record in capturing the risk of prenatal alcohol use. A composite drinking measure incorporating drinks per drinking day and frequency of drinking days was used as 1 of the covariates in the model. Other risk factors included in the model were background other than European American, median household income, and education in years. The valid sample size for physician reports varied from 218 to 278, depending on the risk factor.

Results

Table II lists the percentage of participants with each type of risk factor, according to the source of information. The participant reports are based on the demographic and maternal medical histories obtained during the baseline interview of the study.

When comparing the participant and physician reports, there was almost no discrepancy regarding risk factors linked to height, age, and weight. Approximately 35% of women were at risk for complicated pregnancies because of these factors. However, these differences were extremely small. The difference between percentages was nonsignificant for all maternal demographic factors.
18.0% of doctors. The difference was significant at sexually transmitted diseases (STDs), compared with pants reported in the interview that they had a history of or endocrine condition. In addition, 2.5% of participants reported having thyroid problems, but their physicians recorded that 13.0% had a thyroid problem. Only 5.4% of participants reported the medical conditions known as risk factors during pregnancy. These included autoimmune problems, neurologic problems, pulmonary disease, and endocrine problems. Only 4.0% of participants reported a history of smoking or tobacco use, but their physicians recorded that 9.9% had a history of smoking or tobacco use.

### Maternal demographic factors

<table>
<thead>
<tr>
<th>Participant</th>
<th>Physician</th>
<th>McNemar's test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age &lt;15 y</td>
<td>23.64 (17.70-29.48)</td>
<td>0.69 (P = .4054)</td>
</tr>
<tr>
<td>Maternal age 15 y or more</td>
<td>21.38 (16.38-26.38)</td>
<td>0.69 (P = .4054)</td>
</tr>
<tr>
<td>Maternal weight &lt;100 lbs</td>
<td>10.90 (9.14-14.94)</td>
<td>3.00 (P = .0833)</td>
</tr>
<tr>
<td>Maternal weight 100 lbs</td>
<td>5.40 (2.56-8.24)</td>
<td>17.00 (P &lt; .001)</td>
</tr>
<tr>
<td>Maternal height &lt;5 ft</td>
<td>1.34 (0.00-3.07)</td>
<td>1.34 (P = .3002)</td>
</tr>
<tr>
<td>Maternal height 5 ft</td>
<td>1.34 (0.99-1.85)</td>
<td>1.34 (P = .3002)</td>
</tr>
<tr>
<td>Maternal medical history</td>
<td>27.64 (22.20-33.08)</td>
<td>65.11 (59.33-70.89)</td>
</tr>
<tr>
<td>Previous preterm delivery</td>
<td>0.72 (0.45-1.89)</td>
<td>9.09 (5.53-12.65)</td>
</tr>
<tr>
<td>STD history</td>
<td>2.52 (0.50-4.54)</td>
<td>17.99 (13.29-22.69)</td>
</tr>
<tr>
<td>Uterine anomalies</td>
<td>8.36 (4.93-11.79)</td>
<td>5.07 (2.31-7.83)</td>
</tr>
<tr>
<td>Unknown/Unspecified</td>
<td>2.60 (0.55-4.65)</td>
<td>3.63 (1.25-6.01)</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>3.24 (0.98-5.50)</td>
<td>1.44 (1.03-18.75)</td>
</tr>
<tr>
<td>Autoimmune problems</td>
<td>2.16 (0.27-4.05)</td>
<td>6.94 (3.32-10.56)</td>
</tr>
<tr>
<td>Neurologic problems</td>
<td>0.36 (0.52-1.24)</td>
<td>4.76 (1.64-7.88)</td>
</tr>
<tr>
<td>Seizures</td>
<td>0.00 (0.00-0.18)</td>
<td>2.75 (0.35-15.15)</td>
</tr>
<tr>
<td>Thyroid/endocrine problems</td>
<td>5.40 (2.56-8.24)</td>
<td>13.00 (8.36-17.64)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3.25 (0.50-4.54)</td>
<td>6.47 (3.40-9.54)</td>
</tr>
<tr>
<td>Unknown or other</td>
<td>2.88 (0.73-5.03)</td>
<td>6.53 (3.45-9.61)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>0.00 (0.00-0.18)</td>
<td>1.85 (0.00-3.88)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.00 (0.00-0.18)</td>
<td>4.04 (1.23-6.85)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>0.36 (0.52-1.24)</td>
<td>5.41 (2.21-8.61)</td>
</tr>
<tr>
<td>Mitral valve relapse</td>
<td>0.36 (0.52-1.24)</td>
<td>5.50 (2.24-8.76)</td>
</tr>
<tr>
<td>Hepatitis/liver disease</td>
<td>0.36 (0.52-1.24)</td>
<td>4.05 (1.23-6.87)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2.16 (0.27-4.05)</td>
<td>9.50 (5.41-13.59)</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.08 (0.31-2.47)</td>
<td>19.28 (13.88-24.68)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.24 (0.98-5.50)</td>
<td>6.36 (2.91-9.81)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>2.88 (0.73-5.03)</td>
<td>3.13 (0.63-5.63)</td>
</tr>
<tr>
<td>Eclampsia/preeclampsia</td>
<td>1.80 (0.06-3.54)</td>
<td>29.50 (23.96-35.04)</td>
</tr>
</tbody>
</table>

### Behavioral factors

<table>
<thead>
<tr>
<th>Participant</th>
<th>Physician</th>
<th>McNemar's test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Street drugs</td>
<td>0.73 (0.45-1.91)</td>
<td>3.48 (0.89-6.07)</td>
</tr>
<tr>
<td>Smoking/tobacco</td>
<td>4.72 (2.05-7.39)</td>
<td>9.96 (5.97-13.95)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>100.00</td>
<td>10.79 (6.67-19.41)</td>
</tr>
</tbody>
</table>

* 95% CIs are given in parentheses.

However, when asked for physical, obstetric, or gynecologic problems, participants consistently underestimated the medical conditions known as risk factors during pregnancy. These included autoimmune problems, neurologic problems, pulmonary disease, and endocrine problems. Only 5.4% of participants reported having thyroid problems, but their physicians recorded that 13.0% had a thyroid or endocrine condition. In addition, 2.5% of participants reported in the interview that they had a history of sexually transmitted diseases (STDs), compared with 18.0% of doctors. The difference was significant at P < .05 for medical history variables, both individually and as a group (P < .0001).

Although all the women in this study were at risk for prenatal alcohol use (T-ACE positive), doctors reported only 10.8% as at risk. The majority of participants (82.2%) whom the physicians did not consider at risk actually consumed alcohol during their pregnancy. This finding was consistent across recruitment sites (Fisher exact test P = .014, P = .80).

As physicians identified fewer than 1 in 5 women at risk for prenatal alcohol consumption, a logistic regression predicting physician recognition was developed, as shown in Table III. The effects of median household income for the ZIP code and education were nonsignificant. Physicians were more likely to correctly identify women at risk for prenatal alcohol consumption if those women were nonwhite (odds ratio [OR] = 3.59, P = .0001).
Table III  Coefficients from a logistic model predicting physician identification as at risk for alcohol consumption

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whether nonwhite</td>
<td>3.593 (1.164-11.090)</td>
<td>4.955</td>
<td>.026</td>
</tr>
<tr>
<td>Median household income for ZIP code</td>
<td>17.567 (0.672-459.161)</td>
<td>2.961</td>
<td>.085</td>
</tr>
<tr>
<td>Composite prepregnancy drinking measure</td>
<td>1.005 (0.995-1.015)</td>
<td>1.300</td>
<td>.254</td>
</tr>
<tr>
<td>Education (y)</td>
<td>1.110 (0.903-1.363)</td>
<td>0.981</td>
<td>.322</td>
</tr>
</tbody>
</table>

Comment

The main findings of this study, which compare self-report of medical and behavioral risk factors during pregnancy with those documented in the medical record, are that clinicians and their patients have different perspectives with respect to risk. Whereas clinicians documented substantially higher rates of medical risk factors than the patients did, these same clinicians identified only 10.8% of their patients as being at risk for alcohol use. In contrast, all the participating patients were alcohol-screen positive, and 82.2% of those who the physicians did not consider at risk actually consumed alcohol during their pregnancy.

Explanations for the discrepancy between the reported rates of medical risk factors include the possibility that the women simply did not report them, because either they were unaware of the significance of certain aspects of their medical history, or they chose not to do so during the study interview. The participants may also only have reported medical risk factors they believed to be most relevant to their pregnancy. More medical risk factors may have been reported if the participants were given a self-administered “review of systems.” The obstetric clinicians may have been particularly thorough in their documentation of medical risk factors.

Perhaps the most striking difference between the self-report and medical record involves risk for alcohol use. All participants were T-ACE alcohol-screen positive, and less than 20% were abstinent while pregnant. Possible explanations include reluctance by the participants to disclose their alcohol use to their obstetric clinicians, or that they modified their consumption on receiving obstetric care. Perhaps the participants were more willing to disclose their drinking in a research setting, where more detailed information was obtained but would be kept confidential. Some obstetric clinicians may also have been reluctant to document alcohol use and may have noted only particularly heavy drinkers.

Potential limitations to the study include the fact that all participants completed the alcohol screen, but did not complete a comparable instrument for medical problems, as already noted. Indeed, they may have reported their most salient medical concerns. A positive T-ACE is not necessarily synonymous with severe drinking problems that may have been otherwise identified and documented by clinicians, who did note that 10.8% of their patients were at risk. On the other hand, a real strength of the study was the availability of medical records from diverse obstetric practices within the study hospital and elsewhere, so that it seems less likely that difficulties in identifying risk drinking were unique to 1 particular setting.

Alcohol use by pregnant women is difficult to determine, no matter how conscientious the clinician. Partly because of possible underreporting and partly because of lack of knowledge about the effects of even modest amounts of alcohol consumption, it seems that pregnant women seldom volunteer the type of information needed to identify potential risk drinkers. Of note, physicians were less likely to document that white women were at risk for prenatal drinking, even controlling for income, education, and prepregnancy alcohol use (P = .026). Indeed, pregnant women who drink come from all walks of life, and those who are older (35 years or more), non-Hispanic, well-educated (with more than a high school education), and employed have been found in large surveillance studies to be the most likely to drink prenatally.23 The clinicians reported higher rates of illicit drug use (P = .01) and more cigarette smoking (P = .5) than the participants. Future research should include evaluations of the accuracy of clinician reports of these other behavioral risks and the development of appropriate screening instruments, if indicated. As alcohol is more commonly used than illicit drugs during pregnancy, it may be most efficient presently to screen all pregnant women with an instrument such as the T-ACE, which effectively identifies lifetime alcohol use disorders and not just current drinking, to ensure the best possible birth outcome.

References

Electrical inhibition of preterm birth: Inhibition of uterine contractility in the rabbit and pup births in the rat

Jeffrey Karsdon, MD,a,* Robert E. Garfield, PhD,b Shao-Qing Shi, MD,b William Maner, BS,b George Saade, MDb

Neonatology Department, New York Downtown Hospital, New York, NYa; Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, TXb

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KEY WORDS
Preterm birth prevention
Tocolysis
Uterine contraction
Rabbit
Rat

Objective: The purpose of this study was to inhibit uterine contractility during parturition with an electrical current, which is called electrical inhibition, in the rabbit and the rat.

Study design: We studied the electrical inhibition of in vitro spontaneously contracting preterm or term gestational rat myometrium tissue and in vivo spontaneously contracting uterus either directly in the rabbit and rat or transvaginally in the rat. Values for myometrial tension, intrauterine pressure, pup birth intervals, and electromyographic activity before and after electrical inhibition were compared.

Results: Electrical inhibition decreased rat in vitro myometrial tension by 50%, decreased in vivo rabbit intrauterine pressure by 48%, decreased in vivo rat intrauterine pressure by 80%, and increased birth intervals (latency) by factors of 50 (direct electrical inhibition) and 20 (transvaginal electrical inhibition). All electromyographic activity parameters were reduced significantly.

Conclusion: Electrical inhibition of the uterus is possible. Electrical inhibition is rapid and localized; the duration can be prolonged, and the reversibility is spontaneous. Electrical inhibition may be a new method of tocolysis in the human.

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Preterm birth prevention is still an elusive quest of modern medicine. Currently, pharmaceuticals are the main methods that are used to inhibit uterine contractions (tocolysis). However, some studies show no long-term effect1 or show single drug therapy failure rates of 20% to 40%.2,3

The most common tocolytic agents (ie, beta-adrenergics [eg, ritodrine, prostaglandin synthesis inhibitors (eg, indomethacin, magnesium sulfate, and calcium channel blockers)]) are used systemically with side-effects in the baby too.4

Interestingly, these drugs also affect cardiac contractions. The uterus at term becomes myogenic like the heart. The uterus will contract spontaneously without neuronal control and form gap junctions that interconnect the cells just like the syncytium of the heart.5,6 Both are excitable tissues with similar current flows.7

It is well known that an electrical current can modulate cardiac activity by decreasing contractions (eg, overdrive pacing).8-10
On the basis of these physiologic similarities to the heart, we hypothesized that the uterus at or near term will respond selectively, with minimal side-effects, to an injected electrical current, which is called electrical inhibition (EI).

Material and methods

In vitro studies of rat myometrium

Timed-pregnant Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were killed on gestational day 21 or 22 (full term, 21-22 days). Longitudinal uterine strips (1 cm × 3-4 mm) from 7 rats were placed in a tissue perfusion chamber and mounted approximately 1 mm away from an array of 8 stainless steel electrodes in 10-mL organ chambers filled with Kreb's buffer (37°C; pH ≈7.4) aerated with 5% carbon dioxide in air.

Isometric uterine tensions were recorded online with a computer and data analysis software (WinDaq; Dataq Instruments, Inc, Akron, OH) that calculated the area under the curve (AUC). The electrodes carried a 1- to 6-mA current at 28 msec/pulse, 30 Hz; these parameters were chosen empirically. When the uterine tensions obtained baseline levels, the EI current was turned on for 5 seconds at the different amperages, and the contractions were recorded. AUC was analyzed for the effect of EI at different amperages with the Kruskal-Wallis 1-way analysis of variance on ranks.

In vivo: Rabbit

Fourteen pregnant New Zealand white rabbits (Harlan, Indianapolis, IN) were prepared surgically, as previously described, on days 24 to 26 of gestation (full term, 31-32 days). Sedation and anesthesia was maintained through an ear vein with intermittent intravenous boluses of 0.3 to 0.5 mL of a mixture of ketamine (Ketalar), 30 mg/kg and xylazine (Gemini), 5 mg/kg with spontaneous respirations that were sustained throughout the procedures. Laparotomy was performed, and the ovaries were isolated and removed. Then an incision was made in the ovarian end of each uterine horn, and a balloon-tipped saline-filled polyvinyl catheter (0.03-inch inner diameter; to measure intrauterine pressure (IUP), was passed through the extraperitoneal space from the tubouterine junction to the middle of the uterine horn. This was fixed in place with a purse-string suture. The abdomen was closed, and the catheters were tunneled subcutaneously to exit the neck and stored in an animal vest. After the operation, the rabbits were housed in individual cages and provided commercial feed and water ad libitum.

Daily, the surgical site was examined; the catheters were connected to pressure transducers (model P23ID; Gould, Oxnard, CA), and the IUPs were recorded on a multichannel polygraph to determine whether parturition had begun.

Twenty-four to 48 hours after surgical ovariectomy and a mean gestational age of 30.3 ± 1.6 days (range, 27-32 days), spontaneous uterine contractions that were associated with parturition were monitored. Anesthesia was again started, and the sutures were opened until the uteri were visualized again. A linear array of 8 thin insulated stainless steel electrodes were sutured to the myometrium along the length of 1 uterus, with the central electrodes lying over the balloon catheter tip. The uteri were replaced into the abdominal cavity; the abdominal muscles were clamped closed, and the incision site was covered with a plastic sheet and heating pad to avoid water and heat loss.

After recovering from the suturing of electrodes (study horn), spontaneous uterine contractions returned and were comparable to the uterus without electrodes (control horn). The electrode array was connected to a specially constructed constant current generator. After the control values were recorded, the study horn was exposed intermittently for 10 seconds to 3 minutes at a time to an electrical current of square wave pulses that were chosen empirically (3 mA root-mean-square, which was determined by the formula: current [milliamperes] × duty cycle × 0.707, where the duty cycle equals the pulse width [milliseconds]/[1/frequency (hertz) × 1000]; 40 msec/pulse, 10 Hz), and the uterine response was recorded. At the end of the study, the animal was killed, according to the guidelines of the Animal Care and Use Committee of the California Pacific Medical Center, San Francisco, CA.

Data analysis

EI was analyzed for each animal because the studies had different IUP calibrations; the IUP is expressed in relative values (ie, percent) or AUC rather than absolute values (ie, millimeters of Mercury or centimeters of water). The IUP recordings were evaluated by hand with the use of 2 different methods and were expressed in the following manner:

1) Percent peak IUP (IUP%)
   (a) Control IUP%: The IUP maximal peak was determined before EI was initiated; this was the control 100% value that was compared with other control IUP peaks and averaged for each rabbit.
   (b) EI IUP%: After EI was initiated, the IUP peaks were again determined, averaged, and calculated as a percent of the control IUP% by the following formula: EI IUP% = measured EI IUP%/control IUP% × 100.
   (c) Difference IUP%: For each study, the difference between the 2 values, control IUP% and EI IUP%, was calculated and expressed as difference IUP% by the following formula: Difference
IUP% = ([EI IUP% – control IUP%]/control IUP%) × 100.

(2) Planimetric AUC measurement as function of the contraction time (AUCt).

The IUP recordings on chart paper were traced by hand with a digitalizing pad, and the AUC was determined with a planimetric software program written in BASIC and run on a personal computer. The AUCt was the AUC divided by time. Time was from the beginning to end of contraction(s), without or with EI. If 1 IUP curve was analyzed, then AUCt represents the duration of the 1 contraction; but if EI was applied for 3 minutes, then the control also was for 3 minutes with a variable number of contractions.

**In vivo: Rat**

**Direct EI**

Five groups of adult timed pregnant Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were used; all procedures were approved by the Animal Care and Use Committee of the University of Texas Medical Branch.

The first group of 16 rats served as controls. The remaining groups, on day 18 of gestation, underwent laparotomy with anesthesia/sedation with a 5.0-mL:1.6-mL mixture of ketamine:xylazine that was given intraperitoneally 0.1 mL/100 g weight.

All surgical procedures were performed under sterile conditions. A telemetric transmitter (Data Quest IV System; Data Sciences Inc, Saint Paul, MN) was placed...
in the peritoneal cavity. A gel-filled catheter that was connected to the transmitter for recording IUP was introduced into the lumen of the uterus approximately midway between the ovarian and cervical ends of one of the uterine horns and was fixed there with a purse-string suture. A pair of electrodes for recording electromyographic activity was sutured to the uterine wall overlying the catheter tip. The main transmitter was secured to the peritoneum with 2 nonabsorbable sutures, and the abdominal cavity was closed.

An array of 5 electrodes was made of Teflon-insulated multistranded stainless steel wire (A-M Systems, Everett, WA). The portion of the wire electrode that was sutured to the myometrium was stripped of the Teflon to provide a good contact and implanted along the length of the uterus, directly overlying the IUP catheter. All wire electrodes were passed subcutaneously to the back of the neck and fixed there.

The rats were assigned randomly, with a randomization table, to either the treated group that received an electrical current (EI Direct and EI Vaginal) or to the sham-operated group that did not (Sham Direct and Sham Vaginal).

A second group of 12 rats were sham study rats (Sham Direct), and a third group of 5 rats were EI study rats (EI Direct).

After the laparotomy, the animals were housed individually in cages that were placed on receivers that acquired the radiofrequency signals that were sent by the intraperitoneal transmitter. The signals were collected online with a data acquisition system (Data Science Inc) that was connected to an amplifier (MacLab; AD Instruments, Castle Hill, Australia). All signals were recorded, stored, and computer-analyzed with the use of data analysis software (Chart version 4.0.1; AD Instruments). This software also allowed for a negative “feed-back” loop to turn on intermittently the EI current for 10 seconds when the IUP reached a predetermined value and then turn off the EI current when the IUP was below this predetermined value. The electromyographic acquisition rate was 200 Hz, and the nominal bandwidth was 0.3 to 50 Hz.

On days 21 and 22, the rats started to give birth. After the birth of the first pup, intermittent EI was given for 2 to 10 seconds through the electrodes and consisted of constant current square wave pulses that had been chosen empirically at 1 to 10 mA (approximately 2 mA root-mean-square), 28 msec/pulse, 30 Hz.

After the birth of the first pup, the birth interval (BI) was determined as the time in minutes between subsequent pup births (latency).

The study was ended 12 to 24 hours after the birth of the first pup; each rat was killed, and the total number of pups, both unborn and born, were compared with the total number of pups that were born for the percentage of pups that were born per rat (%B).

**Transvaginal EI**

The transvaginal EI study rats were prepared surgically as described earlier with the placement of the intraperitoneal transmitter but without the electrodes directly on the uterus. Instead, 12 to 24 hours before birth, a 5F 4-ring electrode catheter (EP Technologies, Inc, San Jose, CA) was placed into the vaginal canal with the tip in the posterior fornix and fixed in place by suturing the catheter to the vaginal wall.

The fourth group of 3 rats served as sham control rats (Sham Vaginal); the fifth group of 8 rats were the transvaginal study rats (EI Vaginal).

On days 21 and 22, the rats started to give birth. After the birth of the first pup, EI was given intermittently to the transvaginal study rats through the distal 2 electrodes of the vaginal catheter with the use of the same EI parameters as described earlier. The transvaginal BI and %B was determined as for the direct EI.

**Statistical analysis**

**In vitro: Rat**

The recorded contraction responses were analyzed for AUC and compared the pre- and post-EI values. Mean values were evaluated with a computer-based program on a personal computer. The pre- and post-EI values were compared with the use of 1-way analysis of

---

**Table I**  
EI effect on IUP% in the 14 rabbits during preterm birth

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 160)</th>
<th>EI (n = 160)</th>
<th>Difference IUP% (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control IUP%</td>
<td>46.0 ± 20.6</td>
<td>46.0 ± 20.6</td>
<td>−48.0 ± 20.8</td>
</tr>
<tr>
<td>(5.7-91.8)</td>
<td>(5.7-91.8)</td>
<td>(−5.8 to −91.4)*</td>
<td></td>
</tr>
</tbody>
</table>

Data are given as mean ± SD (minimum-maximum).

* Paired Student t test, P < .05.

---

**Table II**  
EI effect on AUCt in the 14 rabbits during preterm birth

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 160)</th>
<th>EI (n = 160)</th>
<th>Difference AUCt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min/IUP)</td>
<td>0.89 ± 0.74</td>
<td>0.88 ± 0.73</td>
<td>(4.08-0.22)</td>
</tr>
<tr>
<td>IUP (mm)</td>
<td>33.0 ± 15.0</td>
<td>17.6 ± 12.9</td>
<td>(6.3-9.66)</td>
</tr>
<tr>
<td>AUC (mm²)</td>
<td>8.9 ± 6.1</td>
<td>5.8 ± 9.7</td>
<td>(1.0-6.58)</td>
</tr>
<tr>
<td>AUCt (mm²/min)</td>
<td>13.3 ± 3.2</td>
<td>7.7 ± 2.8</td>
<td>(0.9-6.59)</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD (minimum-maximum). Total time was 143.72 minutes for the control group and 141.04 minutes for the EI group.

* Paired Student t test, P > .05 (not significant).

---

In the peritoneal cavity. A gel-filled catheter that was connected to the transmitter for recording IUP was introduced into the lumen of the uterus approximately midway between the ovarian and cervical ends of one of the uterine horns and was fixed there with a purse-string suture. A pair of electrodes for recording electromyographic activity was sutured to the uterine wall overlying the catheter tip. The main transmitter was secured to the peritoneum with 2 nonabsorbable sutures, and the abdominal cavity was closed.

An array of 5 electrodes was made of Teflon-insulated multistranded stainless steel wire (A-M Systems, Everett, WA). The portion of the wire electrode that was sutured to the myometrium was stripped of the Teflon to provide a good contact and implanted along the length of the uterus, directly overlying the IUP catheter. All wire electrodes were passed subcutaneously to the back of the neck and fixed there.

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On days 21 and 22, the rats started to give birth. After the birth of the first pup, intermittent EI was given for 2 to 10 seconds through the electrodes and consisted of constant current square wave pulses that had been chosen empirically at 1 to 10 mA (approximately 2 mA root-mean-square), 28 msec/pulse, 30 Hz.

After the birth of the first pup, the birth interval (BI) was determined as the time in minutes between subsequent pup births (latency).

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The transvaginal EI study rats were prepared surgically as described earlier with the placement of the intraperitoneal transmitter but without the electrodes directly on the uterus. Instead, 12 to 24 hours before birth, a 5F 4-ring electrode catheter (EP Technologies, Inc, San Jose, CA) was placed into the vaginal canal with the tip in the posterior fornix and fixed in place by suturing the catheter to the vaginal wall.

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On days 21 and 22, the rats started to give birth. After the birth of the first pup, EI was given intermittently to the transvaginal study rats through the distal 2 electrodes of the vaginal catheter with the use of the same EI parameters as described earlier. The transvaginal BI and %B was determined as for the direct EI.

**Statistical analysis**

**In vitro: Rat**

The recorded contraction responses were analyzed for AUC and compared the pre- and post-EI values. Mean values were evaluated with a computer-based program on a personal computer. The pre- and post-EI values were compared with the use of 1-way analysis of
variance with the Tukey test of multiple comparison procedures; a probability value of <.05 was considered statistically significant.

**In vivo: Rabbit**
The results for all animals were pooled (n = 160), and a single mean value was determined. All data were reported as mean ± SD, with minimum and maximum values. Mean values were evaluated with a computer-based program on a personal computer. The unpaired Student t test (2-tailed) compared the pre- and post-EI values; a probability value of <.05 was considered statistically significant.

**In Vivo: Rat**
After the first pup was born, the control group non-instrumented rats (controls) was compared with the different treatment groups: sham-instrumented, non–EI-treated...
rats (ShamDirect), instrumented, EI-treated study rats (EIDirect), sham-instrumented, non-EI, vaginally treated rats (ShamVaginal), and instrumented, EI, vaginally treated rats (EIVaginal). The data for all animals in each group were pooled, and a single mean value was determined. All data were reported as mean ± SD. Mean values were statistically evaluated with a computer-based program on a personal computer. The Dunnett’s test compared the controls to the treatment groups: a probability value of \( P < .05 \) was considered statistically significant.

**Results**

All studies, both in vitro and in vivo, showed a similar response to EI. Shortly after the start of EI, there was a rapid decrease in uterine contractility. The contractility remained inhibited for a prolonged amount of time and then returned spontaneously to control values.

**In vitro rat myometrium**

EI of spontaneously contracting rat myometrium started within 10 seconds, decreased significantly, and remained inhibited for 30 minutes then the contractions started again spontaneously (Figure 1, A). The myometrium responded to the EI in a dose-dependant manner (Figure 1, B).

**In vivo rabbit**

The EI effect was only on the study horn, although the control horn contractions were unaffected (Figure 1, C). During EI, the mean peak IUP value was 48% of pre-EI control values (Table I).

**Table III** Results of EI on the births of pups in the in vivo rat

<table>
<thead>
<tr>
<th>Group</th>
<th>Pups (n)</th>
<th>BI (min)</th>
<th>Pups (n)</th>
<th>B%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 16)</td>
<td>141</td>
<td>6.5 ± 0.3*</td>
<td>141</td>
<td>100 ± 0*</td>
</tr>
<tr>
<td>ShamDirect (n = 12)</td>
<td>35</td>
<td>17.5 ± 2.2*</td>
<td>90</td>
<td>89.2 ± 4.75*</td>
</tr>
<tr>
<td>EIDirect (n = 5)</td>
<td>17</td>
<td>357.1 ± 150.3</td>
<td>42</td>
<td>53.4 ± 14.8*</td>
</tr>
<tr>
<td>ShamVaginal (n = 3)</td>
<td>19</td>
<td>17.2 ± 8.3*</td>
<td>26</td>
<td>100 ± 0*</td>
</tr>
<tr>
<td>EIVaginal (n = 8)</td>
<td>36</td>
<td>125.2 ± 43.9</td>
<td>59</td>
<td>44.6 ± 16.5*</td>
</tr>
</tbody>
</table>

* Dunnett’s test, \( P < .05 \).
† Dunnett’s test, \( P < .05 \).

AUCt (Table II) decreased almost 50%. The time of contraction (minutes per IUP) was not affected by EI; the principal reason for the decrease in the AUCt was the significantly reduced peak IUP.

These studies showed that EI reversibly can inhibit in vivo uterine contractions in a localized manner.

**In vivo rat**

The initial direct EI studies recorded only IUP without electromyographic activity (Figure 1, D) and showed a significant EI effect on the IUP.

When the IUP and electromyography are observed together (Figure 2, A), there is a significant EI effect on both the IUP and the electromyography. Of note, there is some electromyographic activity, but with very weak contractions, before it reaches the control values in a step-wise manner. With the transvaginal electrodes with the feed-back loop, this EI effect was able to be maintained for 12 hours (Figure 2, B).

Analysis of the electromyographic activity revealed significant differences. In the pre-EI “burst” of electromyographic activity, there is strong electrical activity (Figure 2, C); however, after EI, the electrical activity is weak (Figure 2, D). Spectral analysis of the electromyographic activity (Figure 3) reveals a decrease in all of the electromyographic burst parameters after EI. The electromyographic currents are smaller than the EI currents that were used in these studies by a factor of 75 to 100.

During EI, the BI was increased, and the %B was decreased (Table III). The sham surgery affected both of these values but not significantly, as did the EI when used either directly on the uterus or transvaginally.

**Comment**

This study supports the hypothesis that a weak electrical current can inhibit preterm and term uterine contractions;
EI was effective with a rapid onset and rapid reversal. This is the first time, to our knowledge, that an electrical current has inhibited in vivo uterine contractions consistently and repeatedly.

In vivo rabbit studies showed that EI produced a localized inhibition of preterm and term uterine contractions (decreased IUP) within 10 seconds and remained for a prolonged amount of time and that contractions would return spontaneously to normal levels. EI was localized to only the desired horn with no obvious systemic effects. The use of the control horn suggests that the EI effect is not based on a systemic mediator such as a hormone or neurotransmitter that would enter the systemic circulation.

The in vivo rat studies confirmed that EI not only prevents the mechanical contractions that result in increased BI and decreased %B but also inhibits the electromyographic activity of the uterus, which is the fundamental mechanism of the birth process, the final common pathway.

Various substances are alleged to be electrically induced smooth muscle relaxants. These include the nerve-ending release of neurotransmitters (eg, low-dose norepinephrine)\(^{13,14}\) and vasoactive intestinal polypeptide\(^{15,16}\) or the interstitial formation of free radicals.\(^{17}\) A neurogenic or a direct involvement of the nerves in the uterus wall also has been suggested.\(^{18}\) However, towards term, the nerves in the uterus degenerate.\(^{19}\)

Other possible mechanisms of EI may be hyperpolarization of the cell membrane or possibly affecting the ion (calcium) membrane channels.

The mechanism of EI remains uncertain at this time. Despite this, these studies show that spontaneous uterine contractions can be inhibited locally and reversibly by EI in the preterm and term pregnant rabbit and rat. Previous unpublished studies with EI of in vitro human myometrium showed results that were similar to the non-human in vitro and in vivo studies (Figure 4). Whether EI will be as effective in the human in the prevention of preterm birth remains to be seen.

**Acknowledgments**

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**References**

Increasing prepregnancy body mass index: Analysis of trends and contributing variables

John Yeh, MD,* James A. Shelton, MS

Department of Gynecology-Obstetrics, University at Buffalo, State University of New York, Buffalo, NY

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Objective: In the United States, obesity has increased steadily. As obesity in pregnancy is a high-risk obstetric situation, important questions are whether there has been a trend toward higher prepregnancy body mass indexes (BMIs) in women who have become pregnant and if there are subgroups at risk. The objective of this study was to analyze the shifts, if any, in the prepregnancy BMIs in women who delivered.

Study design: Analysis of the birth certificate data collected in a regional perinatal data system of all live born deliveries (79,022 cases) occurring in a contiguous 8-county area in upstate New York from 1999 to 2003.

Results: From 1999 to 2003, there was an overall increase in the mean prepregnancy BMI of the total delivery population ($P < .01$). There was a relative 11% increase in the Institute of Medicine (IOM) overweight ($P < .01$) and a relative 8% increase in the obese ($P < .01$) categories. There was an increase in the numbers of women in the IOM overweight or obese categories in these subgroups ($P < .05$): age (all subgroups), ethnicity (white and black), education (all subgroups), insurance type (all subgroups), previous live births (all subgroups), urbanization status (all subgroups), median family income of ZIP code area (all subgroups), and smoking (both smokers and nonsmokers).

Conclusion: There was a significant increase toward higher prepregnancy BMIs across multiple subgroups. Our study demonstrates that increased prepregnancy BMI is an issue that spans almost the entire spectrum of subgroups of patients who delivered.

KEY WORDS
Prepregnancy
Body mass index
Obesity

In the United States, there has been a consistent increase in the proportion of the population who are obese. In reports by Mokdad et al., using data from the Behavioral Risk Factor Surveillance System (BRFSS), the authors found that the self-reported incidence of obesity (body mass index [BMI] \( \geq 30 \)) for women increased from 12.2% in 1991 to 20.8% in 2001. This increase in obesity is of importance to the obstetrician because obesity in a pregnant patient can be a high-risk obstetric situation. Potential obstetric complications from obesity include increased risks of gestational diabetes, pregnancy-related hypertension, preeclampsia, neonatal death, and labor complications including cesarean section.
In a report by the Institute of Medicine (IOM) examining weight gain and nutritional status in pregnancy, the IOM divided BMI into 4 categories using IOM criteria: underweight (BMI < 19.8), normal weight (BMI 19.8-26), overweight (BMI 26.1-29), and obese (BMI > 29). It was concluded that prepregnancy weight for height (BMI) is an anthropometric measurement with documented clinical value.11 Thus, prepregnancy BMIs are considered to have use in the care of obstetric patients and would be relevant to monitor. The objective of this study was to define the changes in the prevalence of women in the different prepregnancy IOM BMI categories in the last 5 years. In addition, we sought to determine which subgroup of patients had changes toward the higher IOM prepregnancy weight categories. To investigate this, we took a population-based approach for upstate New York and analyzed the trends in BMIs of women who delivered. The specific questions addressed in this study are as follows: Was there a change in the prepregnancy BMI of pregnant women over time? What was the shift in the pattern like? Which categories of patients were involved in this shift? With the results obtained in this investigation, we hoped to be able to better define what has occurred in patients who became pregnant in the last 5 years and anticipate potential changes that might occur in the future.

**Methods**

Our initial study population consisted of 84,781 women delivering live births in the contiguous 8 western counties of New York between January 1999 and December 2003. These subjects did not include women who miscarried or terminated their pregnancies. It did include all births, singletons and multiple gestations, as this study’s focus was prepregnancy BMIs and the temporal trends of the BMIs. The data for the deliveries were obtained from the Western New York Perinatal Data System (PDS). The PDS is the regionalized perinatal data system built from the New York Electronic Birth Certificate and contains information on more than 200 demographic, obstetric, medical, and outcome data items. The system accumulates data from each delivery occurring in the 17 hospitals with obstetric services in the region. This study received the approval of the University at Buffalo’s Institutional Review Board before initiation of the study.

BMI was calculated as weight (kg) per height (m^2) and was obtained from maternal height and prepregnancy weight collected in the perinatal data system. BMIs were grouped into 4 categories using IOM criteria:11 underweight (BMI < 19.8), normal weight (BMI 19.8-26), overweight (BMI 26.1-29), and obese (BMI > 29). In addition, information was obtained on variables including information on demographics (maternal age, race, education level, type of insurance, area of residence, and family income) and personal traits (previous live births and smoking). Area of residence included urban area (large urban), urban cluster (small urban), and rural and was determined by matching maternal ZIP code with US 2000 Census Summary File 1. Family income was approximated using maternal zip code and US 2000 Census data, and the 4 categories represent the 4 quartiles of family income.

**Table I** Demographics of patients studied

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>79,022</td>
<td>100.0%</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>7,841</td>
<td>9.9%</td>
</tr>
<tr>
<td>20-34</td>
<td>59,604</td>
<td>75.4%</td>
</tr>
<tr>
<td>≥35</td>
<td>11,577</td>
<td>14.7%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>63,819</td>
<td>80.8%</td>
</tr>
<tr>
<td>Black</td>
<td>9,337</td>
<td>11.8%</td>
</tr>
<tr>
<td>Other</td>
<td>3,048</td>
<td>3.9%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2,818</td>
<td>3.6%</td>
</tr>
<tr>
<td>Education</td>
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</tr>
<tr>
<td>&lt;High school</td>
<td>11,845</td>
<td>15.0%</td>
</tr>
<tr>
<td>High school</td>
<td>23,827</td>
<td>30.2%</td>
</tr>
<tr>
<td>&gt; High school</td>
<td>43,350</td>
<td>54.9%</td>
</tr>
<tr>
<td>Insurance</td>
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<tr>
<td>Medicaid</td>
<td>24,195</td>
<td>30.6%</td>
</tr>
<tr>
<td>HMO</td>
<td>46,473</td>
<td>58.8%</td>
</tr>
<tr>
<td>Private, other</td>
<td>7,338</td>
<td>9.3%</td>
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<tr>
<td>No insurance</td>
<td>1,016</td>
<td>1.3%</td>
</tr>
<tr>
<td>Previous live births</td>
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<tr>
<td>0</td>
<td>31,076</td>
<td>39.3%</td>
</tr>
<tr>
<td>1</td>
<td>26,589</td>
<td>33.6%</td>
</tr>
<tr>
<td>2</td>
<td>13,335</td>
<td>16.9%</td>
</tr>
<tr>
<td>3</td>
<td>4,928</td>
<td>6.2%</td>
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<td>≥4</td>
<td>3,094</td>
<td>3.9%</td>
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<tr>
<td>Urbanization (by ZIP code)</td>
<td></td>
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</tr>
<tr>
<td>Large urban</td>
<td>50,474</td>
<td>63.9%</td>
</tr>
<tr>
<td>Small urban</td>
<td>14,298</td>
<td>18.1%</td>
</tr>
<tr>
<td>Rural</td>
<td>14,250</td>
<td>18.0%</td>
</tr>
<tr>
<td>Median family income (by ZIP code)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;29,325</td>
<td>20,536</td>
<td>26.0%</td>
</tr>
<tr>
<td>29,325-38,097</td>
<td>18,925</td>
<td>23.9%</td>
</tr>
<tr>
<td>39,098-44,103</td>
<td>19,760</td>
<td>25.0%</td>
</tr>
<tr>
<td>44,104+</td>
<td>19,801</td>
<td>25.1%</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>63,398</td>
<td>80.2%</td>
</tr>
<tr>
<td>Smoker</td>
<td>15,624</td>
<td>19.8%</td>
</tr>
</tbody>
</table>

* Family income was approximated using maternal zip code and US 2000 Census data, and the 4 categories represent the 4 quartiles of family income.
Linear tests for trends were conducted on the mean BMI by year using SPSS ONEWAY command to test first-degree polynomial trend components. Trends in each of the 4 IOM BMI categories were tested with the use of SPSS CROSSTAB command’s linear by linear association test (Mantel-Haenszel trend test). In addition, tests for trends were conducted for the IOM BMI categories after controlling for the variables studied. The data were analyzed with SPSS version 11.1 (Chicago, IL). P < .05 was considered statistically significant.

Results

A total of 79,022 patients who delivered in the 5-year period between 1999 and 2003 were studied (Table I). Generally, the patients were between the ages of 20 and 34 (75.4%), white (80.8%), had more than a high school education (54.9%), had HMOs as their insurance (58.8%), did not have a previous live birth (39.3%), lived in urban areas (63.9%), and were nonsmokers (80.2%).

Table II shows the changes in the BMI by year. In 1999, the mean BMI was 25.71 and the BMI increased to 26.17 in 2003 (P < .01). This shift was the result of a decrease in the proportion of women in the IOM underweight and normal weight categories (14% and 3% relative declines, respectively) and a concurrent increase in the proportion of women in the overweight and obese categories (11% and 8% relative increases, respectively). The trend in each of the 4 categories was statistically significant (P < .01). Cumulatively, 40.5% of all patients had prepregnancy BMIs in the IOM overweight and obese categories in 2003, compared with the 37.1% rate of patients in these weight categories in 1999. This represented a relative 9.2% increase over the 5 years of the study.

In Table III, the IOM overweight and obese prepregnancy BMI trend data were stratified as subgroups. In the period studied, the proportion of IOM underweight and normal weight women declined in almost all subgroups (data not shown). When women in the overweight and obese categories were combined, a statistically significant increase was found in all but 2 subgroups during the 5-year period studied. The only 2 exceptions, the ethnic status of “other” and “Hispanic,” also had an increased in the proportion of women in the groups, but this did not reach statistical significance. Thus, the increased proportion of patients in the IOM overweight and obese prepregnancy weight categories was found in almost all subgroups of women studied.

Comment

In this report, we presented the temporal changes of prepregnancy BMIs in a population-based cohort of pregnant women who delivered a live birth. Our study showed that there was an increase in the prepregnancy BMI of pregnant women over time and that this shift resulted in changes to all 4 of the IOM prepregnancy weight categories in the 5-year period. The shift to overweight and obese IOM categories was found across almost all subgroups and confirmed that this health issue was not limited to only specific fractions of our patient population.

Our findings were similar to those reported by others, who analyzed restricted patient populations. Schievel et al12 studied women attending Women, Infants, and...
Children (WIC) clinics in 5 states from 1990 to 1996. This study also showed the change of decreased patient percentage in the low BMI category and an increase in percentage of patients in the high BMI category. Though the subjects were from defined socioeconomic groups and attended special clinics, their findings are in agreement with ours pertaining to a decline in the percentage of patients in the lowest prepregnancy BMI group and an increase in the percentage of patients in the upper 2 prepregnancy BMI groups. Lu et al\textsuperscript{13} examined changes in proportion of women who had BMIs greater than 29 at the first prenatal visit. They studied the 20-year trend of the patients in 9 clinics within a single county in Alabama and found that in 1980, 16.3\% of patients had BMIs greater than 29 and this percentage increased steadily to 36.4\% in 1999. Thus, they demonstrated that there was a doubling of the patients with BMIs greater than 29 over a 20-year period. Our data adds to the literature because our study was able to allow us to make conclusions about temporal BMI increases in specific subgroups of patients.

There are at least 3 papers in which analyses have been performed regarding the distribution of patients by prepregnancy BMI. In the studies by Kaiser and Kirby,\textsuperscript{14} Siega-Riz et al,\textsuperscript{15} and Cogswell et al,\textsuperscript{16} all 3 are consistent with the overall distribution of the BMIs

<table>
<thead>
<tr>
<th>Table III</th>
<th>Subgroup analysis of trends in IOM overweight and obese women (prepregnancy BMI &gt;26), 1999 to 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>23.7% 29.6% 5.9% 24.7% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>20-34</td>
<td>38.4% 41.4% 3.0% 7.9% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>35+</td>
<td>40.1% 42.5% 2.3% 5.8% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>35.8% 39.1% 3.3% 9.2% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Black</td>
<td>46.6% 51.0% 4.4% 9.5% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Other</td>
<td>31.0% 35.3% 4.2% 13.7% P = .16</td>
</tr>
<tr>
<td>Hispanic</td>
<td>39.3% 41.9% 2.7% 6.8% P = .62</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>33.0% 37.9% 4.9% 14.9% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>High school</td>
<td>40.5% 44.7% 4.1% 10.2% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>&gt; High school</td>
<td>36.2% 39.0% 2.8% 7.9% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>40.3% 43.6% 3.3% 8.3% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>HMO</td>
<td>35.9% 38.9% 3.1% 8.5% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Other private</td>
<td>34.8% 38.6% 3.8% 11.0% P &lt; .05\textsuperscript{1}</td>
</tr>
<tr>
<td>No insurance</td>
<td>31.4% 42.3% 11.0% 35.0% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Previous live births</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32.3% 35.5% 3.1% 9.7% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>1</td>
<td>39.2% 41.8% 2.6% 6.6% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>2</td>
<td>38.8% 44.2% 5.4% 13.9% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>3</td>
<td>44.7% 48.1% 3.5% 7.8% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>≥ 4</td>
<td>47.5% 52.8% 5.2% 11.0% P &lt; .05\textsuperscript{1}</td>
</tr>
<tr>
<td>Urbanization (by ZIP code)</td>
<td></td>
</tr>
<tr>
<td>Large urban</td>
<td>36.5% 40.2% 3.7% 10.1% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Small urban</td>
<td>38.0% 40.9% 2.9% 7.6% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Rural</td>
<td>38.1% 40.9% 2.8% 7.3% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Median family income (by ZIP code)</td>
<td></td>
</tr>
<tr>
<td>&lt;29,325</td>
<td>42.1% 45.5% 3.5% 8.2% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>29,325-38,097</td>
<td>39.2% 43.3% 4.2% 10.6% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>39,098-44,103</td>
<td>36.3% 40.2% 3.9% 10.7% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>44,104+</td>
<td>30.2% 33.1% 3.0% 9.8% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>37.0% 40.4% 3.4% 9.1% P &lt; .01\textsuperscript{1}</td>
</tr>
<tr>
<td>Smoker</td>
<td>37.1% 40.5% 3.4% 9.2% P &lt; .01\textsuperscript{1}</td>
</tr>
</tbody>
</table>

* Test for trend analysis used raw data from all years, 1999 through 2003.
\textsuperscript{1} P < .05, statistically significant.
of the patients that we studied here. Therefore, we believe that the data that we have analyzed in this study may be applicable to a general population. In studies in which trends in obesity in the United States have been analyzed, there has been a consistent increase in the proportion of individuals who are considered obese. Data from NHANES shows that between 1960 and 2000, for women aged between 20 and 39, the prevalence of obesity (BMI ≥ 30) increased from 9.3% to 28.4%. Mokdad et al. found that the self-reported incidence of obesity (BMI ≥ 30) for women increased from 12.2% in 1991 to 20.8% in 2001.

As with any study, our report has limitations. First, this study used data obtained from birth certificate information, and therefore contains the limitations associated with such a data set. The New York State birth certificate data, however, has been shown to be reasonably accurate in the information that it contains. In addition, for the prepregnancy BMI information contained in birth certificate data, previous investigators have shown self-reported height and weight information of pregnant women to be relatively reliable. The second weakness of our study is that the abstracted data sets have patient information that is missing. Approximately 7% of the patient data sets were not used in this study because of incomplete information. However, the missing information rate is approximately 7% for each of the years of the study, which makes us more confident about the validity of this temporal analysis. The third weakness is that only women who delivered a live birth are analyzed here. Therefore, it may not have been a full reflection of the prepregnancy BMIs of the population who became pregnant.

In summary, we presented evidence here that show there has been an increase in prepregnancy BMIs in women who delivered in the last 5 years. This change occurred in almost all subgroups of patients analyzed. This increase in the weight of pregnant patients has public health implications that needs to be assessed further in future research. In addition, because women maintain their weights even after their pregnancy, they are at increased risk of obesity-related morbidity in the future. Therefore, the weight change trend data presented here has clinical implications for obstetricians caring for women, for the present and in the future.

References
Cervical anti-inflammatory cytokine concentrations among first-trimester pregnant smokers

Hyagriv N. Simhan, MD, MSCR,a,b Steve N. Caritis, MD,a Sharon L. Hillier, PhD,b Marijane A. Krohn, PhDb

Department of Obstetrics, Gynecology, and Reproductive Sciences, Division of Maternal-Fetal Medicinea
and Division of Reproductive Infectious Diseases and Immunology, b University of Pittsburgh
School of Medicine, Magee-Womens Research Institute, Pittsburgh, PA

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Objective: Anti-inflammatory cytokines play a role in the lower genital tract immune defense. We examined the impact of cigarette smoking in pregnancy on the detection of the 3 most important anti-inflammatory cytokines (interleukin-4, -10, and -13) in the cervix.

Study design: One hundred fourteen gravid women from 4 to 16 weeks of gestation without bacterial vaginosis or sexually transmitted disease were queried regarding demographic factors and smoking. Concentrations of cytokines were determined with a multiplex assay for cervical swabs.

Results: There was a positive linear relationship between the number of cigarettes that were smoked per day and cervical concentrations of interleukin-4, -10, and -13 (P < .001 for each). Median concentrations of interleukin-4 and -10 were greater among women who smoked ≥20 cigarettes per day than among non-smokers or less heavy smokers (P < .05 for both). There was no difference in concentrations of proinflammatory cytokines between smokers and non-smokers.

Conclusion: Cigarette smoking in pregnancy is associated with an increase of cervical anti-inflammatory cytokines without a commensurate increase of proinflammatory cytokines. This may have important impact on the host response to infection.
previously reported on how decreased concentration of several proinflammatory cytokines in the lower genital tract early in pregnancy indicates an immune “hyporesponsiveness” that predisposes subsequent ascending microbial invasion. As reported by Genc et al, it is the balance of pro- and anti-inflammatory components of the cervical immune system that reflects the risk of subsequent preterm birth.

The objective of this study was to compare the inflammatory milieu of the cervix early in pregnancy among smokers and nonsmokers. The proinflammatory cytokines that we selected were interleukin (IL)-1α (IL-1α), IL-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α), and monocyte chemotactic protein-1 (MCP-1). For the purpose of this investigation, the anti-inflammatory milieu of the lower genital tract was represented by concentrations of IL-4, IL-10, and IL-13 in the cervix. These cytokines were selected because they each represent different functional aspects of the immune protection of the genital tract. All 3 of these cytokines attenuate the inflammatory response through effects on proinflammatory cytokine and prostaglandin production from epithelial and endothelial cells and reduce the function of host immune cells such as neutrophils and macrophages. These anti-inflammatory cytokines are important in keeping inflammation in check; however, by attenuating the host immune response, one might speculate that these cytokines might also contribute to a state of “impaired” bacterial killing.

We hypothesize that women who smoke during pregnancy have higher concentrations of anti-inflammatory cytokines in the cervix. We speculate that an altered immune milieu of the cervix among women who smoke during pregnancy might contribute to the well-documented increased risk of spontaneous preterm birth among gravid smokers.

### Material and methods

This is a prospective cohort study of 114 pregnant women who were enrolled at the first prenatal visit (range, 4-16 weeks of gestation; median, 8 weeks of gestation) from the Magee-Womens Hospital Antepartum Clinic from September 15, 2003, to July 1, 2004. Exclusions from enrollment included antibiotic therapy within the past 2 weeks, multiple gestation, current or planned cervical cerclage, vaginal bleeding, vaginal symptoms, and significant medical problems that included immunocompromised conditions.

Women signed a written consent form that had been approved by the Magee-Womens Hospital institutional review board. Demographic and obstetric information was obtained from the medical record. Cervical swabs were obtained for Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, and vaginal swabs were obtained for the diagnosis of bacterial vaginosis. Bacterial vaginosis was diagnosed by vaginal pH ≥ 4.7 and a score of 7 through 10 from a Gram-stained vaginal smear that was interpreted by the Nugent method. The identification of T vaginalis was by culture with Diamonds media and incubated at 37°C in 5% carbon dioxide for up to 5 days. Each day, microscopic identification by direct observation of motile forms was performed. If the culture media was negative for 5 days, the results were considered negative. C trachomatis and N gonorrhoeae were identified with nucleic acid amplification tests and culture, respectively. Women with bacterial vaginosis, N gonorrhoeae, C trachomatis, or T vaginalis were excluded from the analyses in this work because of the possible impact of these conditions on the inflammatory milieu of the lower genital tract.

At enrollment, 2 Dacron swabs were obtained from the cervix for the assay of cytokines. At the time of speculum examination, a Dacron swab was placed in the cervix and left there for 10 seconds to achieve saturation. The swab was then placed in a plastic tube that contained 400 μL of phosphate-buffered saline solution (final dilution, 1:5), immediately transported to the laboratory, and stored at −20°C. The buffer did not contain any other additives, including protease inhibitors. All cytokine analyses were done within 6 months of specimen collection and freezing. For analysis, the specimens were thawed at room temperature. The swab and the remaining diluent were centrifuged in a spin-X centrifuge filter unit (Costar, Cambridge, MA) at 12,000 rpm for 20 minutes. Concentrations of IL-4, IL-10, IL-13, IL-1α, IL-1β, IL-6, IL-8, TNF-α, and MCP-1 were measured with the Luminex LabMAP multiplex system (Luminex Corp, Austin, TX) and a BeadLyte bead kit (Upstate, Lake Placid, NY). Each assay was run with an intra- and interassay variation of <10%.

Race, smoking, alcohol consumption, and drug use were self-reported. Each study subject was asked if she currently smokes cigarettes and, if so, how many cigarettes per day she smokes.

Continuous variables were compared with the use of the Mann-Whitney U Test. Categoric variables were compared with the use of 2-tailed Fisher’s exact test or χ² test for trend, as appropriate. For these analyses, an α value of <.05 was considered statistically significant. Statistical analyses were performed with Stata software (version 8.0 for Windows; Stata Corp, College Station, TX).

### Results

During the study period, 114 women who met the eligibility criteria were enrolled. The cohort had a median age of 25 years (range, 17-41 years) and a median...
pregnancy weight of 71 kg (range, 45-163 kg). Our sample was 48% black, 84% unmarried, with 20 nulliparous women (19%) and 7 women (7%) with a previous preterm birth. Median gestational age at enrollment was 8 weeks 4 days (range, 4-16 weeks). Of these 103 women, 65 women (63.1%) reported current smoking of cigarettes, and 38 women (36.1%) reported not smoking. With respect to the number of cigarettes smoked, of the entire cohort, 43 women (41.8%) smoked <10 cigarettes per day; 17 women (16.5%) smoked ≥10 and <20 cigarettes per day, and 5 women (4.9%) smoked ≥20 cigarettes per day.

There was a highly statistically significant positive linear relationship between the number of cigarettes smoked per day and the concentration of IL-4, -10, and -13 (P < .001 for each). Figures 1 through 3 are box plots that depict the concentrations of IL-4, -10, and -13 in the cohort as categorized into nonsmokers, smokers of <10 cigarettes per day, smokers of ≥10 and <20 cigarettes per day, and smokers of ≥20 cigarettes per day. The median concentrations of IL-4 and -10 are significantly greater among women who smoke ≥20 cigarettes per day than among nonsmokers or less heavy smokers (P < .005 for both, Kruskal-Wallis test). There was a trend towards the same relationship with respect to IL-13 concentration as well (P = .06, Kruskal-Wallis test). There was not a statistically significant relationship between gestational age at enrollment and concentration of IL-4, -10, and -13 (P = .36, .61, .75, respectively, linear regression). As shown in Table, the concentrations of all 6 proinflammatory cytokines were not related to smoking status. We performed additional analyses to evaluate the relationship of race/ethnicity on median concentration of IL-4, -10, and -13. Our data did not demonstrate any significant ethnic differences in the concentrations of IL-4, -10, and -13 (P = .21, .28, .15, Kruskal-Wallis test). We also examined the frequency and quantity of smoking among the white and black subjects in our cohort. There was no ethnic difference in the frequency of smoking (P = .88, χ² test) or quantity of cigarettes smoked when smoking was considered categorically (P = .60, χ² test) or continuously (P = .48, Kruskal-Wallis test).

**Comment**

Our data support the notion that gravid smokers have a different anti-inflammatory milieu in the cervix early in
pregnancy than their nonsmoking counterparts. The significant positive linear relationship between the number of cigarettes smoked and the concentration of these 3 anti-inflammatory cytokines suggests a dose-response relationship. Indeed, the heaviest smokers in our cohort were noted to have higher cytokine concentrations.

It is unknown whether increased concentrations of anti-inflammatory cytokines in the cervix in early pregnancy are associated with subsequent adverse pregnancy outcome. The pathophysiologic mechanism by which such a relationship might exist also has not been elucidated. However, one might speculate that higher concentrations of multiple anti-inflammatory cytokines early in pregnancy may indicate a broad immune hyporesponsiveness that may create a permissive environment for ascending infection. We previously reported this relationship with decreased concentration of proinflammatory cytokines in the lower tract. An exaggerated anti-inflammatory environment in the lower genital tract might also be more permissive to the ascent of organisms into the choriodecidual. Perhaps it is these chronic choriodecidual infections that go on to develop into clinically apparent intra-amniotic infection or preterm birth.

It is possible that the increase in anti-inflammatory cytokine concentrations that is observed among smokers might be the result of a compensatory response to oxidative injury and resultant proinflammatory immune activation in the lower genital tract. Were this the case, we might expect to see elevated concentrations of proinflammatory cytokines among smokers. In fact, in our cohort, the concentrations of IL-1α, -1β, -6, -8, MCP-1, and TNF-α were not significantly related to smoking. Unfortunately, there is no plausible statistical method to summarize the balance between pro- and anti-inflammatory cytokines. Still, we note remarkable consistency of effect of smoking on anti-inflammatory cytokine concentrations without any difference in proinflammatory cytokines.

There are several strengths of our study. First, the assessment of smoking status and cytokine concentrations was performed early in pregnancy. Thus, we avoided the confounding of cytokine concentrations by labor (term or preterm). A second strength of our study is our inclusion of both anti-inflammatory and proinflammatory cytokines. The consistency of the relationship between smoking and the anti-inflammatory cytokine concentrations lends support to the biologic plausibility of our findings.

We recognize that there are limitations of our study. Smoking status was defined by self-report. Several investigators have noted that objective quantification of smoking with cotinine or exhaled carbon monoxide may correlate more closely with adverse perinatal outcome than self-reported quantification. Still, numerous epidemiologic studies demonstrate adverse health of effects of smoking as determined by self-report, so this ascertainment method is valid. Our study was not designed to describe the impact of vaginal microflora or sexually transmitted infections on the relationship between smoking and anti-inflammatory cytokine concentrations. Third, our study is of insufficient sample size to relate either smoking status or cervical anti-inflammatory cytokine concentrations to preterm birth, gestational age at delivery, birth weight, or neonatal outcome. These are important clinical outcomes that require a dramatically larger cohort to address appropriately.

Currently, although the literature supports a potent immunoregulatory function of IL-4, -10, and -13 in gestational tissues, there are no data that describe their concentrations in the lower genital tract with respect to adverse perinatal outcomes such as spontaneous preterm birth. Our data provide potentially intriguing insights into the impact of cigarette smoking on genital tract immunity. Further studies are needed to clarify the role of these cytokines in the predisposition to clinical outcomes that are related to infections, such as infection-related preterm birth.

**References**

Citalopram use in pregnancy: Prospective comparative evaluation of pregnancy and fetal outcome

Anna Sivojelezova, BSc, a,b,* Samar Shuhaiber, MSc, a Lorig Sarkissian, BSc, a Adrienne Einarson, RN, a Gideon Koren, MD a,b

The Motherisk Program, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children a; Department of Pharmaceutical Sciences, University of Toronto, b Ontario, Canada

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KEY WORDS
Citalopram
Selective serotonin reuptake inhibitor
Pregnancy outcome
Poor neonatal adaptation

Objective: Citalopram is a selective serotonin reuptake inhibitor indicated for depression. The safety of this medication in pregnancy has not been fully established. The purpose of this study was to investigate whether citalopram is associated with an increased incidence of adverse pregnancy outcomes.

Study design: Pregnant women who contacted the Motherisk Program, a Teratogen Information Center in Toronto, Ontario, with regard to the safety of citalopram in pregnancy were enrolled in the study. The exposed women were matched to a disease-matched group of women and a nonteratogenic group. All women were matched for age (≥ 2 years) and gestational age at time of first call to the Motherisk (± 2 weeks). A structured telephone follow-up interview was conducted following the expected date of confinement.

Results: The total number of pregnant women enrolled in this study was 396 (132 women in each group). A total of 125 women took citalopram at least in the first trimester. Seventy-one (54%) women continued to take the drug throughout pregnancy. One hundred fourteen women (86%) had live births, 14 (11%) had spontaneous abortions, 2 (1.5%) had elective terminations, and 2 (1.5%) experienced stillbirths. Fetal survival rates, mean birth weights, and duration of pregnancy were not statistically different among the 3 groups. Of 108 live-born infants whose mothers were exposed to citalopram in the first trimester, there was 1 (0.9%) male infant born with a major malformation. There was a relative risk of 4.2 (95% confidence interval 1.71-10.26) in neonates exposed to citalopram close to term to be admitted to special-care nurseries as compared with the unexposed infants.

Conclusion: Citalopram use during the period of embryogenesis in pregnancy is not associated with an apparent major teratogenic risk. Late pregnancy use of citalopram is associated with increased risk of poor neonatal adaptation syndrome, recently described with other selective serotonin reuptake inhibitors.

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Depression is known to affect as many as 10% to 25% of women of child-bearing age. A recent systematic review estimated a prevalence rate of depression in each trimester of pregnancy at 7.4%, 12.8%, and 12%, respectively. However, because of fear of harming the unborn child, some women choose to discontinue their drug therapy in pregnancy, often resulting in increased maternal morbidity. Untreated depression in pregnancy can lead to an increased risk of pregnancy loss, growth retardation, prematurity, and low Apgar scores.

Citalopram is an SSRI approved for the treatment of major depression. As of July 1999, citalopram became registered in 68 countries for depression and has been estimated to have been used by more than 12 million patients worldwide. In Canada, citalopram is 1 of the top 5 prescribed medications and 1 of the top 3 prescribed antidepressants, according to 2003 Intercontinental Marketing Services (IMS) Health Canada report.

In preclinical animal teratology studies, citalopram exposure in pregnant rats produced minimal developmental toxicity in the conceptuses, even at dosages that were toxic to the dams. In rabbits the drug did not cause any adverse effects on embryo-fetal development at the highest dose that could be assessed (16 mg/kg per day).

Two studies confirmed transplacental passage of citalopram. In a placenta perfusion study, both citalopram and to a lesser degree demethylcitalopram (its metabolite) were found to cross the placenta. Another study reported that citalopram and its metabolite were detectable in cord blood of all 4 women studied. The mean ratio of umbilical cord to maternal serum concentration of citalopram and its metabolite was found to be the highest as compared with fluoxetine, paroxetine, and sertraline.

In the manufacturer’s periodic safety reports, almost 80 case reports of pregnancy exposures were documented during the year 2002 (personal communication with N. Courchesne of Lundbeck Canada Inc, in 2003). About 36 cases involved exposure in the first trimester of pregnancy. No specific pattern or clustering of major malformations was observed. Information from the Food and Drug Administration’s Adverse Event Reporting System revealed that of 19 cases of birth defects reported in association with first-trimester citalopram exposure, eye abnormalities (4/19) were most prevalent. However, because of retrospective reporting and lack of the denominator, one cannot establish a causal relationship between these adverse effects and citalopram use in pregnancy.

To date only 3 studies examined the safety of citalopram in pregnancy. A small study of 11 pregnant women with first-trimester exposure to citalopram showed that delivery outcome and neurodevelopment of all children up to the age of 1 year were normal. In another small study of 7 women who were treated with citalopram during pregnancy, all infants were born without major birth defects; however, 1 infant was admitted to the intensive care unit for poor muscle tone and transient tachypnea. A study of 376 women on citalopram did not specify the dose and timing of exposure of the drug and lacked a control group but failed to show any clustering or increased incidence of major congenital malformations.

**Objectives**

The objective of our study was to determine whether citalopram use during pregnancy is associated with an increased risk of adverse pregnancy outcome, including birth defects and neonatal complications.

**Patients and methods**

This was a prospective comparative study with 2 matched comparison groups (a disease-matched and a non-teratogen group).

The study was conducted by the Motherisk Program at the Hospital for Sick Children in Toronto. The Motherisk Program is a teratogen information and counseling center that provides pregnant or breastfeeding women and their health care providers with evidence-based information on the safety/risk of exposures to prescription and over-the-counter medications, natural health products, chemicals, radiation, and infectious diseases.

The women in this study were recruited from the cohort of pregnant women or women planning pregnancy who contacted the Motherisk Program from 1999 to 2002 inquiring about the safety of citalopram and other medications in pregnancy. During an initial interview with a patient, a standardized intake form was completed over the telephone with information regarding general medical and obstetrical history, timing of drug exposure, and its dose schedule as well as information regarding exposures to alcohol, cigarettes, recreational drugs, chemicals, vitamins, radiation. At least 2 months after the expected date of confinement, all women were contacted for a telephone follow-up interview.

A follow-up interview consisted of a comprehensive list of questions with regard to maternal health during pregnancy, pregnancy outcome, delivery, and neonatal health. After completion of the telephone interview, a verbal maternal consent was obtained to send a letter to the infant’s attending physician to corroborate the medical details concerning maternal and neonatal health.
during labor and postpartum period. Before the verbal consent was obtained, the study was explained in detail over the telephone, and each woman was reassured about confidentiality of her and her infant’s medical records. This study was approved by the Research Ethics Board of the Hospital for Sick Children.

There were 3 groups of women in this study. The exposed group of women consisted of women who took citalopram during pregnancy. The disease-matched group (comparison group 1) consisted of pregnant women diagnosed with similar psychiatric conditions in pregnancy as the exposed group but treated with other SSRI antidepressants (e.g., fluoxetine, paroxetine, sertraline). The nonteratogen group (comparison group 2) was comprised of women with nonteratogenic exposures (e.g., acetaminophen, hair dyes, vitamins, etc). The exposed group of women and the 2 comparison groups were matched for the maternal age ($\pm$ 2 years) at the time of conception as well as the gestational stage of pregnancy ($\pm$ 2 weeks) at the time of recruitment. The exclusion criteria for all 3 groups were either an exposure to a known teratogen or a xenobiotic with undetermined safety in pregnancy.

To investigate the incidence of major malformations in the citalopram-exposed group, only those women who had an exposure to the medication during the period of organogenesis were included. Major malformations were defined as structural and/or functional anomalies that have to be corrected surgically or that may alter the social acceptability of the individual. Secondary end points included the number of live births, pregnancy duration, and birth weight.

The incidence of perinatal complications in infants exposed to citalopram close to the time of delivery was compared with infants whose mothers did not use citalopram near term or any other SSRIs in the third trimester of pregnancy. Premature infants and infants exhibiting intrauterine growth retardation were excluded.

One-way analysis of variance with Tukey or Sheffe’s post hoc analyses were performed for continuous, normally distributed data. The Kruskal-Wallis test with Dunn’s post hoc analysis was used for nonparametric and categorical data. The $\chi^2$ test or Fisher exact test was performed when analyzing categorical tabulated data between no more than 2 groups. These tests were used when we analyzed the difference in the rates of major malformations and neonatal complications.

## Results

### Maternal characteristics

The total number of pregnant women enrolled in this study was 396 (132 women in each study group). Pregnant women who were exposed to citalopram had a mean age of 31.9 \pm 4.8 years (range 18-42 years). At

### Pregnancy outcome

Pregnancy outcome and neonatal characteristics can be found in Table II. The number of live births, median birth weights, and length of pregnancy were not statistically different among the 3 study groups. Of the 108 women who were exposed to citalopram in the first trimester, there was only 1 (0.9%) baby born with a major malformation, a case of umbilical and scrotal herniae necessitating a surgical correction (Table III). Although the rate of perinatal complications following third-trimester exposure to citalopram did not differ

### Table I

<table>
<thead>
<tr>
<th>Citalopram dose (N = 118)</th>
<th>Dose, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>0.345</td>
</tr>
<tr>
<td>25th percentile</td>
<td>0.260</td>
</tr>
<tr>
<td>75th percentile</td>
<td>0.460</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Changes in the citalopram doses during pregnancy (N = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased dose</td>
</tr>
<tr>
<td>Increased dose</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T1-T2</td>
</tr>
<tr>
<td>T2-T3</td>
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<tr>
<td>T1-T3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of drug exposure (N = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1, First-trimester exposure; T2, second-trimester exposure; T3, third-trimester exposure.</td>
</tr>
</tbody>
</table>

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statistically from that of the unexposed group of women, there was a 4-fold increased risk of need for the neonatal intensive care (relative risk, 4.2 [95% confidence interval 1.71-10.26]) (Table IV). A full description of all perinatal complications observed among the exposed infants is found in Table V.

Comment

Although several published studies did not associate SSRI antidepressants with major malformations or neurobehavioral problems, many pregnant women and their health care providers are apprehensive with regard to SSRI therapy during pregnancy.

To our knowledge, this study is the first prospective comparative study to examine the possible adverse effects of citalopram during pregnancy. We found only

Table II  Pregnancy outcome and neonatal characteristics

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Exposed (N = 132)</th>
<th>Comparison 1 (N = 132)</th>
<th>Comparison 2 (N = 132)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live</td>
<td>114 (86%)</td>
<td>115 (87%)</td>
<td>118 (89%)</td>
<td>Kruskal-Wallis, 0.69</td>
</tr>
<tr>
<td>SA</td>
<td>14 (11%)</td>
<td>13 (10%)</td>
<td>13 (10%)</td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Still birth</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ectopic</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Gestational age at birth

| Mean (wk) ± SD                  | 39.2 ± 1.7        | 39.4 ± 2.1             | 39.3 ± 1.8             | Kruskal-Wallis, 0.69 |

Preterm (<37 wk)                  | 11                | 10                     | 5                      | Kruskal-Wallis, 0.25 |

Full term (≥37 wk)                | 103               | 105                    | 113                    |         |

Birth weight

| Mean (g) ± SD                    | 3540 ± 530        | 3577 ± 612             | 3436 ± 474             | ANOVA, 0.15 |

Major malformations               | N = 108           | N = 115                | N = 118                |         |

| N (%)                            | 1 (0.9%)          | 3 (2.6%)               | 1 (0.8%)               | \( \chi^2 \), 0.64/0.52 |

SA, Spontaneous abortion; TA, therapeutic abortion; ANOVA, analysis of variance.

Table III  Description of major malformations

<table>
<thead>
<tr>
<th>Exposed group (N = 108)</th>
<th>Comparison group 1 (N = 115)</th>
<th>Comparison group 2 (N = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical and scrotal herniae</td>
<td>Atrial septal defect</td>
<td>Diaphragmatic hernia</td>
</tr>
<tr>
<td>Down syndrome*</td>
<td>Hiatus hernia</td>
<td></td>
</tr>
<tr>
<td>Hypospadias*</td>
<td>Cardiac defect</td>
<td></td>
</tr>
<tr>
<td>Hypospadias and atrial septal defect*</td>
<td>Pierre Robin Syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autism</td>
<td></td>
</tr>
</tbody>
</table>

* Infants not exposed to citalopram during organogenesis.

Table IV  Perinatal complications in infants exposed vs. infants unexposed to citalopram in the third trimester

<table>
<thead>
<tr>
<th>T3 exposure (N = 63)</th>
<th>Non-T3 exposure (N = 158)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications in general</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (32%)</td>
<td>33 (21%)</td>
</tr>
<tr>
<td>No</td>
<td>43 (68%)</td>
<td>125 (79%)</td>
</tr>
<tr>
<td>NICU admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (16%)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>No</td>
<td>53 (84%)</td>
<td>152 (96%)</td>
</tr>
</tbody>
</table>

T3, Third-trimester exposure; CI, confidence interval; NICU, neonatal intensive care unit.

Table V  Description of all perinatal complications in infants exposed to citalopram in the third trimester

<table>
<thead>
<tr>
<th>Description (N = 20)</th>
<th>NICU (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>yes (2)</td>
</tr>
<tr>
<td>Fetal distress, meconium staining</td>
<td>no</td>
</tr>
<tr>
<td>Fetal distress, decreased heart rate</td>
<td>yes</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>yes</td>
</tr>
<tr>
<td>Fetal distress, heart rate variability</td>
<td>yes</td>
</tr>
<tr>
<td>Meconium staining</td>
<td>yes</td>
</tr>
<tr>
<td>Fetal distress, meconium aspiration</td>
<td>yes</td>
</tr>
<tr>
<td>Meconium staining</td>
<td>no</td>
</tr>
<tr>
<td>Meconium staining</td>
<td>no</td>
</tr>
<tr>
<td>Meconium staining</td>
<td>no</td>
</tr>
<tr>
<td>Meconium aspiration, fetal distress, decreased heart rate</td>
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</tr>
<tr>
<td>Fetal distress</td>
<td>no</td>
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<tr>
<td>Fetal distress</td>
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<tr>
<td>Difficulty breathing</td>
<td>no</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>no</td>
</tr>
<tr>
<td>Fetal distress, decreased heart rate</td>
<td>yes</td>
</tr>
</tbody>
</table>

NICU, Neonatal intensive care unit.
1 male infant born with a major birth defect following exposure to citalopram during embryogenesis. This rate did not differ statistically from the comparison groups.

We observed that only 50% of all pregnant women continued with citalopram treatment until the end of pregnancy. Fifteen percent of the women lowered their doses. Of note, at the time of study recruitment, these women were already given reassuring evidence-based information with regard to the use of citalopram in pregnancy by a Motherisk counselor; however, a significant number of women still did not feel comfortable to continue with their treatment.

We found that more women with depression smoked during pregnancy as compared with healthy women. There were 2-fold to 3-fold more smokers in the exposed and the disease-matched groups as compared with a nonexposed comparison group of women. This finding agrees with previous reports that depression is associated with increased smoking in pregnancy.27 There was lower weight gain during pregnancy observed among citalopram-exposed and disease-matched women as compared with nonexposed healthy women, even after excluding all smokers. However, there was no statistically significant difference in the weight gain of those women who remained on citalopram throughout pregnancy versus the healthy control group. Assuming that women who stayed on citalopram throughout pregnancy were more likely to adequately manage their underlying condition, this finding may corroborate previous observations that untreated depression may be associated with poor perinatal health. However, we cannot presently determine whether this effect is drug or disease related.

Several recent studies have documented that late pregnancy exposure to SSRIs is associated with an increased incidence of poor neonatal adaptation syndrome.28-32 Some of the reported symptoms include irritability, respiratory difficulty, constant crying, jitteriness, increased muscle tone, eating and sleeping difficulties, seizures, hypoglycemia, and jaundice. Most described symptoms appear to be time limiting, lasting from a period of a few days to a few weeks. This syndrome, described here for the first time with citalopram, probably reflects a neonatal discontinuation syndrome, similar to what has been described in adults.33 Citalopram crosses the placenta, and it is biologically plausible that it also causes neonatal discontinuation symptoms. We observed a 4-fold increased risk for need of neonatal intensive care among babies exposed to citalopram at term. However, a pharmacokinetic study will be needed to prove this mechanism beyond doubt.

In summary, our findings do not support an association between citalopram with any major teratogenic risk in humans. Our study has an 80% power at alpha = 0.05 to detect a 4-fold increased risk for major malformations above the baseline risk of 1% to 3% observed in the general population. We confirmed for the first time a citalopram-induced poor neonatal adaptation syndrome, similar to other SSRIs. We recommend close monitoring of all infants exposed to citalopram in utero near term. Our data suggest that pregnant women who require pharmacotherapy with citalopram may continue their treatment during pregnancy with close monitoring of their condition by a qualified medical professional.

References


Activity of hepatic enzymes from week sixteen of pregnancy

Angeles Ruiz-Extremera, MD,a,* María A. López-Garrido, MD,b Enriqueta Barranco, MD,c María D. Quintero, MD,b Esther Ocete-Hita, MD,a Paloma Muñoz de Rueda, PhD,b Ana Gila, MD,b Javier Salmerón, MDb

Pediatrics Service,a Gastroenterology Unit,b and Department of Obstetrics and Gynecology,c H. Universitario San Cecilio, Granada, Spain

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KEY WORDS
Pregnancy
Liver enzymes
Alanine-aminotransferase

Objective: This study was undertaken to determine the prevalence, epidemiology, and mother-child repercussions of increased alanine-aminotransferase levels from week 16 of pregnancy.

Study design: A longitudinal observational study of 381 pregnant women. The cause of increased alanine-aminotransferase levels during pregnancy and repercussions on the neonate were studied in 283 cases. Statistical analysis was performed with Mann-Whitney test, χ2 test, or the Fisher exact test.

Results: The mean age of the mothers was 29.9 ± 4.8 years. Twenty-five percent presented increased gamma-glutamyl-transpeptidase, alkaline phosphatase, and dehydrogenase lactate from week 32. Increased alanine-aminotransferase was observed in 7.4% (95% CI, 5.00%-10.57%) of cases. Clinical disorders were light, transitory, and with no apparent cause, except for 1 hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, 3 preeclampsias, and 1 gravidic cholestasis. No statistically significant differences were observed in the group of mother-child with alanine-aminotransferase normal or increased.

Conclusion: Most increases in alanine-aminotransferase from week 16 of pregnancy are transitory, non-specific, and have no repercussions on mother or child.

During pregnancy, liver disorders may occur, with varying, but sometimes extremely severe clinical effects. Comprehensive studies have been made of the hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, gravidic cholestasis, the fatty liver of pregnancy, and other preexisting liver diseases, whether concomitant or pregnancy associated.1-8 However, few studies have been carried out concerning the prevalence of liver disorders and the effects of pregnancy on the biochemical profile. Previous studies have reported a reduction in total bilirubin (BRRI),9 in the free fraction and in gamma-glutamyl-transpeptidase (GGT),9-12 as well as an increase in alkaline phosphatase (ALP)9 through the placenta isoenzyme and in alanine-aminotransferase (ALT).9-11 These changes are evident on comparison...
of serum levels of pregnant women with those of the general population. Some authors have remarked on the need to use comparison ranges that are appropriate for pregnant women, to enable a greater power of discrimination of liver diseases.13-15

The social changes that have taken place in recent years may have had an effect on the normal course of pregnancies. Such changes include the increased proportion of women at work, the possibility of women who have severe illnesses (transplant patients, and those who have chronic disease) becoming pregnant, pregnancy among adolescents, and the appearance of invasive techniques in achieving and monitoring pregnancies. To date, no studies have been performed to show the effects of these changes on the incidence of liver disease among pregnant women. The aims of this study are to determine the behavior pattern of the hepatic biochemical profile, to assess the prevalence of increased ALT from week 16 of pregnancy and to analyze the clinical course of increases in ALT. We also sought to investigate the epidemiologic and socioeconomic factors involved and the possible repercussions on mother and child.

Material and methods

Study site

The study was carried out at the San Cecilio University Hospital in Granada (Spain).

Study participants

A prospective study was made up of 381 women aged between 16 and 42 years, from week 16 of their pregnancy. The study was approved by the hospital’s Ethics Committee, and informed consent was received from all participants. The criterion for inclusion in the study was that the pregnancy should have been normal until week 16, defined as normal maternal-fetal evolution, determined by routine controls performed until that time. Only 1.3% of the participants failed to complete the prenatal observation program.

Data collection procedures and measures

All the participants responded to an epidemiologic survey providing demographic data, personal and obstetric history, information on habits, socioeconomic data, and social risk factors (Tables I and II). Table III shows the data of the pregnant women with increased ALT.

Clinical analytic follow-up

The participants were clinically and analytically evaluated at weeks 16, 28, 32, 36, and 40. On each occasion, BRRT, aspartate aminotransferase (AST), ALT, GGT, ALP, and dehydrogenase lactate (LDH) were determined. The pregnant women presenting ALT values equal to or higher than 40 U/L (the range of normality in our laboratory) were subjected to a study protocol to establish possible etiologic factors, namely, cholesterol,
triglycerides, alpha-fetoprotein (AFP), alpha-1-antitrypsin, copper, ceruloplasmin, iron, ferritin, nonorgan-specific autoantibodies, thyroid study, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus (CMV), herpes virus (HV), and toxoplasma. A hepatobiliary echography was also included in the protocol.

**Study of the neonate**

In 283 cases, details of the birth and of the situation of the neonate were obtained (Table IV).

**Laboratory methods**

Hematologic parameters were determined with the use of a Coulter S-Plus JT analyzer. Biochemical parameters, by using a Hitachi 717 (Boehringer Mannheim, Germany) automatic analyser, according to the standard practice in our hospital. Antinuclear antibodies (ANA) and antimitochondrials (AMA), by means of an Atom (indirect immunofluorescence) automatic analyser with Hep-2 cells for ANA and with the antigens found in the liver, kidneys and stomach of the rat for the AMA. The markers of HAV and HBV, by conventional enzyme immunoassay techniques (Abbott, Chicago, IL), and CMV by enzyme immunoassay techniques (Berhing, Deerfield, IL). HCV, by enzyme-linking immunosorbent assay (ELISA, Ortho, Raritan, NJ), RIBA (Chiron, Emeryville, CA). The thyroid function tests, by competitive immunoassay for total T4 and free T3, and by an immunometric test for thyroid-stimulating hormone (TSH) (Immulite 2000). AFP, by the microparticle enzyme immunoassay (MEIA, Axsym, Abbott).

### Table III

Data for pregnant women with raised ALT

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Diagnosis</th>
<th>Peak ALT</th>
<th>Wks with increased ALT</th>
<th>Medication</th>
<th>Alcohol</th>
<th>Hepatobiliary echography</th>
<th>Tobacco</th>
<th>Abdominal pain</th>
<th>Nausea</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>57</td>
<td>167</td>
<td>—</td>
<td>37</td>
<td>66</td>
<td>36-post</td>
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<td>Normal</td>
<td>0</td>
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<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>70.5</td>
<td>162</td>
<td>—</td>
<td>41</td>
<td>68</td>
<td>16-32</td>
<td>No</td>
<td>Normal</td>
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</tr>
<tr>
<td>3</td>
<td>30</td>
<td>77</td>
<td>163</td>
<td>PET</td>
<td>41</td>
<td>71</td>
<td>32-post</td>
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<td>Normal</td>
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<td>No</td>
<td>No</td>
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<td>4</td>
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<td>160</td>
<td>PET</td>
<td>37</td>
<td>65</td>
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<td>Normal</td>
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<td>6</td>
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<td>157</td>
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*PET, Preeclampsia toxemias; ICP, intrahepatic cholestasis of pregnancy; SMA, smooth muscle antibody.*

*GE, wks gestational age (newborn); —, no date.

† Tobacco, number of cigarettes per day.

‡ Diagnosis: —, normal exhaustive study.

‡ Post, postdelivery.

k Varicella, 33 wks.
Statistical analysis

The quantitative variables were calculated as the arithmetic mean ± the SD and the distribution by percentiles. The Mann-Whitney test for independent samples was applied. The qualitative variables were expressed as percentages and analyzed with the use of the $\chi^2$ test or the Fisher exact test. A level of statistical significance of 95% was applied for all tests and confidence intervals.

Results

General characteristics of the pregnant women

The mean age of the participants was 29.9 ± 4.8 years, and their mean weight at week 16 was 67.7 ± 12 kg. Thirty-nine percent of the women were primiparous, 53% were secundiparous, and only 8% were multiparous. Thirteen percent had an illness before the pregnancy (2% preexisting arterial hypertension, 3.7% digestive illnesses, 1.8% kidney disease, 0.8% diabetes mellitus, 2.4% thyroid disorders, 1.3% connective pathologies, 0.5% heart disease, and the remainder, illnesses with lower degrees of prevalence. In addition, 13% had complications during pregnancy and/or childbirth before the current pregnancy (2% infertility, 2% miscarriages, 1.6% still birth, 0.5% premature birth, 0.5% small-for-gestational-age birth, 5.8% previous cesarean delivery, and 0.8% assisted reproduction). During the current pregnancy, 21% of the participants presented some form of illness, with a prevalence of 0.3% for HELLP and pregnancy-related intrahepatic cholestasis, 2.3% for anemia, 2.6% for gestational diabetes, 4.2% toxemia, and 11.6% for other illnesses. With regard to infectious diseases, 20 of the women (5%) were affected, the most common type being urinary infection (3.7%). The prevalence of hepatotropic viruses was 0.8% for HBV (95% CI, 0.2%-2.4%) and 0.5% for HCV (95% CI, 0.1%-2.1%). Concerning toxic habits during pregnancy, 25% were found to be regular smokers, with an average consumption of 6.6 ± 4 cigarettes per day (range, 1-25), and 3% had consumed some type of toxic substance during pregnancy; only 1 person regularly consumed alcohol. Analysis of these data revealed no statistically significant differences between normal and increased ALT (Table I).

Table II describes the socioeconomic factors presented by the study population. Eighty-one (21%) of the pregnant women had studied at the university; 119 (31%) had studied to the technical level; 168 (44%) had completed primary and/or secondary education; 3 (0.8%) had an incomplete primary education; and 2 (0.5%) had no formal education. Fifty percent had no paid work outside the household.

A large majority of respondents (80%) owned their own home and 80% considered their home to present good living conditions. Of the respondents, 1.5% had carried out prenatal medical check-ups incorrectly and 5% had little information on family planning. With respect to antecedents of risk of liver disease, 4% had received a previous blood transfusion. Analysis of all these factors revealed that the group with increased ALT presented a higher occurrence of single-parent families ($P < .05$) and of antecedents of blood transfusions ($P < .01$).

Behavior patterns of BRRt, AST, ALT, GGT, ALP, and LDH from week 16 of pregnancy until delivery

Having calculated mean values for each parameter at 16, 28, 32, 36, and 40 weeks of pregnancy, we observed that the majority of the pregnant women presented a normal biochemical profile, with very low values of the different parameters, as shown in the Figure. Ninety percent (percentile 90) of the subjects presented total bilirubin levels that were equal to or less than 0.7 mg/dL. For AST and ALT, the 75th percentile was below 25 U/L and for GGT, equal to or less than 12 U/L. ALP increased among all the subjects in the measurements obtained shortly before delivery, with the 75th percentile being slightly more than 300 U/L. The 75th percentile for LDH was below 350 U/L, although after week 32, it rose somewhat among 50% of the subjects.
Prevalence of increased ALT and its relation with the biochemical profile

The prevalence of increased levels of ALT (ALT ≥ 40 U/L) among the study population was 7.4% (95% CI 5%-10.6%). The mean ALT value among the 28 subjects with increased ALT was 67.8 ± 59 U/L (95% CI 46 U/L-90 U/L), whereas among the women with normal ALT levels it was 18.5 ± 10 U/L (95% CI, 17.5 U/L-19.6 U/L) with P < .001. The diagnoses of cause for the 28 pregnant women, obtained from a more exhaustive study, were as follows: 1 case of HELLP, 1 of pregnancy-related intrahepatic cholestasis, and 3 of preeclampsia. Among the remaining subjects (n = 25, 89%), the extended study produced unchanged results; the increase in ALT was transitory, although there was also an increase in AST (P < .001), GGT (P < .001), and FA (P < .05) with respect to subjects with normal levels of ALT.

Occurrences during delivery and study of the neonate

The neonates in the study presented a mean gestational age of 39 ± 2 weeks, a mean weight of 3222 ± 548 g and a cephalic perimeter of 35 ± 1.5 cm. The children whose mothers had increased levels of ALT presented a lower gestational age (P < .05), although the number of premature births was similar in the 2 groups (5%). Anomalous presentation (breech or transverse) was 6%, and 30% of the breech and transverse lie presentations required the use of instruments. Twenty-seven percent of the births occurred over 4 hours after rupture of the membranes, and 6.3% presented an infectious disease at the moment of birth, the most common of these being Group B Streptococcus (4%). Fourteen percent of the neonates had alterations in cardiotocographic control and pathologic amniotic fluid (3% hemorrhagic and 16% meconium stained). Only 18% of the neonates required the application of special reanimation techniques at birth, but 16% presented acidosis. The Apgar score was low for 9% of the neonates at 1 minute after birth and for 3% at 5 minutes. Analysis of all these data revealed no statistically significant differences between the normal and increased ALT groups (Table III).

Table IV (Continued)

<table>
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<th>&lt;4h rupture membranes</th>
<th>Absence of fetal well-being</th>
<th>Instrument delivery</th>
<th>Pathologic amniotic fluid</th>
<th>Complications in reanimation</th>
<th>Umbilical artery pH (acidosis)</th>
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<tr>
<td>76 (27%)</td>
<td>41 (14%)</td>
<td>132 (30%)</td>
<td>53 (19%)</td>
<td>18 (6%)</td>
<td>46 (16%)</td>
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<tr>
<td>69 (26%)</td>
<td>38 (5%)</td>
<td>81 (3%)</td>
<td>50 (19%)</td>
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<td>7 (23%)</td>
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Comment

The biochemical profile obtained for the women at week 16 of their pregnancy enabled us to establish normograms from the percentile distribution of the different analytic parameters, within which 95% of normal subjects should be found. Most of the subjects presented a normal biochemical profile and values were low throughout the period of observation. This latter fact may be explained by the water retention and hemodilution that affects pregnant women. Therefore, it is advisable to establish normality ranges specifically for pregnant women, and not to use those calculated for the general population.13,14 The normograms obtained in the current study, based on the percentile distribution of the different parameters, helped in this respect by setting the values of such parameters that could be considered normal during pregnancy and the levels within which the presence of liver pathologies may be discounted.1,13,15

The prevalence of increased ALT was 7.4%, and most of the cases detected corresponded to transitory phenomena. Nevertheless, this group included 1 case of HELLP syndrome, 1 of gravidic cholestasis, and several of gestosis. Earlier studies have reported a higher prevalence of increased ALT among pregnant women,3-7 but these studies were carried out among subjects presenting some form of gestational pathology, and not among a general obstetric population. Increased AST was also observed among pregnant women presenting higher levels of ALT, although after week 32 of pregnancy, 25% of all pregnant women present increased AST with respect to baseline levels, irrespective of ALT.9

Despite the wide-based epidemiologic and social data survey carried out, which enabled us to obtain a reliable view of the study population, no characteristic was observed that might have made it possible to distinguish the subjects according to the behavior pattern of ALT,
Figure  Behavior pattern of hepatic enzymes and total bilirubin from week 16 of pregnancy until delivery. Note. P5, Percentile 5; P10, Percentile 10; ……., P95, Percentile 95.

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except regarding the greater number of unmarried women and the fact that the gestational age of the neonates was somewhat lower among the group of mothers with increased levels of ALT.

Noteworthy among the demographic and epidemiologic data obtained is the mean age of the mothers, much higher than that found in previous studies carried out in the early 1990s. In addition, 39% of these women were primiparous, a fact which, considered together with that of their age, clearly shows the current tendency for women to delay maternity, particularly concerning the first child.

In the current study, the prevalence of diseases that are characteristic of pregnancy, such as preeclampsia (4.2%), the HELLP syndrome (0.3%), and pregnancy-related intrahepatic cholestasis (0.3%), was lower than that reported in others, but these were carried out with subjects presenting some form of disease. The prevalence of HBV (0.8%) and of HCV (0.52%), although low, coincided with that found in an earlier study carried out with pregnant women in Granada (Spain). HBV and HCV were found in 4 pregnant women with normal ALT and 2 patients with raised ALT. In previous studies on vertical transmission of the HCV, only 26% of the pregnant women had raised ALT. On the other hand, previous transfusions were more often seen in the raised ALT group than in the normal ALT group, despite an absence of viral infection. Recently, new parenterally transmitted viral agents have been recognized, namely, hepatitis G virus (HGV) and transfusion-transmitted virus (TTV).

The rate of unmarried subjects (4.2%), although low, reflects the increasing presence of single-parent families in Spanish society. This is also significant with respect to the increased ALT levels observed. Concerning the prevalence of toxic habits, the high frequency of tobacco consumption is surprising. Sporadic consumption of alcohol was also reported. Only 3 pregnant women with raised ALT had consumed medication or drugs.

The women in the study population, in general, enjoyed a medium-high standard of living (82%) and possessed a university degree (21%), which partially accounts for their delaying maternity, until economic and occupational stability had been achieved. With respect to the neonates, there was a striking proportion of premature births (5%) and instrument-assisted deliveries.

In conclusion, in contemporary society in Spain maternity is undertaken late in life, which, together with low birth rates (only 8% of women have more than 2 pregnancies) might make it advisable to set up specific state-wide programs to reverse this trend. To evaluate liver function, normograms specifically designed for pregnant women should be designed. Increased ALT was observed in 7.4% of cases, but this group included the cases of HELLP, gravidic cholestasis, and gestosis. Most increases in ALT from week 16 of pregnancy are transitory, nonspecific and have no repercussions on mother or child.

References

Adipose tissue from pregnant women with and without gestational diabetes mellitus: Insulin-sensitive but resistant to hyperosmolality

Anthony W. Russell, PhD,a,b,c,* H. David McIntyre, MB, BS,b,c Jon P. Whitehead, PhD,a,b Johannes B. Prins, PhD,a,b

Department of Diabetes and Endocrinologya and Centre for Diabetes and Endocrine Research, University of Queensland,b Princess Alexandra Hospital, Brisbane, Australia; Department of Endocrinology, Mater Misericordiae Hospital, South Brisbane, Australiac

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KEY WORDS
Adipocyte
Pregnancy
Gestational diabetes mellitus
Glucose uptake
Sorbitol

Objective: We sought to determine the contribution of adipose tissue to the insulin resistance of pregnancy. We also investigated whether hyperosmolar stress (induced by sorbitol) stimulates glucose uptake in human adipose tissue and, if so, whether this effect is altered in pregnancy and gestational diabetes mellitus.

Study design: Subcutaneous and omental adipose tissue biopsy specimens were obtained at elective abdominal surgery or cesarean delivery from 16 normal glucose-tolerant pregnant women, 13 pregnant women with gestational diabetes mellitus, and 19 body mass index–matched nonpregnant control subjects. Basal, insulin (100 nmol/L)-, and sorbitol (250 mmol/L)-stimulated glucose uptake levels were measured.

Results: Basal and insulin-stimulated glucose uptake into adipose tissue was not impaired in pregnancy or gestational diabetes mellitus compared with control subjects. Hyperosmolality stimulated glucose uptake in human adipose tissue from the subcutaneous, but not omental depot, and not in adipose tissue from pregnant subjects.

Conclusion: There is no significant difference in insulin sensitivity in adipose tissue from pregnant or nonpregnant women; hyperosmolality stimulates glucose uptake in subcutaneous adipose tissue from nonpregnant women, and adipose tissue from pregnant women is sorbitol resistant. These findings suggest the phosphotidylinositol 3-kinase–independent pathway may have pathophysiologic relevance to glucose uptake in human adipose tissue and may be impaired in pregnancy.

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* Reprint requests: A. W. Russell, Endocrinologist, Department of Diabetes and Endocrinology, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Queensland, Australia 4102.
E-mail: arussell@cedr.soms.uq.edu.au

Pregnancy is well-recognized as a state of insulin resistance. However, the cause of and the mechanisms that create this insulin resistance remain obscure. Furthermore, 5% to 8% of pregnancies are complicated by the development of gestational diabetes mellitus (GDM), which is a state that is generally considered to be characterized by more marked insulin resistance than normal pregnancy. Lessons learned from studying the pathophysiologic condition of insulin resistance in pregnancy and GDM may serve to enhance our knowledge about insulin resistance in type 2 diabetes mellitus (T2DM).

There is now much evidence to suggest that adipose tissue plays a central role in the development of insulin resistance. Adipose tissue itself is insulin responsive and contributes directly, although quantitatively less than skeletal muscle, to whole body glucose disposal. Adipose tissue also indirectly influences whole body glucose disposal by the secretion of ‘‘adipokines,’’ such as leptin, adiponectin, and resistin. Obesity is a risk factor for the development of GDM and visceral obesity is associated strongly with insulin resistance and an increased risk of T2DM. The close association between visceral obesity and insulin resistance suggests that adipose tissue from different depots has different functions and characteristics and indicates the importance of the investigation of both subcutaneous and omental adipose tissue.

Insulin-stimulated glucose uptake in adipose tissue, as in skeletal muscle, is mediated by the insulin-responsive glucose transporter GLUT4. Translocation and activation of GLUT4 is the final step in a complex insulin-signaling cascade mediated by a phosphotyrosine-nositol 3-kinase (PI 3-kinase)–dependent pathway (IRS-1/PI 3-kinase/Akt/PKC). More recently, a PI 3-kinase–dependent pathway (IRS-1/PI 3-kinase/Akt/PKC) has been described, which is thought to be necessary for maximal insulin-stimulated glucose uptake. Components of this pathway include Cbl, CrkII, and TC10 have also been implicated in GLUT4-mediated glucose uptake that is stimulated by hyperosmolarity, which is a PI 3-kinase–independent process. Hyperosmolar-stimulated glucose uptake has not been reported in human adipocytes, but the assessment of the differences in both insulin- and hyperosmolar-stimulated glucose uptake should provide direction about whether to further investigate the PI 3-kinase–dependent and/or PI 3-kinase–independent pathways in insulin resistance.

We investigated the glucose uptake response to both insulin and hyperosmolarity in subcutaneous and omental adipose tissue from subjects with recognized states of insulin resistance, pregnancy, and GDM. Results were compared with those that were obtained in adipose tissue from nonpregnant control subjects. We hypothesized that adipose tissue would be insulin resistant in pregnancy, that this finding would be more marked in women with GDM, and that this insulin resistance contributed to the whole body insulin resistance characteristic of these states.

Material and methods

The study cohort consisted of 16 pregnant women with normal glucose tolerance (NGT), 13 subjects with GDM, and 19 nonpregnant control subjects. Subjects were recruited on the morning of their elective abdominal surgery or elective lower uterine segment cesarean delivery (LUSCS). The pregnant women were all delivered at 37 to 40 weeks of gestation. Retrospectively, information was gathered regarding each pregnant subject’s glucose tolerance status. The Australian Diabetes in Pregnancy Society recommends universal screening for GDM, although the obstetrician may reserve screening for those patients who are at higher risk. Screening tests are performed at 26 to 28 weeks of gestation with either a 50-g or 75-g glucose challenge with 1-hour glucose values of ≥7.8 mmol/L or ≥8.0 mmol/L, respectively, requiring a confirmatory test with a fasting 75-g oral glucose tolerance test. On the oral glucose tolerance test, a fasting venous plasma glucose level of ≥5.5 mmol/L and/or at 2 hours of ≥8.0 mmol/L is diagnostic of GDM. Thirteen of the 16 pregnant women with NGT levels had documented normal 50-g or 75-g glucose challenge tests. Three pregnant women had been considered by their obstetrician to be at low risk, and no formal glucose challenge had been performed. These 3 subjects had fasting glucose levels of <5.5 mmol/L on the morning of the LUSCS. The subjects with GDM were treated initially with dietary therapy. Insulin treatment was added if fasting self-monitored capillary glucose levels (BGLs) of <5.5 mmol/L and/or postprandial readings of <7.0 mmol/L were not achieved. Eight of the 13 patients with GDM required insulin therapy. The 19 nonpregnant control subjects were healthy premenopausal women who underwent elective gynecologic surgery. These subjects had no known history of T2DM, other endocrine disorders, or cancer. None of the nonpregnant women met the diagnostic criteria for diabetes mellitus on the basis of a fasting BGL level of ≥7 mmol/L or a random BGL level of ≥11.1 mmol/L.

Three pregnant subjects and 1 nonpregnant subject had a family history of T2DM. Subcutaneous and omental adipose tissue biopsy specimens were obtained at the beginning of abdominal surgery or just after delivery of the child at LUSCS. Samples were transported without delay to the laboratory in Dulbecco’s modification of Eagle’s medium (DMEM; 1000 mg/L glucose) that contained 2% bovine serum albumin (BSA). Informed written consent was obtained from all participants, and the study was approved by the Princess Alexandra and Mater Misericordiae Hospitals Ethics Committees.
Material

Human recombinant insulin, Actrapid, was obtained from Novo Nordisk Pharmaceuticals (North Rocks, NSW, Australia). [3H]-2-deoxyglucose was purchased from Amersham Pharmacia Biotech (Baulkham Hills, NSW, Australia). DMEM (1000 mg/L glucose), penicillin, streptomycin, glutamine, D-Sorbitol and unlabelled 2-Deoxy-D-Glucose were supplied by ICN Biomedicals (Seven Hills, NSW, Australia). Insta-gel Plus scintillation fluid was purchased from Packard Services (Mt Waverley, Victoria, Australia). All other chemicals were purchased from Sigma-Aldrich (Castle Hill, NSW, Australia).

Adipocyte tissue glucose uptake

Adipocyte glucose transport was determined as previously described. Briefly, whole adipose tissue explants (10-15 mg), with the exclusion of visible connective tissue and blood vessels, were removed from the biopsy material and placed in DMEM (1000 mg/L glucose supplemented with 2 mmol/L L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, and 2% BSA [pH 7.4]). Explants were incubated for 2 hours at 37°C under 5% carbon dioxide. Explants were washed with Krebs-Ringer HEPES (KRH) buffer that contained 1% BSA (pH 7.4) and incubated with 0.5-mL KRH buffer without or with 100 nmol/L insulin or 250 mmol/L sorbitol for 30 minutes at 37°C under 5% carbon dioxide; 50 μmol/L 2-deoxyglucose, 0.04 μmol/L [3H]-2-deoxyglucose (0.66 μCi/mL) was added, and the explants were incubated a further 20 minutes at 37°C under 5% carbon dioxide. Washing the explants in ice-cold KRH buffer stopped glucose transport. The explants were then washed a further 4 times to remove unbound label. Explants were blotted dry and then weighed using Mettler scales (Mettler-Toledo, Port Melbourne, Australia). [3H] radioactivity was determined with a Maxima Scintillation counter from Packard Services. In each experiment, points were determined in triplicate. Nonspecific glucose uptake for each condition was determined in the presence of 50 μmol/L Cytochalasin B, which was added to 1 well of each triplicate 5 minutes before the addition of the [3H]-2-deoxyglucose mix. All glucose uptake values were corrected for nonspecific glucose uptake by subtraction of the nonspecific glucose uptake for each experiment from each glucose uptake value. Data were expressed as disintegrations per minute per milligram of tissue, and responses to insulin and sorbitol were expressed as fold stimulation over basal. For each individual, glucose uptake studies in subcutaneous and omental adipose tissue that compared basal, insulin, and sorbitol treatment were performed in parallel.

Analytic methods

Serum was obtained from the pregnant women in the fasting state immediately before their LUSCS, and fructosamine was analyzed with an enzymatic colorimetric test on the Roche Modular Analyser (Mannheim, Germany).

Statistics

Tests of normality were performed with the Kolmogorov-Smirnov equation. Age and body mass index (BMI) were normally distributed, but glucose uptake values were not. One-way analysis of variance was used to verify differences in age and BMI among all 3 groups of women (nonpregnant, pregnant, and with GDM) and to determine differences in gestation and birth weights between the 2 pregnant groups of women. Post hoc tests were performed with Bonferroni correction for multiple comparisons. Differences in glucose uptake values between groups and depots were assessed with the Kruskal-Wallis test for several independent samples. Treatment effects (basal vs insulin vs sorbitol) within each group were analyzed by the Wilcoxon signed-rank test. Correlations between variables were performed with the Spearman’s rho test. In the text and Tables, data are reported as mean ± 1 SD (unless indicated otherwise). Figures for glucose uptake are presented as box plots with the median, interquartile range, and the highest and lowest values. All analyses were performed using SPSS statistical software (version 10.1 software for Windows package for personal computers; SPSS, Inc, Chicago, IL).

Results

Table I describes the characteristics of the subjects. The nonpregnant group was older than the pregnant group of subjects (42 ± 8 years old vs 33 ± 6 years old vs 33 ± 4 years old, nonpregnant vs NGT vs GDM, respectively; \( P < .001 \) compared with nonpregnant women). There was no difference in BMI between the groups with either the prepregnancy BMI or current BMI. Overall glycemia, as assessed by fructosamine, was comparable between the pregnant women with GDM and NGT.

Basal and insulin-stimulated glucose uptake

Basal and insulin-stimulated glucose uptake in both the subcutaneous and omental depots in the 3 groups of women that were studied (nonpregnant vs NGT pregnant vs GDM pregnant) is presented in Figure 1. Insulin stimulated a significant increase in glucose uptake in both depots and in all groups of women. Irrespective of depot, there was no difference in either basal or insulin-stimulated glucose uptake among the 3 groups of women. There was no difference in the response to insulin (assessed as fold over basal) among the 3 groups of women in either depot (data not shown).

There is a significant depot-specific difference in glucose uptake. All values were higher in the omental
Sorbitol-stimulated glucose uptake

Sorbitol-stimulated glucose uptake in subcutaneous adipose tissue from nonpregnant women is shown in Figure 2, which was an effect that was not significantly different in magnitude from insulin. Sorbitol had no effect on glucose uptake in omental adipose tissue and had no effect on adipose tissue from either depot that was obtained from pregnant women.

Basal, insulin- or sorbitol-stimulated glucose uptake values in the women with GDM did not differ if they were treated with diet and insulin or diet alone.

There were no correlations between sorbitol-stimulated glucose uptake in the subcutaneous depot and clinical variables in the nonpregnant women, despite sorbitol-stimulated glucose uptake correlating with insulin-stimulated glucose uptake \( (r = 0.663; P = .002) \).

Comment

The results of this study did not support the initial hypothesis that adipose tissue from pregnant women would demonstrate reduced insulin-stimulated glucose uptake compared with that from nonpregnant control subjects, nor the hypothesis that insulin-stimulated glucose uptake would be impaired in women with GDM compared with pregnant women with NGT. Rather, we found that basal and insulin-stimulated glucose uptake in both subcutaneous and omental adipose tissues are similar in pregnant and nonpregnant women and similar between pregnant women with NGT and pregnant women with GDM.

We have demonstrated for the first time that hyperosmolarity stimulates glucose uptake in human adipose tissue. This is in accordance with previous results in cell culture systems\(^{10}\) and rodent adipose tissue.\(^{15}\) However, the stimulation of glucose uptake by hyperosmolarity appears limited to subcutaneous adipose tissue from nonpregnant women.

The presence of normal insulin-stimulated glucose uptake in pregnancy and GDM was a surprising finding in light of the fact that in vivo both are known to be states of whole body insulin resistance. This suggests that adipose tissue is not a site of insulin resistance in pregnancy and GDM. To date, of 3\(^\text{18}\) studies have shown impaired insulin-stimulated glucose uptake in adipose tissue from pregnant women. Conflicting results may relate to methodologic differences that include (1) the method of matching body weight in pregnancy with nonpregnant control subjects (prepregnancy relative body weight,\(^{17}\) prepregnancy BMI,\(^{18}\) or a mixture of

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### Table I  Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonpregnant women</th>
<th>Pregnant women with NGT</th>
<th>Pregnant women with GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Age (y)</td>
<td>42 ± 8</td>
<td>33 ± 6*</td>
<td>33 ± 4*</td>
</tr>
<tr>
<td>BMI (kg/m(^2); Before pregnancy</td>
<td>28.4 ± 6.9</td>
<td>25.4 ± 4.4</td>
<td>27.6 ± 7.5</td>
</tr>
<tr>
<td>Gestational week</td>
<td>N/A</td>
<td>38.4 ± 0.7</td>
<td>38.2 ± 1.2</td>
</tr>
<tr>
<td>Fetal birth weight (g)</td>
<td>N/A</td>
<td>3529.8 ± 529.1</td>
<td>3628.2 ± 538.6</td>
</tr>
<tr>
<td>Fructosamine (µmol/L)</td>
<td>N/A</td>
<td>191.2 ± 12.8</td>
<td>190.7 ± 12.7</td>
</tr>
</tbody>
</table>

Data are given as means ± SD; 1-way analysis of variance with post hoc tests performed with Bonferroni correction.

* \( P < .001 \) versus nonpregnant subjects.

### Table II  Spearman \( \rho \) correlations (probability value) between basal and insulin-stimulated glucose uptake in subcutaneous and omental adipose tissue and BMI in the total population that was studied (ie, nonpregnant women \([n = 19]\), pregnant women with NGT \([n = 16]\), and pregnant women with GDM \([n = 13]\) combined)

<table>
<thead>
<tr>
<th>Depot</th>
<th>Treatment</th>
<th>Current BMI</th>
<th>Prepregnancy BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous Basal</td>
<td>+0.115 (.438)</td>
<td>+0.116 (.433)</td>
<td></td>
</tr>
<tr>
<td>Insulin 100 nmol/L</td>
<td>-0.181 (.218)</td>
<td>-0.149 (.313)</td>
<td></td>
</tr>
<tr>
<td>Fold insulin 100 nmol/L</td>
<td>-0.420 (.003)</td>
<td>-0.358 (.012)</td>
<td></td>
</tr>
<tr>
<td>Omental Basal</td>
<td>-0.267 (.067)</td>
<td>-0.258 (.076)</td>
<td></td>
</tr>
<tr>
<td>Insulin 100 nmol/L</td>
<td>-0.285 (.05)</td>
<td>-0.329 (.022)</td>
<td></td>
</tr>
<tr>
<td>Fold insulin 100 nmol/L</td>
<td>-0.021 (.886)</td>
<td>-0.144 (.330)</td>
<td></td>
</tr>
</tbody>
</table>

\( P = .002 \).
obese and lean subgroups; (2) differing methods being used to measure glucose uptake (D-U-[14C]-glucose conversion to total lipid, 3-O-Methylglucose transport), and (3) small subject numbers (n = 17 women).

Our study is the first to compare both subcutaneous and omental adipose tissue depots and to include the largest number of subjects to be studied so far. Our groups have been matched on the basis of current BMI but are also not significantly different in body weight when their prepregnancy BMI levels are compared. We have assessed glucose uptake in adipose tissue explants.
soon after collection in an attempt to maintain the influence of the hormonal milieu of pregnancy.

One previous study has reported comparisons of glucose uptake in adipocytes from pregnant women with GDM and NGT. Garvey et al\textsuperscript{19} demonstrated impaired insulin-stimulated glucose uptake (3-O-Methylglucose) in omental adipocytes in women with GDM (n = 8) compared with pregnant women with NGT (n = 8). However, the mean BMI of the NGT pregnant control subjects and the pregnant women with GDM was significantly different (25 vs 33 kg/m\textsuperscript{2}). This may account for the differences that were seen in glucose uptake because our study clearly demonstrated (Table II) an inverse correlation between insulin-stimulated glucose uptake and BMI. Our finding is also consistent with a previous publication from this group.\textsuperscript{14} We do not believe that the difference in age among the 3 groups in our study should impact on the interpretation of the results because we previously published data that demonstrated that aging per se does not influence glucose uptake in human adipose tissue.\textsuperscript{20}

We propose therefore that adipose tissue in pregnancy is not insulin resistant from the point of view of glucose uptake, which suggests that other insulin-responsive tissues (such as liver or muscle) may be directly responsible for the impairment in the whole body insulin-stimulated glucose uptake that is demonstrated in vivo. There may be not only tissue-specific differences in insulin sensitivity but also differences in sensitivity to the various actions of insulin (ie, glucose uptake vs lipogenesis vs mitogenesis). Assessment of these various actions of insulin and comparisons between different tissues will be the focus of future work.

We are the first to describe a significant but modest effect of sorbitol on glucose uptake in human adipose tissue. This confirms that alternative stimuli, apart from insulin, stimulate glucose uptake in human adipose tissue. If the signaling pathways involved in human adipose tissue are similar to those in rat adipocytes and cell culture systems, then these alternative pathways may warrant further exploration as potential therapeutic targets to increase glucose disposal in T2DM. The correlation between sorbitol and insulin-stimulated glucose uptake suggests that some of the mechanisms that are involved in these pathways are similar. However, in pregnancy, insulin-stimulated glucose uptake is normal, but sorbitol-stimulated glucose uptake is impaired. This paradox could be explained by a reduction of a “sorbitol-responsive” pool of GLUT4, the presence of which has been proposed by Li et al.\textsuperscript{21} Alternatively, there may be an increase in the activity of the PI 3-kinase-dependent pathway (IRS-1/PI 3-kinase/Akt/PKC/GLUT4) to compensate for a defective alternative insulin signaling pathway (CAP/Cbl/APS/CrkII/C3G/TC10/GLUT4) in pregnancy. The defect in sorbitol-stimulated glucose uptake in pregnancy and GDM suggests that this stimulus of glucose uptake may be of physiologic significance. One could speculate that this represents a form of non–insulin-mediated glucose uptake. Non–insulin-mediated glucose uptake has been reported to represent 40% to 70% of postabsorptive glucose uptake in vivo.\textsuperscript{22} There have been conflicting reports as to whether non–insulin-mediated glucose uptake is up-regulated or down-regulated in patients with T2DM.\textsuperscript{23,24} There are no reports on the contribution of non–insulin-mediated glucose uptake to glucose disposal in human pregnancies.

Insulin clamp techniques (traditionally the “gold standard” for quantification of insulin action in vivo) actually measure both insulin-independent and insulin-dependent glucose uptake.\textsuperscript{25} It is conceivable therefore that pregnancy is associated with impaired non–insulin-mediated glucose uptake and that the hyperinsulinemia of pregnancy represents an appropriate compensatory mechanism that is designed to overcome this impairment.

In summary, we have demonstrated that pregnancy and GDM are not associated with impaired insulin-stimulated glucose uptake into adipose tissue. We conclude that adipose tissue is not a direct site of insulin resistance in pregnancy. Further, we have demonstrated that sorbitol stimulates glucose uptake in subcutaneous adipose tissue. However, this effect is not seen in omental adipose tissue from nonpregnant subjects nor in either adipose tissue depot in pregnancy. We propose that the activity of the alternative insulin signaling pathway by way of CAP/Cbl/APS/CrkII/C3G/TC10/GLUT4 may be impaired in pregnancy and further hypothesize (and speculate) that non–insulin-mediated glucose uptake is impaired in pregnancy and GDM.

**Acknowledgments**

We thank P. Imbeault (University of Ottawa, Canada) and E. Bellar (University of Queensland, Australia) for assistance with statistical analysis, the surgeons and obstetricians from the Princess Alexandra and Mater Mother’s Hospitals, and especially to the women for their participation.

**References**


Endocrine functions of the human fetoplacental unit

Egon Diczfalusy


FIG. 6. Concept of the estrogen synthesis and metabolism in the fetoplacental unit (according to Bolli et al. (14)). Arrows with dotted lines indicate unproven reactions. DHA indicates dehydroepiandrosterone, and DHAS its sulfate. N indicates various neutral metabolites of DHAS; A is androstenedione; T testosterone; OE₁, OE₂, and OE₃ estrone, 17β-estradiol, and estriol; and OE₂S, OE₃S, and OE₃S their 3-sulfates. Z stands for a 16-hydroxylated phenolic intermediate formed by the fetus from placental estrone; Y is a 16-hydroxylated neutral metabolite formed from DHAS circulating in the fetus.
Commentary by Lawrence D. Longo, MD

The concept that the placenta and fetus, in concert with the mother, consists of a unit for hormonal synthesis and metabolism derived from the work of Diczfalusy et al.1-4 In the case of steroid biosynthesis, by aromatization, the placenta converts 16α-hydroxy dehydroepiandrosterone sulfate that is made by the fetus from dehydroepiandrosterone sulfate into estriol. This is secreted into the maternal circulation and is the main estrogen metabolite that is excreted in the mother’s urine. The fetus also can initiate the pathways for conversion of cholesterol to pregnenolone and on to dehydroepiandrosterone sulfate. Thus, the placenta, in concert with several fetal organs, plays a unique role in the regulation of steroid hormone production in pregnancy.

Diczfalusy (who was originally from the University of Szeged, Hungary) moved to Stockholm, Sweden, where he became professor and head of the Reproductive Endocrinology Research Unit at the Karolinska Institute. His investigations centered on the metabolism of steroids in the fetus and placenta, their interconversion, and their functional roles.1-4 Although some investigators may question certain aspects of these historic studies, one must remember that these studies were performed under strict guidelines of the Medical Research Council of Sweden with women who had elective termination of pregnancy by the accepted method at that time. In the following years, Diczfalusy became one of the initiators of and the senior consultant to the Human Reproduction Program of the World Health Organization, which is a program with which he is still involved. He is the recipient of numerous international awards and honors.

References


My life with the fetal-placental unit

Egon Diczfalusy, MD*

Ronninge, Sweden

How did I become a reproductive endocrinologist? As a medical student in Hungary, I had been unable to repeat a microbiology study that had been published by the Nobel Laureate Hans von Euler (1873-1964). Subsequently, in 1946 I moved to Stockholm and, during the years 1946 and 1947, became von Euler’s assistant. As it turned out, many of my scientific activities can be characterized as unfinished symphonies, without the qualities of Schubert’s work. In 1947, I had the opportunity to work in the Hormone Laboratory in the Department of Obstetrics and Gynecology of Professor Axel Westman at the Karolinska Hospital in Stockholm. Thus, suddenly I was no longer a bacteriologist, but rather an endocrinologist. In association with the pharmaceutical company AB Leo of Helsingborg, I worked on the metabolism of estrogen phosphates.1 After attending a 1950 meeting of the Biochemical Society in Edinburgh, I became friends with and was
influenced by Guy Frederic Marrian (1904-1981), Sir John (Jack) Henry Gaddum (1900-1965), and some of the younger endocrinologists who worked with these “giants.” Later, at the suggestion of Professor Westman and in partial fulfillment of a thesis for a Swedish academic degree, I worked on chorionic gonadotrophin and estrogens in the human placenta.2

That the placenta is an endocrine organ was first suggested by Joseph Halban3 in a paper that is one of the great classics in reproductive endocrinology. In my thesis I went a step further by saying that “there is some reason to believe that the fetal organism actively participates in the metabolism (possibly also in the production?) of estrogens.” The idea that the placenta and fetus may form a functional unit was certainly in the back of my mind in those early years, judged from the summarizing statement of my paper that was presented at the Symposium of the German Endocrine Society in Bonn, on 5 March 1955. The German text says: “In summary, it should be emphasized that the placenta represents a polyvalent hormone producer with an unknown regulatory mechanism. We believe therefore that it is a fruitful hypothesis to study the placental and fetal metabolism of hormones together as a unit.”4 This suggestion was received with much skepticism at the meeting. One of the major arguments against it was how such a small fetus could produce such quantities of steroids.

When I started my career, the “heroic age” of reproductive endocrinology was over.5 As an example, the most important estrogens were already isolated.5-7 What was left to our generation was to isolate and study these compounds in sources other than pregnancy urine, to isolate additional metabolites, and to follow the advice that had been given in the epilogue of Marrian’s8 Sir Henry Dale Lecture and unravel the mechanisms of action of steroid hormones, which became the major focus for attention in the 1960s and 1970s. Indeed, the Laurentian Hormone Conference paper by Jensen and Jacobsen9 signaled, as early as 1962, that this would be a very fruitful field of research.

Our modest contributions consisted of isolating “old” estrogens from new sources and a few new ones, such as estriol-3-sulphate-16 (17?)-glucosiduronate,9 15α-hydroxyestriadiol,10 and 15α-hydroxyestriol11 from classic sources.

The most significant difference between the heroic age of reproductive endocrinology and its “merry post-war period” was, however, that the previous noble hobby, science, became a profession that provided, for the first time, a living for many people who were engaged in full-time academic research. Medical Research Councils were created in a relatively large number of countries, and the National Institutes of Health (NIH) established an almost revolutionary principle to support research that was conducted outside the United States. Furthermore, in the early 1960s, the Ford Foundation started a multi–million dollar program to support reproductive biology and endocrinology on a truly world-wide basis. Science became again, at least in part, international, as it was before 1914, when, to quote Sir Henry Dale, “we were able to claim that science belonged to the world, knew no frontiers, was one and indivisible.”12

The large number of scientists who decided then to become investigators on a full-time basis did not imagine, of course, in the merry years of the late 1950s and early 1960s that by the 1970s the so-called public faith in unlimited scientific achievements might fade away rapidly, together with a considerable part of the financial support to science and leave behind a general feeling of malaise and frustration not only in the so-called “public opinion,” but also among many disillusioned scientists. At any rate, during the merry post-war period, especially at the beginning of the 1960s, everything was great and dandy. This was the case not only in the United States with a yearly NIH budget that exceeded a billion dollars, but also in my own unit, which was supported not only by the Swedish Medical Research Council but also by the NIH and from 1962 by a major contribution from the Ford Foundation.

Interruptation of gestation for medical and medical-social indications had been legal in Sweden since 1938; the number of second-trimester interruptions was considerable, and the Swedish Medical Research Council believed that this most valuable scientific material should not be wasted. Hence, in the early 1960s, my interest became more and more concentrated on the role of the fetus in the endocrinology of gestation, especially after my collaborator Ove Cassmer demonstrated that severing the umbilical cord, but leaving the fetus in situ (a method widely used at that time in Sweden for the interruption of gestation), resulted in a marked drop in urinary estriol levels but influenced only slightly pregnanediol excretion.13 A further impetus for our research were the stimulating studies by Frandsen and Stake-mann14 that pregnant mothers who bear anencephalic monsters excrete greatly reduced amounts of estriol in their urine. However, they attributed this to the absence of estrogen synthesis by the hypoplastic adrenal cortex of the anencephalic monsters, whereas I believed it more probable that the placental, rather than fetal, elaboration of estrogens is impaired in anencephalic monsters, perhaps as a consequence of the lack of a fetal adrenal precursor of placental estrogen synthesis.15 Last but not least, an important prerequisite for our studies was the development of a suitable technique for the perfusion of previable fetuses by Westin et al.16

Our first paper that directly referred to the fetoplacental unit in its title was published by Mikhail et al.17 Nils Wiqvist, who later became the Head of the Department of Obstetrics and Gynecology at the University of Gothenburg, was the principal clinical investigator in this and many subsequent studies; his important
contributions to our studies deserve considerable credit. I first presented the full concept of the fetoplacental unit at a Federation Meeting in 1964. Unfortunately, I could not attend the meeting, but Claude Villee was kind enough to read the paper for me.

Obviously, a concept like this is not born as a child of an exceptionally favorable moment of imagination. Its foundations are laid by hundreds of investigators, providing, as George W. Corner noted in his Dale Lecture of 1964, all the necessary “pieces of a jigsaw puzzle” to be put together by someone. That this was the case also as far as the concept of the fetoplacental unit is concerned is obvious from reading the careful review of the field by Mitchell in 1967 and also my own review the following year. Who then the “someone” will be depends perhaps on fortunate circumstances (‘sors bona, nihil aliud’, [good fortune, nothing else] as the Hungarian hero of the 17th century, Count Miklós Zrínyi [1620-1664] put it) and does not really matter much. During > 60 years of professional life I have learned that, by the end of the day, all of us become astronauts, traveling with an incredible speed into oblivion. Hence as a fact of life, the investigators who are involved will be forgotten rapidly, just as their disagreements will be forgotten; but the concept, if it is a useful one, will survive.

At any rate, the suggested concept stated that the fetus synthesizes mainly the “primitive” 3β-hydroxy-Δ5 forms of steroids, such as pregnenolone or dehydroepiandrosterone, which reach the placenta chiefly as 3-sulphates. Furthermore, the placenta is an incomplete steroidogenic organ that carries out little, if any, steroid synthesis de novo. However, it has 4 exceedingly active enzyme systems: various types of sulphatases, 3β-hydroxysteroid dehydrogenases, an aromatizing enzyme system, and some other dehydrogenases. Therefore, the placenta converts 3β-hydroxysteroids (and their sulphates) into the corresponding α,β-unsaturated ketones (for instance, pregnenolone into progesterone, dehydroepiandrosterone into androstenedione and testosterone, and 16α-hydroxytestosterone). The C-19 compounds are then rapidly converted by the placenta into the corresponding principal estrogens (estrone, estradiol, and estriol) in an increasing order of quantitative importance. Finally, steroids that reach the fetus from the placenta are exposed to extensive sulphurylation and/or hydroxylation reactions.

Because, in collaboration with Bird et al in Montreal, it was also shown that the adrenals of fetuses who were perfused with labeled progesterone convert this steroid into 17-hydroxyprogesterone, corticosterone, and cortisol, it appeared highly likely that the midgestation fetus is capable of providing itself with a variety of essential adrenocortical steroids, by using placental progesterone as one of the principal substrates for 11α-, 17-, and 21-hydroxylations. Some of these perfusion studies that thus confirmed the results of previous in vitro studies by several investigators in the 1950s and early 1960s, were presented in detail by Solomon et al at the Laurentian Hormone Conference.

Thanks to a fruitful collaboration with Pasqualini et al in Paris, we could demonstrate not only the formation of various adrenocortical hormones (including aldosterone) by the previable fetus but also the significant differences between the fetal and placental metabolism of the various unconjugated and conjugated corticosteroids that were formed. Furthermore, a long-term collaboration with Levitz et al in New York enabled us to investigate in depth the placental transfer and fetoplacental metabolism of the various estrogen conjugates that were formed.

During the period between 1963 and 1972, we could explore systematically the fetal, placental, and maternal interrelations in the formation of steroids and steroids during pregnancy. This information was published in some 80 “full dress” papers, but we modified only slightly the principal concept of 1964.

In a somewhat simplistic enzymologic terminology, the “final” concept states that the placenta is not a true steroid-producing organ, because it cannot form de novo from acetate any squalene, lanosterol, or cholesterol. These reactions take place in the fetal and maternal organism. On the other hand, the placenta can convert cholesterol in the blood to pregnenolone and various Δ5-steroids (eg, pregnenolone) or dehydroepiandrosterone into biologically active Δ4-compounds (eg, progesterone or androstenedione). The placenta also possesses powerful sulphatases, which hydrolyze a variety of steroid sulfates (eg, pregnenolone sulphate, dehydroepiandrosterone sulphate, or estrone sulphate). It also has a potent aromatizing enzyme system, which converts different androgens into the corresponding estrogens (eg, testosterone into estradiol and 16α-hydroxy-testosterone into estriol). Thus, the sequence of placental reactions can be visualized as dehydroepiandrosterone sulphate → dehydroepiandrosterone → androstenedione → testosterone → estriol and estradiol. Hence, the placenta can convert cholesterol into C-21 steroids, 3β-hydroxy-Δ5-compounds to Δ4-steroids, and androgens to estrogens.

The placenta also possesses various sulphatases and different 3β-hydroxysteroid dehydrogenases that, again with few exceptions, are absent in fetal tissues. Because certain enzymes (such as the cholesterol side-chain cleaving enzyme and the aromatizing enzyme system) are functioning in both compartments, and by integration of these functions, the fetoplacental unit can indeed elaborate most, if not all, steroid hormones. On the other hand, the human fetus possesses the cholesterol-synthesizing enzyme system, steroid sulphurylating enzymes, and various hydroxylation enzymes that, with few exceptions, are not present in the placenta.
Because the fetus is capable of carrying out a variety of hydroxylations, it can provide itself with all essential adrenocortical steroids through a series of hydroxylations of placental progesterone. Also, because the fetus can also elaborate all the corresponding $\Delta^2$-steroids, it is likely that parts of these steroids are converted by the placenta into their biologically active $\Delta^4$-counterparts.

Furthermore, the fetus can also easily remove the steroid side-chain and form large quantities of dehydroepiandrosterone sulphate from pregnenolone sulphate, through 17-hydroxypregnenolone sulphate without any hydrolysis of the steroid sulfates. The complexity of the reactions that are involved can be illustrated by recalling that large quantities of dehydroepiandrosterone sulphate that are formed by the fetal adrenals are then 16α-hydroxylated by the fetal liver, hydrolyzed, and further metabolized into the corresponding androgen, 16α-hydroxyandrostenedione, by the placenta, where it is subsequently rapidly converted into the quantitatively most important steroid of human gestation, estriol. Similarly, complex mechanisms exist for the formation of other estrogens.27

The splendid rise of the “fetoplacental empire” came to an abrupt end in 1971, when prostaglandins were introduced in Sweden for the termination of pregnancy. This resulted in such success that, within a short time, it became unethical to interrupt second-trimester gestation by laparotomy. We discontinued our work completely by the middle of 1971, and I wonder whether anyone may ever be able to resume such studies. In retrospect, one of the weaknesses of our approach was that we did not measure the absolute mass of the various steroids, only the amount of radioactive material.

About the time that prostaglandins were introduced for therapeutic abortion, radioimmunoassays for steroids became available. It is interesting to speculate what might have happened if steroid radioimmunoassays had become available some 10 years before the introduction of prostaglandins. Probably, we would have had today a more complete view of the fetoplacental unit in much more quantitative terms. As it happened, in the early 1970s, the human fetoplacental unit virtually ceased to exist as a suitable topic for investigation, and I became richer with another unfinished symphony.

In the final analysis, every scientific contribution is, in a way, an unfinished symphony, the basic motives of which are taken up and developed further by the musicians of a new generation. I sincerely hope that some of the fragments that are presented here may some day entice other investigators to commence anew similar studies. After all, an in-depth study of the “well-established facts” still appears to be an efficient way of obtaining basically new information. As François Villon (1431-ca 1465) stated in one of his immortal ballads:

Rien ne m’est seur que la chose incertaine: Obscur, fors ce qui est tout evident; Doubte ne fais, fors en chose certaine; Science tiens a soudain accident.

The English translation, as I have seen it in Blakemore’s book,28 is equally appealing:

I put all my trust in things that I doubt; The obvious alone is unclear. Certainty never knows what it’s about, And truth from sheer chance will appear.

**References**

SGS is an evolving society of gynecologic surgeons dedicated to promoting the highest standards for gynecologic surgical care for women in a safe, effective and ethical manner. SGS promotes the acquisition of knowledge and the improvement of skills and enhances the understanding of gynecology and gynecologic surgery through basic and clinical research.

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**THIRTY-SECOND ANNUAL SCIENTIFIC MEETING
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Presidential Address: The Chickens

Thomas G. Stovall, MD

Women's Health Specialists, PLLC, Memphis, TN

It is indeed an honor to have been selected and elected as the President of the Society of Gynecologic Surgeons. Because of the circumstances and timing surrounding our joint meeting with AUGS last year, I am the shortest-term president in the history of the Society. As a result, I felt that it would be most appropriate for me to give the shortest address. I’m certain that you’re not unhappy about either of these circumstances, either my short term or my short Presidential Address.

Being President of the SGS is a fun and easy job, because virtually all the work is done by the Secretary, Assistant-Secretary, Program committee, and the various other committee members. In fact, the only significant job of the president is to figure out what you’re going to say that might be worthwhile during the presidential address. This is a daunting task that has perplexed me from the moment I became the President-elect more than 2 years ago. I began by reviewing many of the former presidential addresses and found that these presidents talked about their mentors and those that had helped them along the way. Many provided a challenge to the society or told of their devotion to a specific type or special project that was of national or international interest. I found myself struggling on a number of levels. First, I couldn’t think of anything that was worthy of many of the former challenges that had been put before this society. Many of these have now been accomplished. There was no national project that I was so dedicated to that I felt that others in this society would heed my enthusiasm. And finally, when I approached those who had mentored me either through my life choices or career, none wanted to be mentioned. Thus, I was perplexed. I wanted to provide something to this Society that would provide deep thought and meaning. Something that might even answer some of life’s great questions. Something worthwhile, a something not answered by the great civilizations of the past such as the Romans or Incas.

The Roman Empire was one of the most powerful and important empires of the ancient world. Even today, 1500 years after its fall, there is evidence of the great accomplishments of the Roman Empire in art, architecture, and literature the Romans left behind. At its height, the Roman Empire covered most of Western Europe and parts of Asia and Africa. Their language—Latin—forms the basis of languages spoken today in many parts of the world.

The Incas are a native South American people that once ruled one of the largest and richest empires in the Americas. They numbered more than 10 million people and covered 440,000 square miles. They had mighty armies, efficient organizations, and communication. Incas constructed a paved road system, irrigation canals, and massive stone buildings. But they too were weakened by civil war and unrest, and overwhelmed by a small force of Spanish soldiers.

Yet, these 2 great historical empires didn’t seem to provide an answer to my problem. And so, I did as I often do when I’m faced with a difficult decision. I turned to my chickens. Why? Because the chickens are able to teach us the lessons that these 2 great empires couldn’t.
About 5 years ago now, my then 10-year-old son, Elliott, became interested in horses. One thing led to another and then another. In short time, our family had sold our house in the suburbs, bought a small farm on the outskirts of town, began driving a pick-up truck, wearing blue jeans and boots, bought horses, built a barn, and began barrel racing and steer wrestling. These are rodeo events for those of you who are uneducated in the finer aspects of life. In fact, an extensive search suggests that I’m the only barrel-racing gynecologist in the world. Some might call this a mid-life crisis, while others would provide a different description. I tell you this story so that you’ll know how I came to have 14 chickens, and how I began to study and observe chickens in the first place. Chickens are interesting creatures, and with a little study and lots of observation, one can glean a number of important lessons that can be applied to life in general as well as to managing people and working with physicians. I’d like to share these lessons with you.

Lesson 1: Everyone needs a mentor. Two-day old baby chicks are obtained from the feed store and arrive via Federal Express. Over the next 6 weeks, the chicks have to be nurtured, fed, watered, and their cage cleaned at least twice a day. Chicks smell funny and are very messy. Sort of like students. They also eat a lot. Chickens will eat anything. Similar to residents. But you can’t put the baby chicks in the chicken house until they are almost grown. Baby chicks just can’t take care of themselves. Our kids, our students, and residents are like baby chicks.

After this time of caring and nurturing, the chicks are placed in the chicken yard to continue their growth and maturation process. But they still have to be fed and watered and checked on everyday. Our chicks had been in their newly constructed Ritz-Carlton—like chicken house and outdoor play pen for about a week when we left town for a couple of days and asked someone else to watch the chickens. On the first afternoon, the neighbor was going to check on the chickens when her dog showed up with that look that only a dog who has done something wrong can get.

Lesson 2: You better be careful or the dogs will eat you. How true that is today in medicine more than ever before. There are a lot of dogs out there and they come in all sizes, shapes, and disguises. There are also a lot of foxes out there they will not only steal your eggs, but eat your chickens too.

Lesson 3: Chickens, like many hospital administrators and all managed care administrators, are cannibalistic. You see, chickens peck on everything and they even peck on each other. If during their pecking they draw blood, the pecker will peck the bleeding chicken until he or she bleeds to death. Once completed, they’ll eat the dead chicken. Now, if you’ll let your mind wander just a bit, you’ll be able to see clearly how this applies to hospital and HMOs. Which now leads to the next lesson.

Lesson 4: Pecking order. Everyone one knows the concept of pecking order, but not everyone knows where the term originated. We’ll, it’s yet another lesson that is learned from chickens. Chickens, define their place in the herd through pecking. In other words, if a new chicken is added to the herd, he or she will peck at the lowest chicken in the rank until one of them backs down. If the new chicken wins that battle, they then move to the next one in line, until finally their place in the herd is firmly established. In this respect, chickens are similar to many other herd animals like horses or dogs. Chicken groups are similar to many medical institutions that have a clearly defined pecking order or a clearly defined hierarchy. Physicians, more so than other professionals, are taught in a hierarchical environment in which they are generally afraid to or not allowed to challenge the authority figure. Physicians and chickens have a hierarchy bias. While not all bad by any means, especially if you’ve pecked your way to the top already, it is very different from a business environment. Thus, physicians tend not to do well when working in groups. They tend to be more independent rather than collaborative. In matters of patient care, the physician usually decides and acts alone and lives alone with the results of the decisions. This is not a bad thing when doing surgery, because you don’t want your surgeon to have to develop a consensus during the middle of your operation, but our training does hamper us when we move from the clinical arena to the business realm. Which brings us to our next lesson learned through observation.

Lesson 5: Traveling in a herd provides protection. Chickens like most animals have a herd instinct. They do this for 1 simple reason. If the fox comes, or should I say, when the fox comes, the chickens have a better chance of survival if they are all pecking the fox at the same time. In fact, if the fox or the dog or the coyote starts to dig under the chicken house or tries to get through the chicken wire, as soon as their nose is accessible, the chickens start pecking at it. Much of what is good about medicine is communal. We are grateful for the presence of others who have or who are sharing our journey. But, when will physicians ever learn? If only we could get together and stay together to fight off the fox and the dogs and the coyotes. Which brings us to our next lesson.

Lesson 6: If you fly around out of control, you’ll hit the wall, break your neck, and die. Occasionally, but not very often a chicken will get mad because he/she hasn’t gotten the respect she believes she deserves, or hasn’t gotten enough to eat, or for whatever reason is just having a bad day. The mad chicken will start to peck the other chickens in a sort of peck-and-dash type affair. When they still don’t get what they want, they begin to
fly around and go on the attack. Generally, after a few minutes, the not-so-happy chicken will calm down, and go back to their business of eating and pooping. These are the 2 most important things in a chicken’s life. One day while watching the hens, the cycle began with 1 hen getting mad over her food, she began to fly around. Soon she was out of control, flew into the wall, broke her neck, and died instantly. Know someone or work with someone who doesn’t get their way, starts to fly around, and evidently is out of control? Help them regain control so they don’t break their neck. Which leads us to our next lesson.

Lesson 7: The world looks brighter through rose-tinted glasses. Remember in lesson 3 we learned that chickens peck each other and will occasionally draw blood, which leads the pecking chicken to peck harder. The chicken is ultimately killed and eaten. This presents a problem to the commercial chicken or egg producer. You obviously don’t want your resources being consumed. Chickens become positively mellow when they see the world through rose-tinted glasses—or better yet, fire-engine red contact lens or spectacles. Scientists, and I use the term loosely, aren’t sure why, but a rosy outlook eliminates the pecking order among chickens. Red-eyed birds spend less time fighting and more time laying eggs. They also eat less. And these 2 things together translates into a savings of 2.5 cents per dozen eggs. With 1.2 billion laying chickens multiplied by the 20 dozen eggs each hen yields a year, the savings is almost $600 million dollars. Contact lenses for chickens go for a modest 20 cents a pair, or 15 cents if you buy in bulk. If you want an alternative, you can also buy rose-colored spectacles. The contact lenses are put in place in just a few seconds by holding the bird’s head steady, or the spectacles are held with a strap around the chickens head. They stay in place for the life of the bird. No cleaning or artificial tears are required. You’ve always heard that the world looks better through rose-tinted glasses, but now you know the origin of this truth. So, the next time things seem a little rough or when things aren’t going as smooth as you might like, put in your rose-tinted contact lenses. Each day we have the choice of what our attitude will be. Choosing a positive attitude leads to increased happiness, and improves your productivity. Productivity—is that another lesson.

Lesson 8: Sometimes you just have to put the sitters in time out. A good hen will begin laying at about 8 months of age. You know that a prepubertal chicken is about to start laying when you can put 2 fingers between their pubic arch. Once started, a good hen will lay an egg every 30 hours or so for the next 18 to 24 months. However, occasionally, you’ll get a chicken that goes through a time of sitting. That is, they’ll lay an egg, and just sit there. They don’t get up to eat or drink. They simply keep on sitting. No productivity—just sitting. The only way to get them off their nest and get them back to their job of laying is to put them in time out. You physically take them out of their laying box, put them in solitary confinement away from the other hens, and keep them NPO, except for water. The hen will start laying again. She can return to the herd after about 5 days, and resume a normal productive egg-laying life. There are 2 aspects of this observation that are important. First, we only feed the chickens that are productive, and the more productive you are, the more you are allowed to eat. And secondly, at times you have an unproductive chicken that you need to discipline in order for that chicken to once again become productive.

Lesson 9: Hen-pecked. It’s a lot easier to buy a 2-day old chick rather than to hatch them from a fertilized egg. Therefore, what you really want is a group of good layers without the distractions that a rooster brings. However, because it’s difficult to tell the sex of the chicken, you will sometimes get a rooster mixed in with the hens, which can lead to trouble. So when the rooster begins to do rooster things, and the hen isn’t in the mood, the hen begins to peck at the rooster until he stops. Thus, the term “hen pecked.” Hen pecked is now defined as to dominate or harass one’s husband with persistent nagging, or to subject to petty authority. In a recent survey when 100 married men were asked if they were hen-pecked, 37% said yes, 19% said no, 8% said “What is that?” and 37% said that they’d have to ask their wife. I’m not sure what the lesson is in this, but I thought that at least it would be nice to know the data and where the term comes from.

Least you think that this address has not been scientific or evidence-based, please allow me a moment to mention 1 laboratory-based randomized, controlled trial. For centuries, chickens have held a special place on grandma’s shopping list, especially when anyone in the household started to cough, sniff, or sneeze. Chicken soup has been used through the century. Chicken soup has been prescribed by thousands of healers throughout the century. Chicken soup has been used to treat hemorrhoids, constipation, stress incontinence, vaginal prolapse, and even leprosy. But does it work? Rennard found that a standardized recipe for soup slows neutrophil migration and therefore reduces inflammation and helps to mitigate symptomatic upper respiratory tract infection.

This now brings us to the 2 perplexing questions that everyone has been wondering whether I’d address. These questions have challenged the great minds and philosophers of our history and have been the subject of essays and hundreds of jokes. First, why did the chicken cross the road? Who cares, you go back and forth your whole life. Second, What came first—the chicken or the egg? Do we really care? Does it really matter? We now have both chickens and eggs.
Like the chicken laying the egg, or giving his life for the dinner table or for the chicken soup that heals, all of us have paid a price to become physicians and to practice medicine. Many of you have helped more people than you will ever know, and often times without praise, a pat on the back, or a simple thank you. Please accept my thank you and my praise for all that you have done for me and for those to whom you have ministered.
Racial differences in pelvic morphology among asymptomatic nulliparous women as seen on three-dimensional magnetic resonance images

Lennox Hoyte, MD, MSEECS, John Thomas, MD, Raymond T. Foster, MD, Susan Shott, PhD, Marianna Jakab, MSEECS, Alison C. Weidner, MD

Harvard Medical School, Boston, MA; Duke University Medical Center, Durham, NC; Rush University, Chicago, IL

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Objective: Compare pelvic morphology between asymptomatic African-American and white nulliparous women.

Study design: Resting supine T2-weighted magnetic resonance (MR) images were obtained in 12 African-American (AA) and 10 white American (WA) women without pelvic floor dysfunction. Three-dimensional models were reconstructed from the MR images by a masked investigator, and predefined bony and soft tissue pelvic floor parameters were measured and compared. Nonparametric statistics were used, with significance considered at \( P < .05 \).

Results: Subjects were similar in age and body mass index. Levator ani volume was significantly greater in the AA versus the WA group (mean = 26.8 vs 19.8 cm\(^3\), \( P = .002 \)). The levator-symphysis gap was smaller in the AA (left-18.2, right-18.8 mm) versus the WA group (22.4, 22.6 mm, \( P = .003, .048 \)) on the left and right. Significant differences were seen in bladder neck position, urethral angle, and the pubic arch angle.

Conclusion: The increased muscle bulk and closer puborectalis attachment seen among the African-American nulliparous women may impact the development of pelvic floor dysfunction. These findings need further study.

Female pelvic floor dysfunction (PFD) includes urinary incontinence, pelvic organ prolapse (POP), fecal incontinence, and defecatory dysfunction. PFD is thought to stem from pelvic muscle, nerve, and connective tissue damage sustained during vaginal childbirth.\(^1,2\)

Notably, approximately 75% of the 4 million annual US births are delivered vaginally.\(^3,4\)

There is epidemiologic evidence of a relationship between childbirth and PFD.\(^5\) However, not all women who undergo vaginal childbirth develop PFD.\(^6\) Further, not all nulliparous women are free of PFD.\(^7\) In addition, some have observed anecdotally that urinary incontinence and POP may occur less often in women of African descent, when compared with white women.\(^8,9\)

Work by Sze et al\(^10\) and Handa et al\(^11\) suggested that
bony pelvic shape, rather than race, may be a factor in the development of PFD among parous women. Therefore, we sought to determine whether there were bony and soft tissue differences in pelvic morphology between well-characterized, asymptomatic nulliparous white and African-American women. Magnetic resonance-based 3-dimensional (3D) reconstruction techniques were used as the imaging modality because of the superior tissue definition and high resolution of magnetic resonance imaging (MRI), coupled with the improved visualization of spatial relationships offered by 3D techniques.

MRI has greatly improved our ability to study the organs and tissues of the pelvis in women. Standard 2D MRI has been used to assess the anatomy of the female pelvic floor in cadavers and living women.\textsuperscript{12,13} Three-dimensional reconstruction offers additional advantage over 2D MRI because it affords better visual appreciation of key structures, and superior assessment of volumetric and plane geometry.\textsuperscript{14} Further, 3D reconstruction can minimize the artifacts possible because of variations in MR slice acquisition angle across subjects.\textsuperscript{15}

Material and methods

This is an Institutional Review Board-approved, prospective observational cohort study, examining MRI data from 2 groups of nulliparous women: 12 African-American and 10 white American. All were premenopausal, and had stage 0 or 1 pelvic support as defined by the POPQ system,\textsuperscript{16} by examination in the supine straining position. To be eligible for inclusion, each subject had to deny pelvic floor symptoms of chronic

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**Figure 1**
A, Reconstructed dorsal lithotomy view of the bony and soft tissue pelvis. White: Pelvic bones; pink: vagina; yellow: urethra; brown: levator; gray: symphysis coccyx; dark blue: anal sphincter complex; light blue: rectum. B, Bony pelvic measures: C-F: Pubococcygeal line; B-D: intertuberous distance; A-E: interspinous distance. The angle (B-C-D) is the pubic arch angle. The arrows point to the acetabulae, which are the boundaries of the interacetabular distance.

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**Figure 2**
A, 3D soft tissue measures: The levator hiatus height is shown by the vertical white line. The levator hiatus width is shown by the horizontal black line. B, The levator symphysis gap (LSG). The right LSG is given by the white line, and the left by the black line.
pain, urinary incontinence, prolapse, or defecatory dysfunction. Age, height, and weight were recorded.

Before MR scanning, subjects were asked to empty their bladders. Supine MRI studies were performed as follows: 3D Fast Spin Echo T2-weighted axial source images were obtained with the use of a 1.5T magnet (General Electric Medical Systems, Milwaukee, WI) and a torso phased-array coil wrapped around the pelvis. The following imaging parameters were used: repetition time = 4200 ms, time to echo = 108 ms, 128 phase encodes, 24-cm field of view, 2-mm slice thickness, no gap. Pixel dimensions were 0.625 × 0.625 mm. Total scan time was 13 minutes per subject.

The MR data were transferred to a Dell Dimension 8250 computer with 2 GB of RAM (Dell Inc., Round Rock, TX), and an ATI-RADEON 9800 graphics processor. The 3D Slicer software (www.slicer.org) was used to display the gray scale images and segmented label maps. A combination of manual and semiautomatic techniques were used to segment the axial gray scale images into anatomically significant organs, specifically bladder, urethra, levator complex, bony pelvis, symphysis, and coccyx, and the 3D reconstructions were made in a manner described in our previous work. The reconstructed models were then displayed and the parameters measured onscreen. All MR segmenting and subsequent analysis of the resulting 3D images was performed by 1 individual, L.H., who was masked to subject grouping throughout these procedures.

**Bony pelvis parameters**

The bony pelvic parameters were measured on the reconstructed 3D models. Intertuberous distance was measured from midpoint to midpoint of the iscial tuberosities. The interspinous distance was measured between the medial-most tips of the iscial spines. The interacetabular distance was measured between the medial-most aspects of the femoral sockets. The pubo-coccygeal line (PCL) distance was measured as the distance between the inferior-most aspect of the symphysis pubis and the tip of the coccyx in the midline. The pubic arch angle was
measured as the angle subtended by the inferior pubic rami. The standard diagonal and obstetric conjugates were not available for measurement on the 3D reconstructions because the source axial scans did not reach the sacral promontory, disallowing reconstruction of that landmark. A dorsal lithotomy view of a reconstructed bony pelvis and soft tissues is shown in Figure 1, A. Bony measurements are illustrated in Figure 1, B.

**Soft tissue parameters**

The levator hiatus height was measured in the midline as the distance from the inferior-most aspect of the pubic symphysis to the inner aspect of the levator median raphe. The levator hiatus maximum width was measured as the maximal transverse distance of the innermost surface of the anterior levator opening. The levator-symphysis gap was measured as the distance from the middle of the inferior symphysis to the nearest aspect of the puborectalis muscle on the right and left. The levator measures are illustrated in Figure 2, A and B. The bladder neck to PCL distance (BNPCL) was measured as the perpendicular distance from the posterior aspect of the bladder neck (ie, the junction of the urethra and bladder) to the PCL. Negative values of BNPCL imply a position inferior (caudad) to PCL, positive values of

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**Table I** Comparison of bony pelvic parameters between the groups

<table>
<thead>
<tr>
<th></th>
<th>PCL (mm)</th>
<th>PUBArch (deg)</th>
<th>InterTub (mm)</th>
<th>InterSpi (mm)</th>
<th>InterAcet (mm)</th>
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<td><strong>AA</strong></td>
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<tr>
<td>Mean</td>
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<td>97.4-127.6</td>
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<tr>
<td>Mean</td>
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_PCL_ is the anteroposterior distance from symphysis to tip of coccyx. It is a measure of the depth of the pelvic outlet. _PUBArch_ is the angle of the pubic arch. _InterTub_ is the transverse distance between the middle if the iscial tuberosities. It is a measure of the width of the pelvic outlet. _InterSpi_ is the distance between the tips of the iscial spines. It is a marker for the width of the midpelvis. _InterAcet_ is the distance between the medial-most aspects of the acetabular sockets. It is a marker for the width of the pelvic inlet. AA, African American; WA, White American.

**Table II** Comparison of levator muscle parameters between the groups

<table>
<thead>
<tr>
<th></th>
<th>LHH (mm)</th>
<th>LHW (mm)</th>
<th>LevVOL (cm³)</th>
<th>LSGL (mm)</th>
<th>LSGR (mm)</th>
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<tr>
<td>Mean</td>
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<tr>
<td><strong>WA</strong></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>63.9</td>
<td>31.2</td>
<td>19.8</td>
<td>22.4</td>
<td>18.6-30.5</td>
</tr>
<tr>
<td>Range</td>
<td>56.4-70.2</td>
<td>24.3-36.8</td>
<td>18.6-30.1</td>
<td>18.6-30.5</td>
<td></td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>.056</td>
<td>NS</td>
<td>.002</td>
<td>.003</td>
<td>.048</td>
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</table>

_LHH_ is the distance from the inferior symphysis to the levator median raphe. _LHW_ is the maximal transverse distance of the levator hiatus. _LevVOL_ is the volume of the levator ani complex. _LSG_ is the distance from the inferior mid pubic symphysis to the nearest occurrence of the puborectalis muscle in the left (LSGL), and right (LSGR). AA, African American; WA, White American.

**Table III** Urethral and bladder parameters

<table>
<thead>
<tr>
<th></th>
<th>BNPCL (mm)</th>
<th>BNSym (mm)</th>
<th>UreAng (deg)</th>
<th>Urethra (mm)</th>
<th>BVOL (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AA</strong></td>
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<td></td>
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<td></td>
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</tr>
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<td>Mean</td>
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<td>49.2</td>
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<tr>
<td>Range</td>
<td>7.8-28.2</td>
<td>11.5-22.0</td>
<td>40.6-62.9</td>
<td>23.0-40.3</td>
<td>12.3-138.5</td>
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<tr>
<td><strong>WA</strong></td>
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<tr>
<td>Mean</td>
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<td>56.4</td>
<td>26.2</td>
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<td>Range</td>
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<td>.048</td>
<td>.036</td>
<td>.036</td>
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</tbody>
</table>

_BNPCL_ is the perpendicular distance from bladder neck to pubococygeal line-positive values lie superior to the PCL, negative values lie inferior to the PCL. _BNSym_ is the distance between the bladder neck and the pubic symphysis. _UreAng_ is the angle formed by the long axes of the pubic symphysis and the urethra. _Urethra_ is the length of the urethra along its long axis. _BVOL_ is bladder volume. All linear measures are in millimeters, volumes are in cubic centimeters, and angles are in degrees. AA, African American; WA, White American.
BNPCL imply positions superior (cephalad) to PCL. The bladder neck to symphysis was measured as the distance from the anterior aspect of the bladder neck to the closest point on the symphysis. The bladder neck parameters are illustrated in Figure 3, A. The urethral angle was measured as the angle subtended by the long axis of the symphysis pubis, and the long axis of the urethra, as illustrated in Figure 3, B. The urethral length was measured as the linear distance from distal to proximal tips of the urethra. Bladder volume, urethral volume, and levator volume were computed as the sums of the area on each slice multiplied by the interslice distance. Levator shape was defined as a “U” if the levator moved laterally, then superiorly from its low point at the median raphe in the midline. Levator shape was defined as a “V” if it moved superiorly then outward from its low point at the median raphe in the midline.

The SPSS statistical package was used for all statistical analysis (SPSS, Chicago, IL). Nonparametric Mann-Whitney tests were applied after review of frequency histograms that demonstrated non-normal data. Two-tailed statistical significance is considered at $P < .05$.

Results

Subjects did not differ by age; African-American women had a mean age $\pm$ SD of $30.13 \pm 6.3$ years versus white-American women at $26.4 \pm 4.4$ years, $P = NS$. Similarly, although AA subjects had a slightly higher body mass index (BMI) at $26.5 (7.5) \text{ kg/m}^2$ versus WA subjects at $23.9 (3.3) \text{ kg/m}^2$, this difference was not statistically significant.

Of the bony pelvic measures, only the pubic arch angle was found to be significantly different between the groups. The pubic arch angle was larger by 13 degrees in AA women versus WA women. Bony pelvic comparisons are detailed in Table I.

Levator ani volume was significantly higher in AA women, who also had a significantly shorter levator-symphysis gap bilaterally, compared with the WA women. The bladder neck was closer to the symphysis in the AA women, and the angle of the urethra to the symphysis was also smaller in this group. These differences were statistically significant. Pelvic soft tissue comparisons are detailed in Tables II and III.

Figure 4 shows representative 3D reconstructions from an AA and WA nulliparous women, illustrating the soft tissue differences between the 2 groups.

Comment

Our study data shows increased levator ani muscle bulk among AA nulliparous women when compared with age-matched WA nulliparous women. In addition, the arms of the puborectalis muscle were carried closer to the superior pubic rami bilaterally, suggestive of a longer, denser attachment of the levator muscle to the arcus tendineus levator ani. The bladder neck is held higher and closer to the symphysis in the AA women than in the WA women, and the pubic arch is slightly wider among the AA women. Taken collectively, these differences suggest a levator ani complex in AA subjects that is more intimately associated with its connective tissue and bony attachments.

Previous investigators have reported striking differences in the prevalence and incidence of PFD among different races. There is, however, no consensus in the medical literature on exactly how race impacts the development of PFD. Our data in this preliminary study suggest certain hypotheses: it is possible that the kind of musculoskeletal configuration we have observed in AA women, coupled with a favorably wide pubic arch, is protective against pelvic floor obstetric injury. For instance, perhaps a bulkier levator muscle means that an AA woman can have a more extensive denervation injury before becoming symptomatic. Alternatively,
denser and longer muscle-to-connective tissue attachments may tolerate the same length of tear injury before resulting in symptoms in AA parturients. It is interesting that we found a wider pubic arch in our AA subjects, which is inconsistent with the classic characterization of an anthropoid pelvic shape in such women. However, the clinical significance of the 13-degree difference seen in the pubic arch is unclear. We speculate that our observations are in keeping with those of Howard et al. and Baragi et al. who noted more dynamic muscular attachments and a smaller overall pelvic floor area in AA women. A smaller posterior pelvis was responsible for some of the differences in PFD prevalence between African-American and white groups, the differences were significant in bony pelvic morphology between the two groups. These studies suggest bony parameters that place women at risk for PFD independent of race. Although our pilot data failed to show many significant differences in bony pelvic morphology between the African-American and white groups, the differences noted in soft tissue characteristics may help to account for some of the differences in PFD prevalence between parous African-American and white women. We are presently conducting a larger study to confirm these findings.

References

Is previous cesarean section a risk for incidental cystotomy at the time of hysterectomy?: A case-controlled study

Christopher M. Rooney, MD, Adam T. Crawford, MD, Brett J. Vassallo, MD, Steven D. Kleeman, MD, Mickey M. Karram, MD

Department of Urogynecology and Pelvic Reconstruction, Good Samaritan Hospital, Cincinnati, OH; Department of Obstetrics and Gynecology, Advocate Lutheran General Hospital, Park Ridge, IL

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Objective: The purpose of this study was to determine if previous cesarean section is an independent risk factor for incidental cystotomy at the time of hysterectomy.

Study design: This is a case-controlled study that evaluated all cases of incidental cystotomy at the time of hysterectomy between January 1998 and December 2001. Five thousand and ninety-two hysterectomies were performed in the time period mentioned above, and 51 cases of incidental cystotomy were identified. Each case of incidental cystotomy was then matched to 3 controls with similar patient characteristics, medical histories, and surgical histories, as well as the absence of incidental cystotomy at the time of hysterectomy.

Results: Overall, 5092 hysterectomies were performed during the study period (total abdominal hysterectomy [TAH] 3140 [61.7%], total vaginal hysterectomy [TVH] 1519 [29.8%], laparoscopically-assisted vaginal hysterectomy [LAVH] 433 [8.5%]). Fifty-one cases of incidental cystotomy were identified (TAH: 24 [47.1%], TVH: 19 [37.3%], LAVH: 8 [15.7%]). The overall incidence of cystotomy was 1.0%.

When considering TAH, there were 24/3141 (0.76%) cases of incidental cystotomy, with 8 (33%) of these patients with a history of previous cesarean section. During TVH, we encountered 19/1519 (1.3%) cases of incidental cystotomy, with 4 (21%) of these women having undergone a previous cesarean. Finally, during LAVH, there were 8/433 (1.8%) cases of incidental cystotomy. Five (62.5%) of these patients had a previous history of cesarean section.

In comparison, 19/72 (26.4%) TAH controls had a previous history of cesarean. Four out of 57 (7.0%) TVH controls had a history of cesarean section. Finally, 2/24 (8.3%) LAVH controls had a history of previous cesarean.

Conclusion: Previous cesarean section is indeed a significant risk factor for damage to the lower urinary tract at the time of hysterectomy (odds ratio [OR] 2.04; 95%CI 1.2-3.5). When analyzed separately, the OR of incidental cystotomy at the time of TAH, TVH, and LAVH in a woman with a history of previous cesarean was 1.26, 3.00, and 7.50, respectively. Only the value for LAVH was statistically significant (P = .005; 95%CI 1.8-31.4).

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In the United States, hysterectomy is the most commonly performed gynecologic procedure, with over 600,000 performed annually. The rate of bladder injury during hysterectomy has been reported to range from 0.37% to 2%. More recent reports have placed the incidence consistently between 1% to 2%. The reason for the increase in reported incidence is unknown, but some have speculated that it is secondary to the ever-increasing rate of cesarean section.

Cesarean section is the most commonly performed surgery on women, with rates at an all-time high of 20% to 30% of all deliveries. With up to 20% of these women likely requiring a hysterectomy by the age of 55, adherence of the bladder to the lower uterine segment will make dissection at the time of hysterectomy more difficult.

While statistical analysis has been applied to several series of hysterectomies in an attempt to define risk factors associated with incidental cystotomy; a value for the risk attributable to previous cesarean section alone has not been reported. The purpose of this study was to determine if previous cesarean section is an independent risk factor for incidental cystotomy at the time of hysterectomy.

Material and methods

After obtaining Institutional Review Board approval, all cases of incidental cystotomy at the time of hysterectomy between January 1998 and December 2001 were identified by diagnostic and procedural codes as recorded in the TriHealth Database (Good Samaritan, Bethesda Oak, and Bethesda North Hospitals, Cincinnati, Ohio). After identification, charts were reviewed and the following patient information was extracted: age, race, surgeon, insurance, gravidity, parity, number of vaginal deliveries, and number of cesarean sections. In addition, a patient history of endometriosis, leiomyomata, genital tract malignancy, incontinence, pelvic organ prolapse, previous tubal sterilization, previous pelvic surgery, and/or a history of pelvic infection was collected.

After review of the records, the individual cases were compared to the TriHealth database. The database was then used to match 3 controls (total of 153 controls) to each case of incidental cystotomy. The controls were matched according to age, type of hysterectomy (total abdominal hysterectomy [TAH], total vaginal hysterectomy [TVH], laparoscopic-assisted vaginal hysterectomy [LAVH]), primary and secondary diagnoses, the need for adhesiolysis, the need for a concurrent anti-incontinence procedure or procedure for pelvic organ prolapse, as well as the absence of incidental cystotomy. The medical records of the controls were then examined for the same epidemiologic, diagnostic, and surgical history data, as listed above.

Medical records reviewed included inpatient charts for the admission during which the procedure took place. Records examined included patient face sheets, discharge summaries, preoperative and inpatient progress notes, history and physical, operative notes, laboratory studies, as well as nursing and anesthesia records. Data for the variables included in the final analysis were collected in all of the case and control charts. Data regarding gravidity, parity, and number of previous vaginal deliveries were incomplete and, therefore, not included in the final analysis.

In 3 of the cases, the cystotomy occurred during either a LAVH or TVH, at which point in time the procedure was converted to a TAH. These cases were analyzed in the study as the original procedure (ie, LAVH or TVH) and not as TAH.

The case and control data were then compiled into 2 separate Excel spreadsheets. The dichotomous variables were compared using chi-square tests, while continuous variables were analyzed with t tests. All statistical calculations were performed using SPSS 12.0 (Chicago, IL) for Windows.

Results

Overall, 5092 hysterectomies were performed at the TriHealth network between January 1998 and December 2001 (TAH: 3140 [61.7%], TVH: 1519 [29.8%], LAVH: 433 [8.5%]). A total of 51 cases of incidental cystotomy were identified (TAH: 24 [47.1%], TVH: 19 [37.3%], LAVH: 8 [15.7%]). The overall incidence of incidental cystotomy was 1.0%.

When all hysterectomies were considered together, 17 of the 51 (33.3%) cases of incidental cystotomy had a history of previous cesarean section, while only 25 of the 153 (16.3%) controls had a history of previous cesarean delivery. This difference was significant at $P = .0164$, with an OR of incidental cystotomy at the time of hysterectomy for patients with a previous cesarean section $> 2.0$ (OR 2.04; 95% CI 1.2-3.5).

The rate of previous cesarean section in women who had a cystotomy during TAH was 8/24 (33%) compared with a rate of previous cesarean section of 19/72 (26.4%) in the TAH control group. The rate of previous cesarean section in women who had a cystotomy during TVH was 4/19 (21%) compared with the TVH control group who had a rate of previous cesarean section of 4/57 (7%). Finally, the rate of previous cesarean section in women who had a cystotomy during LAVH was 5/8 (62.5%), compared with the LAVH control group who had a rate of prior cesarean section of 2/24 (8.3%). As a group, 17 of the 51 cases (33.3%) and only 25 of the 153 matched controls (16.3%) had a history of at least 1 cesarean section. Of the 17 cases, 7 had 1 previous cesarean, 6 had 2 previous cesareans, and 4 patients had 3 or more previous cesarean sections. In the control group, 13 had a history of 1 previous cesarean, while 19 had 2 previous cesareans, and 3 patients had a history of 3 or more previous cesarean sections.
The epidemiologic, diagnostic, and procedural data of the cases and controls can be found in the Table. No cases of previous pelvic infection or radiation were documented in the medical records examined.

Comment

The results of this study demonstrate that previous cesarean section is indeed a significant independent risk factor for damage to the lower urinary tract at the time of hysterectomy (OR 2.04; 95% CI 1.2–3.5), a finding supported in the recent literature. The 1% incidence of hysterectomy (OR 2.04; 95% CI 1.2–3.5), a finding factor for damage to the lower urinary tract at the time of cesarean section is indeed a significant independent risk. The results of this study demonstrate that previous hysterectomy is stratified by route of hysterectomy (TAH: 0.76%, TVH: 1.3%, LAVH: 1.8%), the data are also consistent with reports in the literature (TAH: 0.3–1%, TVH: 1.6%, LAVH: 1.8%). When analyzed separately, the OR of incidental cystotomy at the time of TAH, TVH, and LAVH in a woman with a history of previous cesarean section is 1.26, 3.00, and 7.50, respectively. Only the result for LAVH is statistically significant (95% CI 1.8–31.4).

To our knowledge, this study is the first to examine cases of incidental cystotomy at the time of hysterectomy and attempt to isolate the risk attributable to previous cesarean alone. Other larger studies have analyzed the overall complication rates associated with previous cesarean section in patients who have undergone hysterectomy, particularly via the vaginal route. Variables analyzed have included operative time, blood loss, ureteral injury, formation of pelvic hematoma, operative site infection, the need for laparotomy, as well as the incidence of incidental cystotomy. Most of these studies have concluded that complication rates are not significantly higher in patients undergoing TVH who have a previous history of cesarean section. Boukkerou et al reported a greater frequency of complications at the time of vaginal hysterectomy in patients who had a history of cesarean section. This was not found, however, to be a contraindication to vaginal hysterectomy. Unfortunately, the incidence of incidental cystotomy in patients with a previous cesarean section in these studies is too small to make direct comparison with our data.

In review of the routes of hysterectomy considered in this study, 433 patients underwent LAVH with 8 patients suffering an incidental cystotomy. Five of the 8 (62.5%) had a history of previous cesarean section, while only 2 of the 24 (8.3%) controls shared a similar history. As previously mentioned, this achieved statistical significance, and suggests that patients with a history of cesarean section are at higher risk of incidental cystotomy at the time of LAVH.

There are several limitations to the analysis reported in this study. First, while we attempted to control for all patient and surgical variables that could potentially increase the difficulty of the hysterectomy, 2 important variables were overlooked during data collection: patient weight and uterine size. Both extreme patient weight and large uterine size are factors that limit visibility and, therefore, complicate dissection and advancement of the bladder flap. The data on uterine size could potentially be added to the analysis in the future after revisiting the medical records, but accurate data on patient weight are unlikely to be available.

The second limitation of the study concerned the fact that only incidental cystotomies recognized intraoperatively were included in the final analysis. Harkki-Siren et al reported that only 58% of bladder injuries in a retrospective review of 62,379 hysterectomies were diagnosed intraoperatively. This figure left over 40% to be diagnosed up to 30 days postoperatively, many as fistulas.

Next, the data regarding gravidity, parity, and number of previous vaginal deliveries were incomplete and, therefore, not included in the final analysis. Boukkerou et al concluded that a history of at least 1 vaginal delivery was not significant when looking at complications at the time of vaginal hysterectomy in patients with a previous cesarean section. Unger et al, however, reported that the overall complication rate, when considering incidental cystotomy, blood loss, and operative time was lowered for patients who had at least 1 previous vaginal delivery (3.2% vs 17.6%, P = .004).

Attributing all bladder injuries during LAVH to the laparoscopic portion of the case was another limitation of the study. While this limitation does not affect the overall attributable risk assigned to previous cesarean delivery, it does potentially affect the individual incidence of incidental cystotomy during LAVH. More detailed review of the operative reports could potentially remedy this error.
The applicability of the findings in this study to the general population is likely influenced by 2 factors. First, these patients had their procedures performed at teaching institutions where resident physicians performed the majority of the cases. In private practice, an adherent bladder secondary to previous cesarean section might pose less of a challenge to an experienced surgeon comfortable using sharp dissection to advance the bladder flap. Second, the ratio of abdominal to vaginal hysterectomy in our population was closer to 2:1 than the 3:1 ratio reported in the literature.

In summary, a history of previous cesarean section has long been regarded as a risk factor for incidental cystotomy at the time of hysterectomy. The results of this study indicate that when all routes of hysterectomy are considered together, the risk posed by previous cesarean section is significant and more than doubles the chance of incidental cystotomy. This risk appears less for abdominal hysterectomies than for the vaginal or laparoscopic approaches. The 20.6% incidence of previous cesarean section in our study population is consistent with reports in the literature, therefore allowing the results to be applicable to teaching institutions with a TAH:TVH ratio of approximately 2:1 when more difficult vaginal hysterectomies are being attempted.

References

Bleeding complications with the tension-free vaginal tape operation

Dieter Kölle, MD, a Karl Tamussino, MD, b Engelbert Hanzal, MD, c Ayman Tammaa, MD, d Oliver Preyer, MD, c Arnim Bader, MD, b Hermann Enzelsberger, MD, PhD, e George Ralph, MD, f Paul Riss, MD, g for the Austrian Urogynecology Working Group

Departments of Obstetrics and Gynecology, Medical University of Innsbruck, a Innsbruck, Austria; Medical University of Graz, b Medical University of Vienna; Wilhelminenspital Vienna, d Vienna, Austria; Landeskrankenhaus Steyr, e Steyr, Austria; Landeskrankenhaus Leoben, f Leoben, Austria; Thermenklinikum Mödling, g Mödling, Austria

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KEY WORDS
Stress incontinence
Surgical treatment
Tension-free vaginal tape

Objective: This study was undertaken to analyze bleeding problems with tension-free vaginal tape (TVT) operations in a national registry.

Study design: We studied patients for whom increased intraoperative bleeding or reoperation for bleeding/hematoma with TVT operation were reported to the registry.

Results: Bleeding problems were reported for 151 of 5578 (2.7%) TVT operations. Increased intraoperative bleeding was reported for 106 (1.9%) and reoperation (or conversion) in 45 (0.8%) patients (both in 5 patients). Increased intraoperative bleeding was managed conservatively in 103 patients (95%). Overall, 45 (0.8%) patients required reintervention for bleeding or hematoma. The reinterventions comprised 34 laparotomies, 4 transvaginal evacuations of hematomas, 3 revisions for bleeding from a suprapubic catheter site, and 2 revisions of the vaginal incision (details unclear in 1 patient). Bleeding was considered arterial in 12% (including 1 external iliac artery injury and 1 obturator artery injury) and venous or unknown in 88%. Of reoperated patients, 39% were reoperated within 24 hours, 20% within 2 to 10 days, and 41% within 11 to 56 days after TVT placement. Overall, 19 patients received blood transfusions (range, 1-10 units). There were no deaths from bleeding complications.

Conclusion: Bleeding complications were reported with less than 3% of 5578 TVT operations. Most cases of increased intraoperative bleeding were managed conservatively; 0.8% of patients required conversion or reoperation.

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When the tension-free vaginal tape (TVT) operation was introduced in Europe in 1998 there was scant literature1,2 on the procedure or its complications. The procedure was adopted quickly and widely to treat stress incontinence in women, but concern persisted about complications. To gather data on the perioperative course and complications associated with the new procedure, the Austrian Working Group for Urogynecology in 1998 set up a voluntary nationwide registry into which participating hospitals across the country could
TVT operations (Table I). Increased intraoperative bleeding problems were reported for 151 of 5578 (2.7%) TVT operations performed. The registry was subsequently expanded to include alternative systems as these became available. The present study analyzes intraoperative and postoperative bleeding problems with the TVT operation in the Austrian Vaginal Tape Registry.

Material and methods
When the registry was closed in 2003, a total of 5898 operations had been entered, 5578 (95%) of which were TVTs (Gynecare TVT, Gynecare/Ethicon, Norderstedt, Germany). The initial results of the registry were reported in 2001. The registry was subsequently expanded to include alternative systems as these became available. The present study analyzes intraoperative bleeding problems with the TVT operation in the Austrian Vaginal Tape Registry.

Material and methods
When the registry was closed in 2003, a total of 5898 operations had been entered, 5578 (95%) of which were TVTs (Gynecare TVT, Gynecare/Ethicon, Norderstedt, Germany). The initial results of the registry were reported in 2001. Centers participating in the registry completed a 14-item data sheet per operation. The data sheet included the items “Increased intraoperative bleeding” and “Reoperation due to bleeding/hematoma.” We identified operations for which 1 or both of these items were checked and contacted the centers reporting these operations to obtain details on the nature and management of the bleeding problem and perioperative management (such as the use of low molecular weight heparin for thromboembolic prophylaxis and transfusion requirements). Bleeding problems clearly caused by concomitant operations (such as bleeding from adnexal pedicles after hysterectomy) were excluded.

Results
Bleeding problems were reported for 151 of 5578 (2.7%) TVT operations (Table I). Increased intraoperative bleeding was managed conservatively (ie, compression, tamponade) in 101 of 106 patients (95%); 5 of 106 (5%) patients required laparotomy (1 immediately for laceration of an external iliac artery, 2 on the day of surgery, and 2 later) (Table I). The patient with laceration of an external iliac artery shifted during passage of the needles, and the surgeon thought this to be the cause of the injury. Thirteen patients with reported increased intraoperative bleeding subsequently had hematomas develop that were managed expectantly. Further details are available on 72 of the women with increased intraoperative bleeding. Fifty-seven of these 72 patients received thromboembolic prophylaxis with low molecular weight heparin perioperatively. The source of bleeding was considered arterial in 4 patients (the laceration of an external iliac artery, 1 arterial bleeder at the site of bladder perforation with the TVT needle managed with cystoscopic coagulation, 2 unclear); in the remainder of the cases the nature of the bleeding was considered venous or unknown. In 2 patients with venous bleeding drains were attached to the needles and placed into the retropubic space. These patients have been described previously, and Flock et al have used a similar maneuver. One patient with increased intraoperative bleeding subsequently received 3 units of packed red cells and developed a 10-cm hematoma that eventually resolved.

Reintervention for bleeding or hematoma was reported for 45 (0.8%) of the 5578 TVT operations overall (Table I). The reinterventions included 34 laparotomies, 4 transvaginal evacuations of hematomas, 3 revisions to control bleeding from a suprapubic catheter site, 2 reoperations for bleeding from the vaginal incision, and 1 aspiration of a retropubic hematoma; in 1 case the nature of the reoperation was unclear. Details are available for 41 of the 45 patients who underwent reintervention. Low molecular weight heparin was used in 37 of these 41 patients. The source of bleeding was considered arterial in 12% (including an injury of an external iliac artery and 1 injury of an obturator artery) and venous or unknown in 88%. Of the 41 reoperated patients for whom details are available, 16 (39%) were reoperated within 24 hours, 8 (20%) within 2 to 10 days, and 17 (41%) within 11 to 56 days after TVT placement. Eighteen of the 35 women received blood transfusions (range, 1-10). There were no deaths from bleeding complications.

Comment
Overall, the rate of bleeding complications with the TVT operation is low. Bleeding complications were reported with less than 3% of 5578 TVT operations, with 0.8% of patients overall requiring reoperation or conversion. The large majority of cases of increased intraoperative bleeding were managed conservatively. The transfusion rate was approximately 0.3%.
There appear to be immediate hematomas and delayed hematomas. In our series 39% of patients undergoing reoperations for bleeding problems were reoperated within 24 hours; the remainder up to 56 days after the initial operation. Only 2 bleeding complications were attributed to vessels with names: 1 external iliac artery and 1 obturator artery. Immediate hematomas probably have an arterial component, whereas delayed hematomas may result from ongoing venous bleeding. A number of reports and cases in the present series indicate that asymptomatic hematomas in stable patients resolve without sequelae with expectant management. Tseng et al performed suprapubic ultrasonography in a series of 31 patients 1 day after TVT placement and found retropubic hematomas greater than 5 cm in diameter in 5 (16%). All but 1 of these patients were asymptomatic and managed expectantly. Also, it may be that sonography shortly after TVT placement shows residual local anesthetic in the retropubic space. Probably some of the delayed hematomas in our series that were surgically evacuated could have been managed expectantly with good results.

Bleeding is a concern with any operation in the retropubic space (Table II). Although Ulmsten et al reported no intraoperative or postoperative bleeding problems in their initial description of the TVT operation, there were 2 hematomas (both of which resolved spontaneously) in the second series. In the United Kingdom and Ireland randomized trial of TVT versus abdominal colposuspension, estimated intraoperative blood loss was significantly higher with colposuspension but postoperative bleeding complications and hematomas were more common with TVT. The 3 retropubic hematomas after TVT in this trial were apparently managed conservatively, whereas 1 patient with injury of an aberrant obturator artery required reoperation and blood transfusion. In a registry of 1455 TVT operations in Finland, Kuuva and Nilsson reported 27 cases (0.9%) of intraoperative blood loss of more than 200 mL, 34 hematomas (2.3%), and 3 reinterventions for bleeding complications. The Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) Database contains 27 patients with bleeding complications (12 cases of intraoperative bleeding and 15 hematomas).

A number of case reports have addressed bleeding problems and their management. Zilbert and Farrell described laceration of an external iliac artery in a patient who moved during the operation, similar to the case in the present series. Walters et al indicated that even large hematomas can be followed expectantly if the patient is stable. They managed 2 women with hematomas up to 10 cm in diameter, 1 of whom required red cell transfusion, expectantly, and both hematomas resolved within 6 months. Elard et al controlled bleeding from an inferior vesical artery with selective embolization of the vessel. Flock et al evacuated 3 retropubic hematomas via a laparoscopic approach. Neuman reported 2 hematomas that became infected among 238 operations, an experience that has not been shared by other authors.

A registry such as ours is subject to potential inclusion and exclusion bias (centers overreporting or underreporting complications). Participation in the registry was voluntary and we relied on the institutions to report their data completely. About 12,000 TVT sets were sold in Austria during the study period, indicating that we have data on about half of all operations performed. We did not have input from urologic units or private hospitals. The data sheet for our registry did not explicitly define increased intraoperative bleeding and this may have been underreported if the data sheets were filled out at a later date by someone other than the surgeon. Similarly, there was no item on the data sheet to record hematomas managed expectantly and some such were probably missed.

Recently suburethral tapes have been inserted via transobturator approaches, and a number of systems are now available. The theoretical rationale for these approaches is that by staying outside of the pelvis they...
have a lower incidence of bladder perforation and injury of major vessels. The data from our registry indicate that serious bleeding complications occur with less than 1% of TVT operations. In the absence of large series or randomized trials, the incidence of bleeding problems with transobturator systems remains to be determined.

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Participating investigators and centers: P. Riss, Ther- menklinikum Mödling; A. Staudach, Landesfrauenklinik Salzburg; G. Wagner, Krankenhaus der Barmherzigen Brüder, Vienna; A. Bader, A. Giuliani, K. Tamussino, R. Bad Ischl; W. Breinl, Graz; A. Kerak, Krankenhaus Tulln; W. Grün- Lang, Krankenhaus der Barmherzigen Brüder Eisenstadt; A. Aburumi- mieh, F. Nagl, Krankenhaus Melk; W. Grünorschl, Krankenhaus Voitsberg; W. Tews, Landesfrauenklinik Linz; all in Austria.

References


Rectoceles and the anatomy of the posterior vaginal wall: Revisited

Steven D. Kleeman, MD, Cynthia Westermann, MD, Mickey M. Karram, MD

Division of Female Pelvic Medicine and Reconstructive Surgery, Department of Obstetrics and Gynecology, Good Samaritan Hospital, Cincinnati, OH

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Objective: The purpose of this study was to histologically evaluate the posterior aspect of the pelvis, specifically, the relationship between the perineum, posterior vagina, anterior rectum, and all other intervening tissue.

Study design: The perineum, posterior vaginal wall, and upper part of the rectum were removed en bloc from 4 fresh cadavers without pelvic prolapse. Length of the specimens ranged from 6 to 7.9 cm and width 3 to 4 cm. Seven to 26 serial sections were taken from each cadaver. Sections were stained with hematoxylin and eosin (H&E), Masson trichrome, and Verhoeff Von Gieson elastic stain.

Results: All 4 specimens showed dense connective tissue and no plane of cleavage for 3 to 3.5 cm proximally from the posterior forchette. Proximal to this, all 4 specimens showed space between the muscular wall of the vagina and the muscular wall of the rectum, which was composed of adipose tissue with discontinuous bands of fibrous tissue or loose areolar tissue. This appears to be a natural line of cleavage. Histologically, no evidence of fascia or a rectovaginal septum was identified.

Conclusion: Histologically, there is no evidence of a distinct fascial layer between the posterior vaginal wall and anterior wall of the rectum. Clinically, it is the splitting of the adventitia and fibromuscular layers of the vagina that are used in defect-specific rectocele repairs to support the anterior rectal wall.

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There has been renewed interest in the anatomic structure and ultimate relationship between the posterior vaginal wall and the anterior wall of the rectum. Richardson1 is credited with beginning this new understanding starting with his work on anterior vaginal wall relaxation and, subsequently, posterior vaginal wall relaxation.2,3 Richardson describes breaks in the rectovaginal fascial layer that can be identified surgically and repaired primarily. Delancy further supported this theory but added the importance of the interactions between connective tissue and striated muscle.4 However, the presence or absence of a vaginal fascia or rectovaginal septum has been debated for well over 100 years. Some authors deny the existence of a rectovaginal septum,5,6 and others believe that a rectovaginal septum exists.7-10
Adding to the confusion, terms and definitions commonly used by surgeons are not always the same as those used routinely by pathologists and histologists. The purpose of this study was to histologically section and stain the posterior vaginal wall in fresh cadavers, without prolapse, from the perineum to the vaginal apex. These findings are compared with previously reported findings in the literature. These findings are used to comment on the repair of posterior vaginal wall defects.

Material and methods

Institutional Review Board approval was waived by the IRB at Good Samaritan Hospital. Four fresh cadavers were obtained. All cadavers were white, and all had undergone previous hysterectomy. All 4 cadavers had a well supported pelvic floor. Initially, the perineum, posterior vaginal wall, and anterior part of the rectum were removed en bloc. All specimens were fixed in 10% neutral buffered formalin, embedded with paraffin, and sectioned. Seven to 26 serial sections were taken from each specimen. Sections were stained with hematoxylin and eosin (H&E), Masson trichrome, or a Verhoeff Von Gieson elastic stain.

Results

Length of the specimens ranged from 6 to 7.9 cm, and width from 3 to 4 cm. Table I shows perineal thickness, vaginal length, and distance from the dentate line to the anal verge from all 4 cadavers. All sections from the 4 specimens revealed similar results.

Table I  Measurements from cadavers A to D

<table>
<thead>
<tr>
<th>No. of sections taken</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineal thickness (cm)</td>
<td>2.8</td>
<td>3.0</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Specimen length (cm)</td>
<td>7.9</td>
<td>7.8</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Dentate line from anal verge (cm)</td>
<td>2.7</td>
<td>3.0</td>
<td>2.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Figure 1  Hematoxylin and eosin (H&E) horizontal section of the midvagina. (A) Vaginal epithelium, (B) lamina propria of the vagina, (C) fibromuscular wall of the vagina, (D) adventitia, (E) outer muscular wall of the rectum, (F) inner muscular wall of the rectum, (G) lamina propria of the rectum, (H) rectal mucosa.

of the vagina shows some blue staining of collagen but with abundant interposing adipose tissue, nerve fibers, and blood vessels. Figure 3 shows a similar section but stained with Verhoeff Von Gieson elastic stain. This stain will show muscle to be pale yellow brown, as seen in the muscular wall of the rectum (E). Collagen retains a red color. Above the rectal muscular wall (E) is the adventitia of the vagina (D). There is evidence of collagen staining in this layer; however it is discontinuous and interspersed with adipose tissue, blood vessels, and muscle fibers. In Figures 1 through 3 there is no evidence of a continuous sheet of dense collagen, which would be called fascia by histologic criteria.

Figure 4 shows a lateral H&E section of the vagina along with levator ani muscle. The levator ani muscle is seen to the left of the figure. There is a dense layer of connective tissue that lays over the levator ani muscles. Toward the center of the figure, the fibromuscular layer of the vagina and adventitia layer can be seen. The fibromuscular layer becomes much thicker as it merges with the dense connective tissue overlying the levator ani muscle.

Figure 5 shows a horizontal H&E section of the proximal third of the vagina. Again, the layers of the
vaginal and rectal walls are labeled A through H. In the proximal third of the vagina, the vaginal and rectal walls become thinner compared with the distal and middle third of the vagina. There is a layer of adipose tissue that becomes more homogeneous between the 2 walls. Table II shows wall thickness measured in the distal, mid-, and proximal part of the vagina.

Figure 6 shows a sagittal H&E section through the distal third of the vagina. A small portion of the vaginal mucosa can be seen in the upper righthand corner of the figure. The rectal mucosa is out of view of the bottom of the figure. It can be seen that the rectal wall and vaginal wall are tightly fused without any intervening adipose tissue.

General observations that could be made from all specimens are as follows: 1) The distal aspect of all specimens showed dense connective tissue with no plane of cleavage between the vaginal and rectal wall for 3 to 3.5 cm proximally. 2) Sections from the midportion of the posterior vaginal wall showed an intervening layer between the outer muscular wall of the rectum and the fibromuscular wall of the vagina. This layer was uniformly composed of adipose tissue with admixed discontinuous bundles of fibrous tissue, numerous blood vessels, and nerves and frequent elastic fibers. 3) Sections from the proximal end of the specimens showed the layer between the fibromuscular layer of the vagina and the rectum to be composed predominately of adipose tissue.
Comment

It is interesting that although there is debate about the structure of the posterior vaginal wall, the findings of this study are not new and have been described by others throughout the 20th century.

Goff, in his classic paper, defined 2 types of fascia, an areolar type, which surrounds viscera, blood vessels, and nerves, and a denser type, which sheathes and unites voluntary muscles of the body. The specimen used for his study was a 27-year-old female cadaver. Goff describes “The posterior vaginal wall will be loosely attached to the wall of the rectum from above downward until the point at which the rectum begins to turn backward to become the anal canal. At this point the rectal and vaginal walls become very firmly united.”

Microscopically, Goff took 3 sections: above the perineal body, the midvagina, and the apex (posterior cul-de-sac). On the first section he found no fascia, but on the next 2 sections he found areolar fascia that became denser as one proceeded laterally toward the levator ani muscles. This is similar to our findings shown in Figure 4. He stated there is no tissue that would be defined as fascia in any part of the vagina. In his conclusions, he defines this areolar fascia as a layer that would be impossible to dissect as an individual layer, and impossible to use in vaginal plastic operations. If used at all, it must be used in conjunction with the overlying wall of the vagina. Our microscopic findings concur with Goff’s findings; however, we disagree with the term “areolar fascia” and prefer to use the term adventitia (Figure 1, D). We believe the tissue used in correction of rectocele is the separated adventitia and fibromuscular wall of the vagina.

Ricci et al studied 22 specimens microscopically. The authors disagreed with the term fascia as used by Goff and stated, “In reality, this intervening areolar mesh consists of loosely scattered and tangentially interwoven connective tissue fibrils of a spider web texture; it is not sheet like, is entirely devoid of tensile strength and calling it a fascia perpetuated a misconception.” Ricci et al found that on dissection there was a line of cleavage between the rectum and vagina that extended to the perineal body. At the perineal body the 2 were tightly fused. The authors conclude that there is no fascia between the posterior vaginal wall and the rectum. They further stated, “The gynecologist who succeeds in isolating indispensable fascia for reconstructive purposes has split the fibromuscular elastic vaginal wall into two layers, the innermost of which he erroneously designates as a fascia.”

In 1948, Uhlenhuth et al described their findings based on a large number of gross anatomic observations in male and female, adult and infant cadavers. The authors felt the rectovaginal septum adhered closely to the undersurface of the vagina, and was of peritoneal origin that resulted from the fusion of the ventral and
dorsal wall of the rectovesical pouch during embryologic development. In a second paper in 1957,3 Uhlenhuth again concluded “there is no need of histologic sections to prove the existence of a vaginal fascia.”

In 1968, Miley and Nichols published their findings on the rectovaginal septum.5 They evaluated surgical specimens, fixed and unfixed cadavers, and fetal material. They concluded the rectovaginal septum is a constant and normal structure in the human female. Histologically, the dissected rectovaginal septum consisted of a “fibrо-muscular elastic layer of dense collagen, abundant smooth muscle and elastic fibers.”

Although the work of Uhlenhuth and Miley and Nichols would seem to contradict our findings and the findings of Goff and Ricci et al, we believe they are in agreement. Both Uhlenhuth and Miley and Nichols were able to create a sheet of tissue by blunt dissection of the posterior vaginal wall. Uhlenhuth did not perform any microscopic sections but Miley and Nichols did. Their microscopic findings would seem to correlate with the adventitia (Figure 1, D) and fibromuscular wall of the vagina (Figure 1, C) that we found on our microscopic sections.

Farrell et al also used surgical specimens and found it was histologically indistinguishable from the deep layer of the vaginal wall, and thought this “fascia” was created by surgical artifact.11 Weber and Walters reviewed the anatomy of the anterior vaginal wall,12 and felt that vaginal “repair involves plication of the muscularis and adventitia (not vaginal “fascia”).” The absence of fascia to explain apical enterocele prolapse can be seen in a paper by Tulikangas et al.13 They histologically evaluated 13 women with posthysterectomy apical vault prolapse. They compared this group with 2 control groups, 5 women undergoing hysterectomy without prolapse, and 13 women undergoing radical hysterectomy. The authors found no difference in vaginal wall thickness between the 2 groups and no evidence of peritoneum in direct contact with vaginal epithelium.

Richardson described a diaphragm-like configuration of fascia that was attached laterally to fascia of the levator ani muscle, distally to the perineal body and apically to the uterosacral-cardinal ligaments. Richardson felt that breaks in this diaphragm layer should be identified and repaired primarily. Leffler et al further championed this idea by describing the lateral attachment of the rectovaginal fascia.14

Delancy published his findings on anatomy as it relates to rectoceles.4 He emphasized the importance of the interaction between levator ani muscle and connective tissue. He does add that endopelvic fascial fibers attach to the vaginal wall laterally, but few fibers cross the midline. He speculated that surgically useful fascia separating the rectum from the vagina includes portions of the vaginal muscularis. We also believe it is this interaction of connective tissue and muscle that supports the middle and upper parts of the posterior vaginal wall.

It has been the authors’ experience that when opening the posterior vaginal wall for correction of posterior vaginal wall defect, the only identifiable “fascia” or tough connective tissue is in the distal one third of the vagina, where the vagina and rectum are densely fused and above this, the vagina is easily separated from the anterior rectal wall; however, it is difficult to find usable surgical “fascia” above this level. Some surgeons identify the proximal edge of this connective tissue as a transverse break of the rectovaginal septum and then advocate pulling this edge cranially to attach it to the uterosacral-cardinal ligament complex. Some surgeons split the vagina into layers and plicate them across the midline in order to support the anterior rectal wall.

Our findings would suggest that there is no fascia between the posterior vaginal wall and the anterior rectal wall. The “fascia” found surgically is actually the separation of the adventitial and fibromuscular layer from the lamina propria of the vagina. The walls of the vagina and rectum are tightly fused in the distal vagina (Figure 5). Looking at Figures 1 through 3, there appears to be a plane of cleavage developing between the walls of the rectum and vagina. This is seen by an increase in adipose tissue. The plane of dissection taken when opening the posterior vaginal wall will dictate what the surgeon will identify as usable tissue to reduce an anterior rectal wall prolapse. If the plane of dissection is close to the rectum, any usable tissue will be left on the vagina. If the dissection plain is closer to the vaginal epithelium, discontinuous sheets of connective tissue may be seen left behind on the anterior rectal wall. The correct plane of dissection should be thin, leaving as much of the adventitia and vaginal wall behind so that it

<table>
<thead>
<tr>
<th>Table II</th>
<th>Wall width (mm) at 3 different points in cadavers A to D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Distal vagina</td>
</tr>
<tr>
<td></td>
<td>A  B  C  D</td>
</tr>
<tr>
<td>Vaginal wall</td>
<td>7  8  8  5</td>
</tr>
<tr>
<td>Rectal wall</td>
<td>8  13  9  7</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>0  0  0  0</td>
</tr>
</tbody>
</table>

### References
1. ... 11. Weber and Walters
12. ... 14. Delancy published his findings on anatomy as it relates to rectoceles.
can be plicated later to help support the anterior rectal wall. Looking at Figure 6, one can see that the ability to separate any useful tissue for plastic operations will become more difficult because the vaginal wall becomes thinner and the layer of adipose tissue much more defined.

Several issues then arise. First, it seems obvious that the concept of a well-defined continuous sheet of connective tissue that stretches from the perineum to the uterosacral ligaments and to the pelvic sidewall that helps support the anterior rectal wall is much too simplistic. Second, the plane of dissection taken when opening the posterior vaginal will greatly influence what the surgeon will see. The authors would submit that most “breaks” in connective tissue are actually created by the surgeon during dissection.

Although the work presented here is not new or original, several conclusions can be made. First, there is no fascia in the posterior vaginal wall, and the tissue used for vaginal repair of anterior rectal wall prolapse is the dissected layers of adventitia and fibromuscular layers from the vagina. Second, the term fascia, Denonvilliers fascia, or rectovaginal septum, should not be used to describe any layer in the posterior vaginal or anterior rectal wall because it is inaccurate. Using the term fascia oversimplifies a complex interaction of connective tissue and muscular fibers that support the anterior rectal wall.

There are several limitations to our study. First, we had no information such as past medical history on the specimens we used. Second, we only had 4 specimens in our study and the number of sections taken was not equal between the specimens. We chose not to do additional sections because there was no difference in the layers of the vagina or the rectum between cadavers. We believe, however, our results correlate well with studies done by previous authors.

References

A six-year study of surgical teaching and skills evaluation for obstetric/gynecologic residents in porcine and inanimate surgical models

Gretchen M. Lentz, MD, Lynn S. Mandel, PhD, Barbara A. Goff, MD

Department of Obstetrics and Gynecology, University of Washington, Seattle, WA

**Objective:** This study was undertaken to evaluate an ongoing teaching and objective surgical skills testing program for obstetric/gynecologic residents in a laboratory setting, and assess the impact on residents of having 4 years of a surgical laboratory curriculum.

**Study design:** From 1997 through 2002, we conducted surgical skills training sessions for all obstetric/gynecologic residents, using both inanimate and animal (porcine) models. Once a year we tested each resident on 12 structured surgical bench tasks. At the end of each year, we conducted formal objective structured assessment of technical skills (OSATS) with all residents attempting multiple surgical procedures. We compared residents who had 4 years of laboratory training with those who started residency earlier and had only 1 or 2 years of the new curriculum. We also compared residents’ own performance from year to year and cohort performance by resident year.

**Results:** PGY3 and PGY4s who had 4 years of surgical laboratory training did significantly better on bench laboratory skills than PGY3 and PGY4s with fewer years of training sessions (total scores of 48.8 vs 30.3, \( P < .001 \)). However, no significant improvement in surgical procedures as measured by global OSATS was found. When comparing residents’ own performance between the beginning and the end of 1 year, global OSATS scores improved significantly on laparoscopic salpingotomy \( (P < .001) \) and open oophorectomy \( (P < .001) \). For the cohort of PGY4s completing 4 years of laboratory training, average global OSATS scores showed statistically significant improvement \( (PGY1, PGY2 < PGY3 < PGY4, P < .001) \).

**Conclusion:** Residents who completed the 4-year curriculum showed significantly better technical skills on bench tasks but not on OSATS compared with those with less training. Resident surgical skills evaluated by OSATS significantly improve over time both individually and as a cohort by resident year.

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Much concern has been expressed about the challenges of surgical training in gynecology and meeting the Accreditation Council for Graduate Medical Education (ACGME) competency standards.\textsuperscript{1,2} Rapidly changing surgical technology, concern about medical errors, and decreased numbers of gynecologic surgical procedures available to residents all argue for a paradigm shift in surgical education.\textsuperscript{1-3} A survey of 203 obstetrics and gynecology residency programs showed only 29\% had formal surgical skills curricula, although 54\% offered animal laboratory experience and 68\% bench laboratory training.\textsuperscript{4} The optimal format for teaching surgical skills, evaluating performance and competency and giving feedback has yet to be defined, but more research is underway in all of these areas.\textsuperscript{5-8}

In 1997, we started a formal laboratory-based surgical skills program at the University of Washington. This included training outside the operating room in both open and laparoscopic skills as well as formal assessment of technical skills. We have previously published on the curriculum development and reliability and validity of the testing techniques.\textsuperscript{9-13} The purpose of this study is to assess the feasibility of administering a 4-year surgical laboratory curriculum and assess its impact on residents’ surgical skills.

### Material and methods

Starting in 1997 and continuing to the present, we implemented a formal surgical training and assessment program for all 24 obstetrics and gynecology residents at the University of Washington. The first step was to start a 10-hour surgical orientation program for incoming postgraduate year 1 (PGY1) residents during their orientation week. This began with a 40-question written pretest described previously\textsuperscript{11} and didactics on surgical instruments, suture properties, electrocautery, and principles of laparoscopy. Hands-on training with suturing, knot tying and basic laparoscopic skills was done with bench models. A 4-hour surgical experience using an animal (porcine) laboratory followed for teaching basic surgical tasks (Tables I and II). We started with laparoscopic procedures and then opened the abdomen for laparotomy procedures. Second, we conducted twice-yearly 6-hour surgical skills training sessions (1 summer, 1 winter) for all obstetric/gynecology residents using both inanimate models and animal laboratories.\textsuperscript{11,12} The second laboratory of the academic year was to reinforce skills and provide additional opportunity for supervised practice with immediate feedback. Examples of the skills regularly taught are in Tables I and II. These sessions were taught by attendings in gynecologic oncology (B.G.), urogynecology (G.L.), and by reproductive endocrinology fellows or obstetric/gynecologic generalists. Teaching was intensive, with 3 faculty present for every 6 residents. Once a year, additional 2-hour sessions were conducted in a bench laboratory setting to teach particular skills such as hysteroscopy, cystoscopy, laparoscopic knot tying, and introduction to new laparoscopic or hysteroscopic equipment (eg, endometrial ablation, laparoscopic pretied sutures, laparoscopic stapling devices).

At the beginning of each academic year, we assessed 12 bench skills to document baseline skills and potential improvement. These tasks included 3 knot tying, 3 suturing, and 6 laparoscopic exercises.\textsuperscript{11} Scoring for bench tasks was on a 5-point scale. In May of each year,

<table>
<thead>
<tr>
<th>Table I: Animal laboratory laparoscopic surgical teaching tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laparoscopy PGY1, PGY2</strong></td>
</tr>
<tr>
<td><strong>Instruction in:</strong></td>
</tr>
<tr>
<td>Knowledge of equipment—light, camera, screen, scope</td>
</tr>
<tr>
<td>Verres needle placement and tests to verify placement</td>
</tr>
<tr>
<td>Insufflation process/machine/tubing/safe pressures</td>
</tr>
<tr>
<td>Trocar types/techniques</td>
</tr>
<tr>
<td>Viewing—systematic viewing of pelvis, upper abdomen</td>
</tr>
<tr>
<td>Walk uterus and fallopian tube with 2 graspers</td>
</tr>
<tr>
<td>Cauterize tube ( \times 3 ) and cut (simulating tubal ligation)</td>
</tr>
<tr>
<td>Open fallopian tube</td>
</tr>
<tr>
<td>Adhesions—bladder as model</td>
</tr>
<tr>
<td>Clips on tube (simulating tubal ligation)</td>
</tr>
<tr>
<td>Endoloop*</td>
</tr>
<tr>
<td>Endoclose* the trocar site</td>
</tr>
<tr>
<td>Use of several endoscopic devices (bags, pre-tied sutures)</td>
</tr>
<tr>
<td>* US Surgical.</td>
</tr>
<tr>
<td>* US Surgical.</td>
</tr>
</tbody>
</table>

Lentz, Mandel, and Goff 2057
we conducted formal objective structured assessment of technical skills (OSATS) with all residents attempting multiple surgical tasks. Faculty obtained checklist and global ratings. Maximum global rating scores were 35 and maximum possible checklist scores ranged from 26 to 52 so were based on a percentage of total checklist score. Some evaluators were blinded to resident year as we invited obstetric/gynecologic faculty from outside the University of Washington to perform OSATS testing.7 The tasks include both endoscopic and open abdominal tasks and were varied from year to year, so the residents did not know what skill would be tested. The tasks were also varied in difficulty with some able to be successfully performed by PGY1s and others successfully performed only by more senior residents. Reliability and validity of OSATS was high.9 After validating the inanimate models,12 we changed from animal (porcine) models to life-like models.

After each laboratory, residents were asked to complete a formal evaluation. A 5-point scale ranging from poor (1) to excellent (5) was used for scoring 5 to 8 questions depending on the type of laboratory held. Questions included evaluating the pretest, lectures, bench laboratory tasks, the laparoscopic and the laparotomy parts of the animal session, an overall rating, and attending teaching. Additional comments and suggestions for improvement were left as open-ended items.

With 6 years in the surgical program completed, we have compared residents who had all 4 years of training sessions (exposed) to those who started residency earlier and had only 1 or 2 years of the surgical laboratory curriculum (controls). We also compared residents’ own performance from year to year and cohort performance by resident year. Statistical analyses were performed with SPSS for Windows, version 12.0 (SPSS, Inc, Chicago, IL). One-way analysis of variance, Student t tests, and $\chi^2$ were used to assess resident performance.

The University of Washington Animal Care Committee reviewed and approved the protocol in 1997 and yearly thereafter. From 1997 to 2002 we had Institutional Review Board exemption for research in surgical education.

### Results

Starting in 1997, each resident received 3 intensive surgical teaching interventions per year. In addition, at the end of each academic year the residents participated in OSATS. Because only 6 to 8 residents could be accommodated in the laboratory, 3 faculty members were required to teach 56 sessions over that same 4 years that equaled 228 hours of faculty time. Each animal (porcine) laboratory costs $1,500. During 1999 to 2002, we spent $48,000 on animal laboratories. This cost was higher in 1997 to 1998 when our OSATS testing was also performed in the animal laboratory. In comparison, we now perform the OSATS testing with inanimate models and spend $3,000 per year on supplies for OSATS.

Evaluation of the 12 bench laboratory skills showed PGY3 and PGY4s who had 4 years of surgical laboratory training did significantly better than those PGY3 and PGY4s with 1 to 2 years of the laboratory-based surgical curriculum (total scores of 48.8 vs 30.3, $P < .001$, Table III). In breaking down those 12 skills, the PGY3 and PGY4s with additional training did significantly better on both the laparoscopic and open laparotomy bench skills (Table III). They also scored significantly higher on the written test ($P < .001$).

With OSATS testing in either the animal or inanimate surgical models, the skills had to vary every year so the resident could not predict what would be tested.

### Table II

<table>
<thead>
<tr>
<th>Animal laboratory open surgical teaching tasks</th>
<th>Laparotomy PGY1, PGY2</th>
<th>Laparotomy PGY3, PGY4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasks:</td>
<td>Same as PGY1, PGY2 tasks plus:</td>
<td></td>
</tr>
<tr>
<td>Pfannenstiel incision</td>
<td>Oophorectomy</td>
<td></td>
</tr>
<tr>
<td>Retractors</td>
<td>Burch</td>
<td></td>
</tr>
<tr>
<td>Packing bowel/ running bowel</td>
<td>Abdominal sacrocolpopexy</td>
<td></td>
</tr>
<tr>
<td>Palpate upper abdomen</td>
<td>Cystotomy repair</td>
<td></td>
</tr>
<tr>
<td>Open pelvic sidewall</td>
<td>Pelvic and para-aortic node dissection</td>
<td></td>
</tr>
<tr>
<td>Identify ureter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identify pelvic sidewall vessels</td>
<td>Nephrectomy</td>
<td></td>
</tr>
<tr>
<td>Identify/ligate infundibulopelvic ligament</td>
<td>Inferior vena cava injury and repair</td>
<td></td>
</tr>
<tr>
<td>Identify/ligate hypogastric artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pomeroy tubal ligation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystotomy repair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterotomy repair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close abdominal incision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midline incision, and closure</td>
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</table>

### Table III

<table>
<thead>
<tr>
<th>Exposure vs control to laboratory-based surgical curriculum: PGY3 and PGY4 scores on surgical bench tasks</th>
<th>Mean (ranges)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparotomy total score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control n = 12</td>
<td>12.7 (10-15)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Exposed n = 18</td>
<td>22.5 (15-25)</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic total score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control n = 12</td>
<td>17.7 (14-21)</td>
<td>.001</td>
</tr>
<tr>
<td>Exposed n = 18</td>
<td>26.3 (4-33)</td>
<td></td>
</tr>
<tr>
<td>Overall total score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control n = 12</td>
<td>30.3 (26-52)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Exposed n = 18</td>
<td>48.8 (26-58)</td>
<td></td>
</tr>
<tr>
<td>Written test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control n = 12</td>
<td>28.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Exposed n = 15</td>
<td>33.8</td>
<td></td>
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</tbody>
</table>
Therefore, there were fewer residents who worked on the same individual tasks, thus limiting the power of our comparisons. OSATS scores were higher in the residents with 3 or 4 years of laboratories versus those with only 1 or 2 years, but none of the differences reached statistical significance (Table IV). A nonstatistically significant improvement was seen in exposed group compared with the comparison group (minimal training) in laparoscopic suturing with an Endostitch (US Surgical, Norwalk, CT), (27.0 vs 22.3, \(P = .14\)).

At the start of the program (1997) and coinciding with the start of the academic year, we conducted an OSATS pretest. In May of that same academic year, we conducted a posttest in the PGY1 and PGY2s so they served as their own controls. Table V shows significant improvement in the global OSATS scores for laparoscopic salpingotomy and open oophorectomy (\(P < .001\)) as well as the percent of the total checklist score for laparoscopic salpingotomy (\(P = .002\)). As this was the year the surgical laboratory training began, the pretest was before any exposure to OSATS and the laboratory.

The average global OSATS scores were calculated for PGY4s in 1997-1998 (1-2 years of laboratory training) versus those who were PGY4s in 2001 and 2002 (3-4 years of laboratory training). There was no significant improvement in the exposed group compared with controls (30.7 vs 29.6, \(P = .36\)). However, when looking at average global OSATS scores for the cohorts that received all 4 years of the laboratory curriculum (Figure), there was significant stepwise improvement almost every year (PGY1, PGY2 < PGY3 < PGY4, \(P < .001\)). This demonstrates construct validity.

Residents rated the laboratory training as excellent, with a mean of greater than 4 of 5 for almost all aspects (range of 3-5). Comments were uniformly positive with many residents requesting additional laboratories to practice skills. Other frequent comments praised the direct supervision, guidance and feedback, the exposure to surgery without the stress of the operating room, the self-analysis possible when letting residents make mistakes in the laboratory, exposure to new techniques, and building confidence. The lectures and written pretest received the lowest scores.

### Table IV:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean</th>
<th>(P) value</th>
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</thead>
<tbody>
<tr>
<td>Laparoscopic salpingotomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 24)</td>
<td>28.5</td>
<td>.26</td>
</tr>
<tr>
<td>Exposed (n = 17)</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Repair of deserosalized bowel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>29.5</td>
<td>.47</td>
</tr>
<tr>
<td>Exposed (n = 9)</td>
<td>30.6</td>
<td></td>
</tr>
<tr>
<td>Vessel ligation with clips</td>
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<td></td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>27.8</td>
<td>.73</td>
</tr>
<tr>
<td>Exposed (n = 8)</td>
<td>28.8</td>
<td></td>
</tr>
<tr>
<td>Endostitch</td>
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<tr>
<td>Control (n = 12)</td>
<td>22.3</td>
<td>.14</td>
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<tr>
<td>Exposed (n = 15)</td>
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<tr>
<td>Intracorporeal knot</td>
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<tr>
<td>Control (n = 6)</td>
<td>28.8</td>
<td>.57</td>
</tr>
<tr>
<td>Exposed (n = 6)</td>
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</table>

* Maximum score possible = 35.

### Table V:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mean</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic salpingotomy global</td>
<td></td>
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</tr>
<tr>
<td>Before exposure (n = 12)</td>
<td>14.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>After exposure (n = 12)</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic salpingotomy percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before exposure (n = 12)</td>
<td>63%</td>
<td>.002</td>
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<tr>
<td>After exposure (n = 12)</td>
<td>85%</td>
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<tr>
<td>Open oophorectomy global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before exposure (n = 12)</td>
<td>14.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>After exposure (n = 12)</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td>Open oophorectomy percent</td>
<td></td>
<td></td>
</tr>
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<td>Before exposure (n = 11)</td>
<td>59%</td>
<td>.242</td>
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<tr>
<td>After exposure (n = 12)</td>
<td>70%</td>
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</tr>
</tbody>
</table>

* Maximum score possible = 35.

### Figure:

Resident cohorts’ performance after completing 4 years of surgical skills laboratories. \(P < .001\), PGY1 and PGY2 < PGY3 < PGY4.

Comment

We found the most significant improvements in surgical skills with laboratory training in the single skill bench tasks and in the junior residents when first introduced to a complex surgical procedure. Rogers and Julian expressed concern over the increased variety of procedures to be taught to obstetric/gynecology residents and the declining surgical cases. During the study time, the
University of Washington obstetric/gynecology residency program surgical case volume was stable by Residency Review Committee statistics for both open and laparoscopic surgeries. Yet, even with stable case numbers, laboratory training improved skills in several areas. For residency programs with declining surgical volumes or inadequate laparoscopic cases available for training, a laboratory-based surgical skills program could be even more valuable to supplement resident operating room experience. Furthermore, the significant improvement in surgical skills with the first exposure to a procedure may prove important for the introduction of new procedures and argues for laboratory-based training. Teaching residents to perform procedures competently first in models should improve both safety and efficiency in the operating room.

Interestingly, during the study period the incidence of one procedure, laparoscopic salpingostomies, dramatically declined at the University of Washington. The changing incidence of sexually transmitted diseases in Seattle and medical treatment of ectopic pregnancies has led to 7 of 12 PGY4s finishing training in 2003 or 2004 to perform no laparoscopic salpingotomies (range 0–4, average 1). Despite this, all graduating residents have been able to competently perform a laparoscopic salpingostomy and remove an ectopic when tested by OSATS. Compared with the control PGY3 and PGY4s with fewer laboratories (1997–1998), the exposed residents maintained their laparoscopic salpingotomy skills based on OSATS testing, even with no clinical exposure to the procedure, which is likely because of the 4-year laboratory training curriculum.

Although we could not show statistically significant improvement on the OSATS in exposed versus control senior residents, every skill tested showed a slightly higher score in the exposed group. It was possible there was no absolute difference, but several limitations existed. The necessity of changing the tested tasks each year led to small numbers of residents to compare for individual tasks. Because we could not randomly assign residents to laboratory versus no laboratory training for 4 years, we did not have a true, nonexposed control group for senior residents. To overcome the latter limitation, we did have the PGY1 and PGY2 residents serve as their own controls 1 year and showed statistically significant improvement in both an open and a laparoscopic task. This group of residents had little exposure to these procedures in the operating room and little exposure to OSATS, making it more likely the surgical laboratory training influenced their ability to perform these tasks. Also, our group recently published on OSATS examinations performed at other residency programs in the United States. Some of these residency programs had laboratory-based surgical curriculum and some did not. We found that residents who received surgical laboratory training had significantly higher OSATS scores suggesting that the laboratory training actually does make a difference in surgical skills. Repeated exposures to the testing, even with varying the tasks tested, remains a confounding issue.

Validity is the extent to which an examination measures what it aims to measure. Statistically significant improvement in the cohort OSATS testing over 4 years demonstrates construct validity. We cannot prove the surgical laboratory experience caused the improvement, as the result could also be achieved by the 4 years of residency training or from increased emphasis on testing certain skills.

Considerable resources are spent conducting these surgical training sessions. Careful study is critical to demonstrate whether residents’ surgical skills can truly improve with alternative training methods and to establish standardized and reliable surgical performance measures. The direct cost of supplies is measurable as is faculty hours in the laboratory. However, the faculty time calculated includes only time spent in the laboratory, not the additional time for curriculum development, grant writing, laboratory setup, supply ordering, or analysis. Better methods are needed to quantify the benefits to residents’ training versus the total costs.

The laboratory surgical training was highly valued by the residents. The learning value of being allowed to make mistakes in the animal laboratory, such as cutting a ureter or causing major bleeding, is difficult to quantify. Obviously this type of freedom to get immediate feedback cannot be allowed in the operating room with actual patients. However, studies have shown that practicing technical skills in an environment where mistakes are permissible and having that practice observed and critiqued are 2 of the most important components of teaching surgical skills.

This study summarizes 6 years of experience with a formal laboratory-based surgical skills program. We are establishing validated criteria to assess technical skills and are able to evaluate progress over 4 years of residency in an objective way. This research is critical because many educators are calling for new standardized methods to teach and measure surgical skills.

References


Ovarian remnant syndrome

Paul M. Magtibay, MD,a,* Jessica L. Nyholm, MD,b Jose L. Hernandez,a Karl C. Podratz, MD, PhD b

Division of Gynecologic Surgery and the Division of Biostatistics,a Mayo Clinic, Scottsdale, AZ; Division of Gynecologic Surgery, b Mayo Clinic, Rochester, MN

KEY WORDS
Bilateral salpingo-oophorectomy
Ovarian remnant syndrome
Pelvic pain

Objective: This study was undertaken to examine surgical management of patients with ovarian remnant syndrome.

Study design: Data were abstracted from records of patients with a history of bilateral salpingo-oophorectomy who were treated surgically at Mayo Clinic between 1985 and 2003 for pathologically confirmed residual ovarian tissue. A follow-up questionnaire was also mailed.

Results: Records review identified 186 patients (mean age, 37.6 years; mean follow-up, 1.2 years). Of 180 patients with available data, 153 (85%) underwent oophorectomy by laparotomy, 13 (7%) by laparoscopy, and 14 (8%) by transvaginal approach, mostly for endometriosis (56.8%). Of 186 patients, 105 (57%) presented with pelvic masses and 89 (48%) with pelvic pain. Remnant ovarian tissue was associated with a corpus luteum in 78 (42%) and endometriosis in 54 (29%). The intraoperative complication rate was 9.6%. Of 142 patients, 12 (9%) required subsequent re-exploration (1 ovarian remnant identified).

Conclusion: This heavily pretreated population has modest risk of bowel, bladder, or ureteral trauma with definitive pelvic sidewall stripping and apical vaginal excision. However, subsequent recurrence is minimal (<1%). More than 90% of patients reported resolution or marked improvement of symptoms.

Risk factors associated with incomplete removal of an ovary and subsequent development of ORS include a history of endometriosis, pelvic inflammatory disease, multiple previous surgeries, and pelvic adhesive disease. Patients most frequently present with chronic pelvic pain, pelvic pain associated with a pelvic mass, or an asymptomatic pelvic mass.2 Definitive criteria for diagnosis of ORS include a history of BSO with histologic documentation of ovarian tissue obtained during subsequent surgical excision.3

The recommended treatment for ORS is surgical excision by laparotomy or, more recently, laparoscopy.4 We present a cohort of 186 patients who were surgically managed with a definitive histologic diagnosis of ORS.

Ovarian remnant syndrome (ORS) refers to a condition occurring in women who have had a bilateral salpingo-oophorectomy (BSO), with or without a hysterectomy, that leaves behind ovarian tissue. This residual ovarian tissue then results in pelvic pain or a pelvic mass. ORS contrasts with residual ovarian syndrome in which an ovary, intentionally left in place during gynecologic surgery, later causes pelvic pain.1

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The recommended treatment for ORS is surgical excision by laparotomy or, more recently, laparoscopy.4 We present a cohort of 186 patients who were surgically managed with a definitive histologic diagnosis of ORS.
We believe that a few fundamental surgical principles must be adhered to for successful results.

Material and methods

A computer-generated search was performed to identify all patients surgically managed for ORS between January 1, 1985, and October 31, 2003, at Mayo Clinic, Rochester, Minn. After approval from the Mayo Foundation Institutional Review Board, we reviewed patient records, abstracted data, and performed follow-up telephone or mail surveys. Inclusion criteria were a documented history of prior BSO and pathologic confirmation of residual ovarian cortical tissue at the time of surgical exploration and excision at Mayo Clinic. Only patients who underwent surgery with the preoperative diagnosis of ORS and histologic verification of residual ovarian tissue were included in the study. All patients in our series underwent laparotomy for resection of their ovarian remnant. The same basic surgical principles were followed in each case: (1) high religation and resection of gonadal vessels, (2) bilateral stripping and excision of the pelvic sidewall peritoneum, and (3) wide excision of tissue surrounding the remnant ovary.

Our surgical approach follows that described by Webb in 1989.3 The pelvic peritoneum lateral and parallel to the ovarian vessels is incised and the retroperitoneum is opened widely. The paravesical and pararectal spaces are dissected, and the anterior division of the internal iliac artery is divided. After the ureters are identified, the ovarian vessels are ligated cephalad to the pelvic brim, above the level of the aortic bifurcation. High ligation of the ovarian vessels ensures that no remnant ovarian tissue is missed along the vascular pedicle. This vascular segment is sent for routine pathologic assessment as it may contain residual ovarian cortical tissue. The ureters are mobilized laterally, off the pelvic sidewall peritoneum, and traced down to their entrance into the bladder. Dissection and ligation of the anterior division of the internal iliac artery facilitates the dissection of the ureter to its point of entry into the bladder allowing complete resection of the pelvic sidewall peritoneum. In most patients, the remnant piece of ovary lies on the pelvic sidewall peritoneum, near the angle of the vaginal vault, and is encased in dense scar tissue. However, the residual ovary can be located anywhere along the pelvic sidewall and therefore the entire pelvic sidewall peritoneum is stripped and resected. The bladder is dissected off the vaginal vault and wide excision of the remnant is performed. Segmental resection of a portion of the vaginal vault, bladder, ureter, or adjacent bowel is necessary if the ovarian remnant is densely adherent to these structures ensuring complete resection of all residual ovarian tissue.

Follow-up information and results were obtained by reviewing patient records, correspondence with referring physicians, and responses to follow-up standardized telephone or mail-in surveys. If data were missing, an attempt to contact the patient by telephone or letter was made to try to obtain the incomplete information. Results of therapy were defined as dichotomous variables: pain free/marked improvement (yes/no), recurrent mass (yes/no), and recurrent treatment for ORS (yes/no). Pelvic examination was performed routinely as part of postoperative follow-up on all patients. Only patients who had persistent symptoms or a palpable mass underwent postoperative pelvic imaging. Perioperative complications were defined as any untoward side effects that occurred within 30 days of the surgical procedure.

Results

The mean age of the cohort of 186 ORS patients identified in the search of the institutional database was 37.6 years (range, 20-73 years). In 180 of 186 patients for whom data were available, 153 (85%) underwent prior BSO by laparotomy, 13 (7%) by laparoscopy, and 14 (8%) by a transvaginal approach. The most common indication for BSO was endometriosis (57%), an ovarian mass (9%), pelvic inflammatory disease (7%), or other (28%; most performed at the time of hysterectomy). The mean number of laparotomies and laparoscopies patients had performed before BSO was 1.4 (range, 0-8) and 0.77 (range, 0-10), respectively. In 147 (79%) of the 186 patients, at least 1 abdominal surgery had been performed before BSO.

Of 186 patients, 65 (35%) had undergone a previous attempt at surgical resection of an ovarian remnant before presenting to Mayo Clinic. Some patients were also treated medically for a presumed diagnosis of ORS before treatment at our institution. Danazol therapy was used in 7 (4%) patients, with 4 patients showing symptomatic improvement; gonadotropin-releasing hormone agonists were used in 17 (9%) patients, with 11 experiencing improvement; and contraceptive agents were used in 6 (3%) patients, with 3 reporting symptomatic improvement. In addition, 2 (1%) patients underwent radiotherapy in an attempt to ablate the residual ovarian tissue.

Presenting symptoms and signs in our cohort of patients with ORS included constant pelvic pain (84%), pelvic mass (66%), dyspareunia (26%), cyclic pelvic pain (9%), cyclic vaginal bleeding (8%), dysuria (7%), and painful defecation (6%). Estrogen replacement therapy was initiated in 41.4% of patients immediately after BSO. Despite not receiving estrogen replacement therapy, 37% of patients experienced no symptoms of estrogen deprivation. In patients who had preoperative hormonal evaluation, premenopausal levels of follicle-stimulating hormone (FSH) (<30 IU/dL) and estradiol (>35 pg/mL) were recorded for 42 (69%) of 61 patients and 38 (63%) of 60 patients, respectively.
Ultrasonography showed a pelvic mass in 93 (93%) of 100 patients who had preoperative testing; computed tomograms were positive for a pelvic mass in 67 (92%) of 73 patients. Magnetic resonance imaging conducted in 9 women identified a mass in 7 (78%). In 14 patients, the integrity of the urinary collecting system was assessed by preoperative intravenous pyelograms, and 4 patients were found to have abnormalities (ie, stenosis at the ureteropelvic junction unrelated to the ovarian remnant, extrinsic compression of the distal ureter or bladder dome, and bilateral hydronephrosis from scarring related to ovarian remnants). All 4 patients underwent cystoscopic examination with ureteral stents placed before or during surgery. The findings of preoperative barium enemas were negative in 9 patients.

Intraoperative complications in the 186 patients included enterotomy or colotomy in 10 (5%), cystotomy in 3 (2%), and ureteral injury in 2 (1%) patients. In 3 of 10 patients with enterotomy or colotomy, 1 of 3 patients with cystotomy, and 1 of 2 patients with ureteral injury, the surgeon intentionally resected portions of those organs to obtain wide surgical clearance around the remnant ovarian tissue. In addition, 22 patients (12%) required transfusion of packed red blood cells and 3 patients (2%) required a return to the operating room within 30 days of the primary surgery, 2 for postoperative hemorrhage and 1 for an intestinal perforation after small-bowel resection (see following text).

Thromboembolic events complicated the postoperative course of 3 (2%) patients (2 with pulmonary emboli and 1 with pelvic deep venous thrombosis). Gastrointestinal complications included 1 (0.5%) intestinal perforation requiring reoperation after small-bowel resection. This patient later had an enterocutaneous fistula develop that was surgically repaired after parenteral nutrition and bowel rest. An adynamic ileus or partial small-bowel obstruction resulting in extended hospitalization occurred in 14 (8%) patients, all of whom responded to conservative therapy. One patient (0.5%) required surgical intervention for a persistent mechanical obstruction of the small bowel. Infectious complications included abdominal wound infection in 7 patients (4%), intraabdominal abscess in 2 (1%), pneumonia in 2 (1%), and overt sepsis in 3 (2%). Urinary tract complications included ureteral obstruction or stricture in 3 patients (2%), 1 of whom required placement of a nephrostomy tube and antegrade ureteral stenting, and 2 of whom underwent retrograde ureteral stenting by cystoscopy. A ureteral tear occurred in 1 patient treated by retrograde ureteral stenting without untoward sequelae. Malignant hypertension unresponsive to medical therapy developed in 1 patient several months postoperatively. Imaging studies demonstrated a nonfunctional kidney with hydronephrosis and hydroureter consistent with a distal ureteral obstruction. After nephrectomy, the hypertension resolved.

Histologically, remnant ovarian tissue was associated with a corpus luteum in 78 (42%) patients, endometriosis in 54 (29%), follicular cyst in 12 (7%), simple cyst in 45 (24%), cystadenofibroma in 3 (2%), serous cystadenoma in 2 (1%), and cystadenoma in 1 (0.5%).

The mean follow-up time was 1.2 years (range, 0.1-15.6 years). Follow-up of more than 2 years was recorded for 78 (42%) patients. Follow-up data from clinical records or telephone/mail questionnaire responses was available in 142 of the 186 patients. With a mean surveillance of 15 months, 12 patients underwent surgical reexploration related to ORS, 10 for persistent pelvic pain and 2 for ureteral stenosis. Only 1 of these 12 patients had an ovarian remnant identified, for a recurrence rate of less than 1% (0.7%). We were not able to identify any factor(s) unique to the 9 of 10 patients with persistent pelvic pain that would explain their continued symptoms, despite lacking evidence of persistent ORS at the time of repeat exploration.

Comment

In 1979, Symmonds and Pettit reported 10 cases of ORS in a 7-year span at Mayo Clinic. Subsequently, Pettit and Lee reported on 31 patients with a diagnosis of ORS at our institution between 1980 and 1985. We now present the largest case series in the medical literature of 186 patients with histologic confirmation of ORS managed surgically at Mayo Clinic during the ensuing 19 years. Although the size of the representative referral patient population is unknown, the incidence of ORS has progressively increased during the past 4 decades.

ORS results from incomplete removal of all ovarian tissue during BSO. Incomplete removal of ovarian tissue is invariably because of the adherence of ovaries to the surrounding peritoneum or adjacent pelvic structures or a suboptimally designed or executed surgical procedure. Factors that predispose to adhesion formation and incomplete removal of the ovaries include endometriosis, pelvic inflammatory disease, ovarian or uterine neoplasms, inflammatory bowel disease, a history of appendectomy, or a history of multiple previous abdominal surgeries. In addition, intraoperative conditions (eg, intraoperative bleeding, anatomic variation, or deviation from sound surgical principles as described in the following text) may contribute to incomplete removal of the ovaries.

Ovarian tissue adherent to pelvic peritoneum or adjacent pelvic viscera has the potential to become neovascularized and responsive to gonadotropins despite ligation of the blood supply to the ovaries. Shemwell and Weed demonstrated in felines that transplanted ovarian tissue may revascularize and remain functional. It is therefore imperative to remove en bloc the ovaries and surrounding peritoneum or visceral serosa during the
BSO. Blunt dissection in an attempt to free the ovaries from surrounding tissues must be avoided, as it risks leaving behind remnants of the ovarian cortex.

During any adnexectomy, we incise the peritoneum lateral to the ovarian vessels and widely open the retroperitoneum. This approach allows for easy and accurate identification of vital structures, including the ureters and pelvic vessels. The gonadal vessels are then ligated high, cephalad to the ovaries, and the adnexa and surrounding peritoneum are resected en masse. We avoid blunt dissection of the surrounding peritoneum adjacent to the ovaries, theoretically reducing the risk of ORS. With increased numbers of gynecologic operative procedures being performed with laparoscopy, it is important to emphasize that the same surgical principles must be maintained during laparoscopic adnexectomy as are observed with laparotomy. We do not advocate the common technique of placing traction on the ovaries medially and transecting the pedicle with endoscopic staplers or endo-loops. Not opening the retroperitoneum increases the potential for leaving minute fragments of fractured neovascularized ovarian tissue attached to the pelvic peritoneum.

Preoperative evaluation in patients suspected of having an ovarian remnant includes studies of serum FSH and estradiol. The likelihood of ovarian remnant increases when values are within the premenopausal range and the patient is not receiving exogenous estrogen replacement therapy. It is important to remember, however, that ORS cannot be completely ruled out when values are in the postmenopausal range, because some women with ORS have postmenopausal levels of FSH and estradiol. Preoperative imaging techniques with computed tomography, ultrasonography, or magnetic resonance imaging may help detect a pelvic mass consistent with an ovarian remnant. Some authors advocate the use of clomiphene citrate stimulation before pelvic imaging to identify remnant ovarian tissue preoperatively. Kaminski et al.10 examined 6 patients with a history of BSO who continued to have pelvic pain and negative pelvic imaging. When clomiphene citrate was administered for 10 days, repeat pelvic sonography showed cystic structures consistent with ovarian follicles in 4 of the women. Kaminski et al.10 have therefore recommended such testing for identification of residual ovarian tissue and as an aid to its surgical removal. However, not all anovulatory women will be unresponsive to ovarian stimulation with clomiphene citrate, so residual ovarian tissue occurring with ORS may not respond to exogenous stimulation.

Intravenous pyelography, cystoscopy, or barium enema may be more useful in determining the extent of surgical resection required and should be ordered on a case-by-case basis. Indeed, no single test or series of tests can make a definitive diagnosis of ORS. Instead, confirmation requires surgical exploration, excision, and histologic documentation. A high index of suspicion must, however, be maintained in patients at risk for ORS, including a history of pelvic adhesive disease (ie, prior endometriosis, pelvic inflammatory disease, or multiple pelvic surgeries), FSH and estradiol levels suggestive of the presence of functional ovarian tissue, and presence of a pelvic mass on imaging studies, in the patient with a prior history of BSO.

Surgical excision is the preferred approach to the definitive management of ORS. In our series, all operations for ORS were performed by laparotomy. Our surgical approach (detailed in the Materials and methods section of this article) has always been that described by Webb5 in 1989. The pelvic peritoneum is incised, the retroperitoneum is opened widely, paravesical and pararectal spaces are developed, and the ureters are identified, mobilized, and traced to their junction with the bladder. In most patients, the remnant of ovary lies on the pelvic sidewall peritoneum, near the angle of the vaginal vault, and is encased in dense scar tissue (Figure). The bladder is dissected off the vaginal vault and a wide excision of the remnant is performed.

A segmental resection of a portion of the vaginal vault, bladder, ureter, or adjacent bowel may be necessary when the ovarian remnant is densely adherent to these structures. It is critically important that the radicality of the surgical procedure not be compromised to preserve the integrity of adjacent organs. These operations are often technically challenging because of dense, fibrotic adhesions, bleeding, and involvement of organ systems other than the female genital tract. An experienced surgeon, adequately prepared to deal with such situations, is therefore ideal to ensure success of the procedure.

We recognize the obvious flaws associated with this study as with any retrospective case series. Because ORS is a relative rare condition, a prospective study yielding any significant case numbers is an unrealistic expectation.
from any institution, including our own. Our study, however, is the largest cohort published to date examining the management of ORS using the same surgical principles, at a single institution, for nearly the past 20 years. Although follow-up information was not available on all patients, every attempt was made to collect data through review of patient charts, physician correspondence, or when necessary, by telephone or mail survey. We were able to obtain accurate follow-up information in 76% (142/186) of the cohort with a 91% reporting resolution of symptoms.

ORS is a rare condition occurring after BSO. When the diagnosis is entertained and surgical management is being implemented, adherence to certain basic surgical principles is vital to the success of the operation. In our series of 186 patients, only 1 patient was definitively identified as having a recurrent ovarian remnant, with more than 90% of patients having complete resolution or marked improvement in symptoms after surgery. There is modest risk of bowel, bladder, or ureteral injury in this population of patients; however, a compromise in surgical radicality risks a reduction in the rate of success for the procedure.

References

Regret, satisfaction, and symptom improvement: Analysis of the impact of partial colpocleisis for the management of severe pelvic organ prolapse

Thomas L. Wheeler II, MD,a,* Holly E. Richter, PhD, MD,a Kathryn L. Burgio, PhD,b,c David T. Redden, PhD,c C. C. Grace Chen, MD,a Patricia S. Goode, MD,b,c R. Edward Varner, MDb

Division of Medical Surgical Gynecology, Department of Obstetrics and Gynecology,a Division of Gerontology and Geriatric Medicine, Department of Medicine,b University of Alabama at Birmingham; Birmingham/Atlanta Geriatric Research, Education and Clinical Center (GRECC), Department of Veterans Affairs Medical Center,c Birmingham, AL

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KEY WORDS
Colpocleisis
Regret
Satisfaction
Outcomes

Objective: The purpose of this study was to assess a cohort of patients who underwent a colpocleisis procedure more than 1 year post operation to determine: 1) the proportion of patients who regretted having the procedure, 2) patient satisfaction with the procedure, and 3) changes in symptom severity after surgery.

Study design: Using the University of Alabama at Birmingham (UAB) Genitourinary Disorders Center database, a prospective analysis was performed on 54 patients who underwent colpocleisis between August 1996 and April 2003. From August to October of 2004, participants were contacted by an investigator not involved with the surgery and were asked 1) “do you regret having your surgery, and, if so, why?,” 2) “how satisfied are you with your progress (completely, somewhat, or not)?,” and 3) to repeat the short form Incontinence Impact Questionnaire/Urogenital Distress Inventory (IIQ-7/UDI-6).

Results: Fifty-nine percent (32/54) of potential candidates participated in the study. Nine percent (3/32) of patients regretted having colpocleisis performed. Fifty-seven percent (16/28) were completely satisfied, 29% (8/28) somewhat satisfied, and 14% (4/28) not satisfied. Mean IIQ score improved significantly from 40.9 (±31.7) at baseline to 14.1 (±26.7) at last interview (P = .003). Mean UDI score improved significantly from 63.1 (±24.3) at baseline to 24.2 (±26.7) at last interview (P = .001). There was a negative correlation between change in UDI scores with time since procedure (r = −.397, P = .055) and age (r = −.435, P = .034).

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* Reprint requests: Thomas L. Wheeler II, MD, Fellow-Female Pelvic Medicine and Reconstructive Pelvic Surgery, University of Alabama at Birmingham, Medical Surgical Gynecology, 619 19th Street South, NHB 219, Birmingham, AL 35249-7333.
E-mail: twheeler@uabmc.edu

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Partial colpocleisis with levator myorrhaphy and perineorrhaphy can be chosen as the surgical approach for severe pelvic organ prolapse. While the resulting vaginal septum and narrowed genital hiatus alleviates the prolapse, it also precludes the possibility of vaginal intercourse. Shorter operative time and less surgical risk are the advantages of this approach over vaginal reconstructive procedures. Therefore, candidates are typically older, with no desire for vaginal function, and usually have concomitant medical problems.

Objective surgical outcomes from case series on partial colpocleisis report high success rates up to 100%. Reporting of regret and satisfaction is limited. One case series for partial colpocleisis and 3 for total colpocleisis report regret rates which ranged from 0 to 10%. One description of satisfaction outcomes from a case series on total colpocleisis found 5% of patients not satisfied. To the best of our knowledge, no published pre- versus postoperative comparison, using a validated quality-of-life instrument, exists.

Because it is estimated that one third of women over 78 years are sexually active, it is important to understand the incidence of regret after partial colpocleisis. Furthermore, because of the impact of patient preferences and goals on surgical success, subjective outcomes such as satisfaction and symptomatology are also important. The purpose of this report was to assess a cohort of patients who underwent a partial colpocleisis procedure more than 1 year post operation to determine regret, satisfaction, and urogenital symptom change.

**Material and methods**

Institutional Review Board approval was obtained. The University of Alabama at Birmingham (UAB) Genitourinary Disorders Center database was used to identify patients who underwent a colpocleisis procedure between August 1996 and April 2003. Thirty-five of these 54 patients were contacted by an investigator not involved with the surgery and were asked 1) “do you regret having your surgery, and, if so, why?,” 2) “how satisfied are you with your progress (completely, somewhat, or not)?,” and 3) to repeat the short form Incontinence Impact Questionnaire/Urogenital Distress Inventory (IIQ-7/UDI-6). Preoperative baseline IIQ-7/UDI-6 scores were obtained from the Genitourinary Disorders Center database. All patients underwent reduction urodynamic testing before surgery to help determine if an incontinence procedure versus a Kelly type procedure or no further procedure be performed for urinary incontinence.

**Surgical technique**

Rectangular portions of the anterior and posterior vaginal walls were dissected off the underlying fibromuscular connective tissue, leaving a lateral 2-cm bridge of vaginal mucosa. The lateral vaginal canals were created using 2 0-gauge polydioxanone sutures. The anterior fibromuscular connective tissue was approximated to the posterior fibromuscular connective tissue, creating a septum of support with 3 or 4 interrupted 0-gauge vicryl sutures. The distal anterior and posterior vaginal borders were then closed. Next, a levator myorrhaphy and perineorrhaphy was performed using O-gauge prolene suture, after resection of the overlying vaginal epithelium. Dissection of the vaginal epithelium was initiated with an incision from the 3 o’clock to 9 o’clock positions outside of the hymenal ring and resulted in removal of a triangular shaped area of posterior vaginal mucosa, exposing the connective tissue overlying the puborectalis muscle laterally. After the initiation of the vaginal epithelial closure, care was taken to place the prolene sutures (usually 2) in a perpendicular orientation to the levator muscle/fascial fibers, approximately 3 cm from the puborectalis insertion into the pubic symphysis. If another suture was needed to ensure adequate distal vaginal closure, 0-gauge polydioxanone was used. The perineorrhaphy was then completed as in an episiotomy repair. Upon completion of the procedure the measured genital hiatus is typically between 1 and 2 cm and the vaginal depth is 3 to 4 cm.

**Statistical analysis**

Preoperative versus postoperative IIQ-7/UDI-6 scores were analyzed with the Wilcoxon signed rank test. Subscale UDI-6 analysis was performed with α set at .0083 to account for multiple testing (ie, .05 divided by 6). Wilcoxon rank sum was used to test for the effect of concurrent incontinence procedure on UDI/IIQ change. Spearman rank correlation coefficient was used to correlate change in UDI scores with time since procedure and age. All other data were analyzed with descriptive statistics.

**Results**

Fifty-four patients were identified as having undergone colpocleisis between August 1996 and April 2003. Retrospective chart review revealed that 4/54 (7.4%) had...
recurrent prolapse, defined as prolapse to the hymenal ring. Fifteen patients were excluded from being contacted, 6 for an existing diagnosis of dementia, and 9 were deceased. Four patients were lost to follow-up, leaving 35 candidates. Three of the 35 candidates declined participation, 1 who had recurrent prolapse, 1 who was too ill, and 1 who did not give a reason (Figure).

Patients who participated in the study were compared with nonparticipants on age and follow-up interval, as well as available baseline data from the IIQ-7 and UDI-6. Nonparticipants tended to be older than participants ($P = .051$) and had longer follow-up intervals ($P < .001$). However, the groups were not significantly different on the measures of impact on incontinence ($P = .472$) or urogenital distress ($P = .239$).

The mean age at follow-up of the 32 participating patients was 81.4 ($\pm 5.1$) years (median 82; range 69-93). The mean follow-up interval was 27.5 ($\pm 13.7$) months (median 24.0; range 12-78).

Three patients (9.3%) regretted having colpocleisis performed. Two cited recurrent prolapse as the reason for regret. Prolapse recurrence occurred at 5 and 7 months’ postoperation. The other patient, who had undergone a modified Pereya procedure at the time of colpocleisis, cited continued stress incontinence. No participant cited loss of sexual function as a reason for regret. One patient with recurrent prolapse that occurred 4 months postoperation did not regret having the procedure done.

Satisfaction data were obtained for 28 patients (28/32, 87.5%). Fifty-seven percent (16/28) were completely satisfied, 29% (8/28) somewhat satisfied, and 14% (4/28) not satisfied. Mean IIQ-7 score improved significantly from 40.9 ($\pm 31.7$) at baseline to 14.1 ($\pm 26.7$) at the interview ($P = .003$). Mean UDI-6 score improved significantly from 63.1 ($\pm 24.3$) at baseline to 24.2 ($\pm 26.7$) at interview ($P = .001$).

Nineteen participants (59.4%) had a concurrent incontinence procedure (13 pubourethral ligament plications, 5 tension-free vaginal tape procedures, and 1 modified Pereya needle suspension). There was a negative correlation between change in UDI-6 scores with time since procedure ($r = -.397$, $P = .055$) and age ($r = -.435$, $P = .034$). There was no significant difference in change in UDI-6 scores ($P = .439$) between patients who had an incontinence procedure and those who did not have an incontinence procedure. On subscale analysis of the UDI-6, no statistical difference ($\alpha < .00833$) was found for irritative, obstructive/discomfort, or stress symptoms between patients having a concurrent incontinence procedure versus those who did not (UDI questions 1-6; $P = .36$, .03, .23, .25, .68, and .58, respectively).

**Comment**

One previous report describes patient regret and satisfaction after partial colpocleisis. Ubachs et al reported regret and satisfaction rates of 10.7% and 90.3%, respectively, in 84 patients. Recurrent prolapse accounted for regret in 5 of the 9 cases (55.5%). The 4 other cases of regret were attributed to unspecified factors other than the surgery. It was unclear how these data were obtained.

Three recent retrospective case series for total colpocleisis report subjective outcomes that include regret. Harmanli et al had no reports of regret at any follow-up visit for 41 patients. Von Pechmann et al asked patients “have you ever regretted losing the ability to have intercourse?” Among 62 patients, 3.2% answered yes, and 9.7% answered somewhat, however, only 1 of these patients would not go through the procedure again. These patients were also asked, “Are you satisfied with how well the surgery repaired the dropped organs?” Only 4.8% answered not satisfied. In 33 patients, DeLancey found 3.0% regret concerning loss of sexual function.

Our experience with partial colpocleisis, levator myorrhaphy, and perineorrhaphy revealed a regret rate of 9.3%, which is consistent with previous findings. Recurrent prolapse was the reason given for 2 out of 3 cases of regret. Unlike Delancey and von Pechmann, loss of sexual function was not found to be a reason for regret in this series. However, these studies specifically...
queried about regret over loss of sexual function, while our study only asked for a reason if regret was present. It is not unreasonable to accept that the framing of a regret question impacts patient perception over the loss of sexual function. Either way, regret and the impact of loss of sexual function appears to be low.

The 2 patients with regret secondary to recurrent prolapse are currently being managed with a pessary. One patient had failed a previous abdominal sacrocolpopexy. Of note, the patient with recurrence (which is 1 cm outside the hymenal ring) and no regret did not desire pessary. Considering these observations and results of previous reports, patients should be counseled with respect to an approximate 10% chance of surgical failure.

Fourteen percent of patients were not satisfied with their surgery. This is higher than that of previous reports, but 4 patients that participated in other aspects of this report did not answer this question, which could have lowered it to 12% or increased it to 25%. Unlike the regret question, the satisfaction question did not ask for a reason for the participant’s response.

Large improvements were observed in the IIQ-7 and UDI-6 scores, indicating significant reduction in symptom-related distress and impact of incontinence. Furthermore, we did not find that a concurrent incontinence procedure was solely responsible for the improvement in the UDI-6 total score. The subscale analysis of the UDI-6, which encompasses irritative, obstructive/discomfort, and stress symptoms, suggests that partial colpocleisis made a positive impact on these symptoms regardless of whether a concurrent incontinence procedure was performed. Secondary to small numbers, the incontinence procedures were not sub-grouped for statistical analysis.

Because the majority of 22 nonparticipating patients were deceased or demented, we were not surprised to find a greater age and follow-up interval for them compared with the 32 participating patients. However, the baseline IIQ-7/UDI-6 scores were not statistically different, suggesting that the sample of participants was reflective of the larger group of patients in terms of symptoms and impact.

The strengths of this study include the measurement of regret rate, prospective use of validated condition-specific questionnaires, and incorporation of a satisfaction question. Limitations of this study include its small numbers and loss to follow-up with the resultant potential biases. A prospective cohort study encompassing validated QOL instruments comprehensively addressing a broader range of pelvic floor symptoms, including fecal incontinence, urinary incontinence, and pelvic pain needs to be performed. It should assess patient expectations, including reasons for dissatisfaction and impact on subjective, as well as objective, outcomes. Such a study would give additional valuable information with which to counsel this growing patient cohort.

References

Fecal incontinence (FI) is commonly defined as the accidental loss of liquid or solid stool. Several studies have documented the quality-of-life (QOL) impact of this embarrassing and socially isolating condition. Only a minority of patients with FI, however, report their symptoms to their physician. Efforts to document the community-based prevalence of FI have been difficult, leading many investigators to examine specific populations, such as postpartum women, or limited potential risk factors, such as delivery type and urinary incontinence (UI).

Among studies of community-dwelling adults, FI is estimated to affect 2% to 13% of respondents, with rates varying depending on the definitions and data collection methods utilized. Higher prevalence rates are found in studies requiring as few as 1 accident in the last year for a positive response, while lower rates are found with data collection methods that lack anonymity, such as in-person interviews.
Studies reporting on subpopulations of women estimate FI prevalence at 3% to 10%. FI in women is of particular interest because of the potential impact of childbirth and common pelvic surgeries, like hysterectomy, on bowel function. In epidemiologic studies, increasing age and UI have been consistently associated with FI, while operative vaginal delivery, cesarean section, and hysterectomy have yielded conflicting or uncertain results. Most studies have been unable to link survey data to medical findings, such as physician diagnoses, and large epidemiologic surveys have not been performed in community-based samples of women in the US, where different risk factors may predominate. This study’s objectives were to determine the prevalence of and factors associated with FI in a population-based sample of community-dwelling women aged 30 to 90 years.

Material and methods

The participants of this 2002 study were female enrollees of Group Health Cooperative (GHC), a health maintenance organization serving approximately 550,000 individuals in Washington State. GHC enrolls 1-in-10 Washington residents and provides traditional group and individual care plans, as well as Medicare, Medicaid, and government employee coverage. A 15-page self-report form was mailed to an age-stratified random sample of 6000 female enrollees aged 30 to 90 years. The survey contained questions about medical, surgical, obstetric, and gynecologic history; medications; bowel and bladder symptoms; depressive symptoms; functional status; QOL; and demographics. Exclusion criteria were inability to locate, death, disenrollment from GHC, paralysis, mental or physical barriers to completing a questionnaire, and current urinary tract infection (UTI). An initial and 2 reminder questionnaires were sent. The sample was linked to longitudinal automated data, including inpatient and outpatient diagnoses, which was available for respondents and nonrespondents. Participants provided informed consent, and the GHC Human Subjects Committee approved the study.

Frequency of stool loss was characterized as never, less than monthly, monthly, or weekly, with separate inquiries into loss of liquid and solid stool. FI was defined as loss of liquid or solid stool occurring at least monthly. Participants were asked whether they wore a pad or altered their lifestyle because of stool loss. The questions were adapted from the Wexner Continence Grading Scale, which correlates well with clinical impression of FI. Participants also reported their number of bowel movements per week and their predominant stool type (normal, constipated, diarrhea, or combined).

Frequency of urine loss was characterized as never, less than monthly, monthly, weekly, or daily. Amount of urine lost was quantified as a few drops, a small, moderate, or large amount. UI was defined as leakage of any amount occurring at least monthly. We characterized the degree of UI (mild, moderate, severe) using the Sandvik severity index, which has been validated against pad-weighing tests.

The categorical variables of race, ethnicity, education, income, employment, smoking, alcohol use, menopausal status, and history of hysterectomy were assessed by self-report. Self-reported height and weight were used to calculate body mass index (BMI) in kg/m². Respondents were asked to list each child birth, delivery type, whether a forceps or vacuum-assisted device was used, whether an episiotomy or vaginal laceration occurred, and infant birth weight. Delivery types were categorized by theoretical risk of pelvic floor injury as nonoperative vaginal deliveries only; cesarean deliveries only; history of any operative vaginal delivery; and other mixed/unknown delivery type.

Current major depression was diagnosed with the PRIME-MD Patient Health Questionnaire 9-item (PHQ-9), which has excellent agreement with diagnosis of major depression by structured interview. GHC automated data were used to determine the presence of diabetes mellitus, and to generate the RxRisk chronic disease score, a measure of medical comorbidity based on prescription drug use for the previous year. The questionnaire also included the World Health Organization Disability Assessment Schedule II (WHO-DAS II), a functional status measure assessing disability, reported as a continuous score.

Statistical analyses were performed using Stata version 8.1 (Stata Corporation, College Station, TX). Descriptive statistics were used to characterize the overall sample and participants with and without FI. FI prevalence rates were calculated for the study population according to decade of age. A population-based
prevalence was also calculated, according to the age distribution of GHC’s total female population. Bivariate comparisons of variables by FI status were conducted using chi-square tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Using factors determined a priori and significant factors from the bivariate analyses, we created a series of multivariate logistic regression models to predict odds of FI among women.

To assess potential response bias, we examined differences between survey respondents and nonrespondents using automated data. We estimated the probability of being a respondent as a function of the following: age, RxRisk score, primary care visits, depression diagnosis, and diabetes diagnosis. We used a weighted analysis with weights inversely proportional to the estimated probability of response, rescaled to sum to the observed sample size. In this analysis, persons with a low probability of responding are given a higher weight to represent the larger number of nonrespondents with similar characteristics. Our comparison of weighted and unweighted analyses showed negligible differences in survey estimates; therefore, we report analyses based on observed data.

### Results

Reasons for ineligibility were death (n = 34), invalid address (n = 162), mental/physical barriers (n = 151), disenrollment from GHC (n = 96), paralysis (n = 9), and current UTI (n = 17). Of the remaining 5531 potential participants, 3536 returned the questionnaire for a response rate of 64%.

The prevalence of FI among respondents was 7.2%. After adjusting for oversampling the youngest age groups, the population-based prevalence was 7.7%. Prevalence increased markedly with age (Figure 1). Among women with FI, 63% reported monthly and 37% reported weekly FI episodes. Loss of liquid stool was reported by 47% of women with FI, loss of solid stool was reported by 23%, and loss of both liquid and solid stool was reported by 30%. Seventy percent of participants with FI had comorbid UI, and 12% of participants with UI had comorbid FI. Further analysis by UI severity revealed comorbid FI in 8% of women with mild UI, 15% of women with moderate UI, and 26% of women with severe UI.

Women with fecal incontinence were older, had higher BMIs, had a higher number of deliveries, and

### Table I  Characteristics of respondents*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 3444)</th>
<th>No FI (n = 3195)</th>
<th>FI (n = 249)</th>
<th>f or $\chi^2$ statistic$^1$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.9 ± 16.5</td>
<td>52.2 ± 16.3</td>
<td>61.9 ± 16.3</td>
<td>81.67</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BMI (mean)</td>
<td>27.4 ± 6.7</td>
<td>27.2 ± 6.5</td>
<td>29.3 ± 8.3</td>
<td>21.23</td>
<td></td>
</tr>
<tr>
<td>RxRisk Score (mean)$^2$</td>
<td>2270 ± 2049</td>
<td>2166 ± 1937</td>
<td>3600 ± 2833</td>
<td>116.97</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>42.4% (n = 1426)</td>
<td>40.4% (n = 1260)</td>
<td>69.5% (n = 166)</td>
<td>76.87</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Major depression</td>
<td>3.8% (n = 126)</td>
<td>3.2% (n = 101)</td>
<td>10.5% (n = 25)</td>
<td>32.45</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.6% (n = 227)</td>
<td>5.9% (n = 188)</td>
<td>15.7% (n = 39)</td>
<td>35.88</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Non-white race</td>
<td>13.1% (n = 442)</td>
<td>13.3% (n = 416)</td>
<td>10.7% (n = 26)</td>
<td>1.39</td>
<td>.238</td>
</tr>
<tr>
<td>Education (≥ high school)</td>
<td>20.8% (n = 712)</td>
<td>20.0% (n = 635)</td>
<td>31.1% (n = 77)</td>
<td>17.00</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9.2% (n = 312)</td>
<td>9.1% (n = 285)</td>
<td>11.2% (n = 27)</td>
<td>1.23</td>
<td>.267</td>
</tr>
<tr>
<td>Moderate alcohol</td>
<td>19.5% (n = 661)</td>
<td>20.1% (n = 632)</td>
<td>12.0% (n = 29)</td>
<td>9.22</td>
<td>.002</td>
</tr>
<tr>
<td>(≥ 3 drinks/wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripostmenopausal</td>
<td>57.1% (n = 1898)</td>
<td>55.1% (n = 1703)</td>
<td>83.0% (n = 195)</td>
<td>69.14</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>H/O hysterectomy</td>
<td>20.7% (n = 704)</td>
<td>19.4% (n = 612)</td>
<td>38.3% (n = 92)</td>
<td>48.65</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>H/O vaginal hysterectomy$^3$</td>
<td>33.7% (n = 246)</td>
<td>34.5% (n = 203)</td>
<td>37.9% (n = 33)</td>
<td>0.36</td>
<td>.549</td>
</tr>
<tr>
<td>Deliveries (mean #)</td>
<td>2.0 ± 1.5</td>
<td>2.0 ± 1.5</td>
<td>2.42 ± 1.6</td>
<td>20.67</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Delivery type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonoperative vaginal deliveries only$^4$</td>
<td>43.2% (n = 1488)</td>
<td>43.4% (n = 1388)</td>
<td>40.2% (n = 100)</td>
<td>17.65</td>
<td>.001</td>
</tr>
<tr>
<td>Nulliparous (no deliveries)$^1$</td>
<td>19.4% (n = 668)</td>
<td>19.8% (n = 632)</td>
<td>14.5% (n = 36)</td>
<td>19.22</td>
<td>.002</td>
</tr>
<tr>
<td>H/O operative vaginal delivery$^1$</td>
<td>24.4% (n = 840)</td>
<td>23.7% (n = 757)</td>
<td>33.3% (n = 83)</td>
<td>19.98</td>
<td>.001</td>
</tr>
<tr>
<td>Cesarean sections only$^1$</td>
<td>6.9% (n = 238)</td>
<td>7.1% (n = 228)</td>
<td>4.0% (n = 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown/mixed birth type$^1$</td>
<td>6.1% (n = 210)</td>
<td>6.0% (n = 190)</td>
<td>8.0% (n = 20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Includes survey respondents who completed questions necessary for a diagnosis of FI.

1. Comparing respondents with and without FI: df for $\chi^2$ is 1; df range for f is 3339 to 3444.

2. Medical comorbidity measure.

3. Among those with history of a hysterectomy.

4. Delivery type categories.

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Melville et al 2073
were more likely to have current UI (Table I). They were more likely to have a previous hysterectomy, greater medical comorbidity, including major depression and diabetes, and a history of operative vaginal delivery. Information on vaginal laceration or episiotomy could not be analyzed because 19.8% of women did not know or did not remember if laceration or episiotomy had occurred. In the final logistic regression model, older age, increasing medical comorbidity, current major depression, current UI, and history of operative vaginal delivery were associated with increased odds of FI (Table II).

One half of women with FI reported a QOL impact attributable to their stool incontinence, with 47% reporting use of a pad and 53% reporting alteration of their lifestyle. Functional status was also affected, with women with FI reporting significantly higher mean WHO-DAS II scores, indicating greater functional disability, than women without FI (23.8 vs 10.9; f(1, 3442) 186.65, P < .001).

Bowel habits also differed among women with and without FI. Women with FI reported a significantly higher mean number of bowel movements per week (14.1 vs 8.1; f(1, 3380) 218.73; P < .001). Women with FI were also significantly more likely to report ≥15 bowel movements per week (Figure 2) and a greater percentage of abnormal stool types (Figure 3).

**Comment**

In this large population-based study of FI, 7% of women reported experiencing loss of liquid or solid stool at least monthly, and the prevalence of FI increased nearly linearly with age. The impact of FI on QOL, alteration of lifestyle, and functional status was significant. Like Perry et al, we found that half of subjects with FI reported that their bowel symptoms had a large impact on their QOL. The women with FI in our study also reported moderate functional impairment, with a mean WHO-DAS II score of 23.8. This is consistent with levels of impairment in individuals with chronic medical conditions like back pain (mean WHO-DAS II score 22.75).

Our study confirms the current evidence for age and UI as factors associated with FI. That aging is highly

![Figure 2](image2.png) **Number of bowel movements per week, comparing respondents with and without FI, Pearson \( \chi^2(2) = 218.11; P < .001. \)**

![Figure 3](image3.png) **Predominant stool type, comparing respondents with and without FI, Pearson \( \chi^2(3) = 285.40; P < .001. \)**

<table>
<thead>
<tr>
<th>Table II</th>
<th>Adjusted odds of FI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictor</td>
<td>Adjusted Odds Ratio</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>50-69&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2.11</td>
</tr>
<tr>
<td>70-90&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2.22</td>
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<tr>
<td>Major depression</td>
<td>2.73</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>2.32</td>
</tr>
<tr>
<td>Medical comorbidity</td>
<td></td>
</tr>
<tr>
<td>Moderate&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.76</td>
</tr>
<tr>
<td>High&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>2.58</td>
</tr>
<tr>
<td>Birth type</td>
<td></td>
</tr>
<tr>
<td>H/O operative vaginal delivery&lt;sup&gt;§&lt;/sup&gt;</td>
<td>1.52</td>
</tr>
<tr>
<td>Cesarean deliveries only&lt;sup&gt;∥&lt;/sup&gt;</td>
<td>0.87</td>
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<td>Mixed/unknown delivery types&lt;sup&gt;‡&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Nulliparity&lt;sup&gt;∥&lt;/sup&gt;</td>
<td>1.35</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Overweight (BMI 25-29)&lt;sup&gt;∥&lt;/sup&gt;</td>
<td>0.95</td>
</tr>
<tr>
<td>Obese (BMI &gt;29)&lt;sup&gt;∥&lt;/sup&gt;</td>
<td>1.38</td>
</tr>
</tbody>
</table>

<sup>*</sup> Reference group age 30 to 49.
<sup>†</sup> RxRisk score in 2nd tertile; reference group RxRisk score 1st tertile.
<sup>‡</sup> RxRisk score in 3rd tertile; reference group RxRisk score 1st tertile.
<sup>§</sup> Reference group H/O nonoperative vaginal deliveries only.
<sup>∥</sup> Reference group BMI <25.
associated with FI is an important finding, not only in terms of etiology, but also as an indicator of the services and treatments that will be needed with the aging of our population. Practitioners that care for women, especially those over the age of 50, should be aware of the prevalence of FI and the significant impact it can have on the quality of a woman’s life. FI is not present in the majority of elderly women, however, and should not be treated as a normal part of aging. UI was also highly associated with FI, indicating the need to query women who present with UI about possible comorbid FI symptoms.

Our study found a strong association between current major depression and FI, similar to the findings we have observed between major depression and UI. To our knowledge, this is the first study that has examined major depression as a potential risk factor for FI. This link between major depression and FI may be bidirectional. Altered neurotransmitter function in depressed patients could affect the complex bowel innervation, altering gastrointestinal motility or pelvic floor function, leading to FI. Alternately, the embarrassment from loss of stool may lead to progressive social isolation and subsequent depression over time.

Anal sphincter damage after operative vaginal delivery has been well documented. Although higher rates of sphincter damage have been demonstrated with forceps, higher rates of FI have been seen with vacuum deliveries. We examined any history of operative vaginal delivery, since self-report of exact operative method may not be reliable. We found a history of operative vaginal delivery to be significantly associated with increased odds of FI, compared with a history of only nonoperative vaginal deliveries (OR 1.44 [1.04,1.98]). We did not find having only cesarean deliveries to be associated with decreased odds of FI, confirming a recent report by Chaliha et al that cesarean section is not protective against FI. We were unable to examine the role of episiotomy or laceration because 19.8% of women did not know or did not remember if episiotomy or vaginal laceration occurred. Recent evidence suggests that sphincter laceration may be associated with symptoms of FI immediately postpartum, but as women age the prevalence of FI is the same between nulliparous and parous women and between parous women with and without sphincter laceration. Our study agrees, as nulliparity was not associated with decreased odds of FI. This may indicate that aging plays a more important role than sphincter laceration in the development of FI in women.

Women with FI reported more bowel movements per week and more abnormal stool types when compared with women without FI. These findings may be consistent with a diagnosis of irritable bowel syndrome (IBS), but this cannot be determined from our study. At the time our survey was designed, a self-report instrument providing a diagnosis of IBS was not available. Additionally, many women believe they carry a diagnosis of IBS but do not meet ROME II diagnostic criteria. Because a self-report instrument to diagnose IBS is now available, future epidemiologic studies can carefully examine IBS as a risk factor for FI.

Strengths of this study are the population-based sampling of a large number of women over a broad age range and the accurate assessment of comorbid medical conditions. We also addressed potential responder bias through a propensity analysis, showing that the results are representative of our population. The comprehensive data collected and the large number of participants allow for analysis of many potential risk factors. Limitations already addressed include our inability to evaluate episiotomy or laceration and IBS as potential risk factors for FI. Another limitation is our cross-sectional design, which prevents determination of the causal relationships between FI and associated factors.

With the aging of our population and available treatments for FI, increased attention should be paid to this debilitating condition. Clinicians should have a heightened awareness of the possibility of FI in women with major depression, UI, increased medical comorbidity, and a history of operative vaginal delivery.

References

Objective: Surgery is the cornerstone of management in ovarian cancer. However, in high-risk and elderly patients there is a tendency for less aggressive surgery upfront. The aim of this study was to review cytoreductive surgery, with focus on complications and outcomes in patients with multiple surgical risk factors.

Study design: Charts of patients with ovarian cancer from 1998 to 2002 were retrospectively reviewed.

Results: One hundred and forty patients were treated for ovarian cancer. Sixty-three patients (45%) were elderly (≥65 years), and 69 patients (49%) had comorbidities. Optimal debulking (≤1 cm) was achieved in 123 patients (88%). There was no significant relation between complications and type of procedure, elderly age, comorbidities, or transfusions. Optimally debulked patients had a significantly longer survival than patients with suboptimal debulking (P < .001).

Conclusion: Aggressive optimal cytoreduction can be achieved in the majority of patients with multiple surgical risk factors and is associated with a low complication rate.

Ovarian cancer is the leading cause of death in women with gynecologic malignancies. In 2004, an estimated 25,580 new cases of ovarian cancer were diagnosed in the United States, leading to 16,090 deaths from the disease.1 The most dramatic demographic change in the world’s population has been the increase in age.2 Individuals over age 65 comprised less than 1% of the total world population in 1900, 6.2% in 1992, and are projected to be about 20% by 20501. Based on Surveillance, Epidemiology, and End Results (SEER) data, it is estimated that 48% of ovarian cancer is diagnosed in women older than 65 years of age.3

Therefore, gynecologic oncologists will face an increasing population of elderly patients in the future. These older patients are also likely to present with other chronic diseases and age associated declines that make them perceivably poor surgical candidates. Data of the
SEER program indicate that older cancer patients are less likely to be treated by surgery. There are also several studies that have noted that elderly patients are treated with less aggressive surgery. However, there are ample data to suggest that surgery is the cornerstone in management of ovarian cancer. During the platinum era, maximal cytoreduction (generally defined as residual disease of ≤1 cm) is the most powerful determinant of cohort survival in patients with advanced ovarian cancer. Despite adjustments for stage, significant differences in survival occur by age, with older women exhibiting significantly poorer survival rates.

It has been suggested that the lower survival rates in elderly patients with ovarian cancer may be related to the less aggressive surgical intervention received up front. With recent improvements in anesthesia, perioperative care, and surgical techniques, the surgical exclusion criteria has been reduced for patients who are older and have major comorbidities. The aim of this study was to review the experience with cytoreductive surgery at a single, major cancer institute, with a special focus on outcomes and complications in patients with multiple surgical risk factors.

Material and methods

Patients that were treated for invasive epithelial ovarian cancers with primary cytoreductive surgery between January 1998 and December 2002 at Roswell Park Cancer Institute were identified. Patients with neoadjuvant chemotherapy, primary cytoreductive surgery at another institute, borderline cancers, and nonepithelial type ovarian cancers were excluded. After appropriate institutional review board approval, 140 patients were identified. The charts of these patients were reviewed and information on the following was collected: age at diagnosis, medical comorbidities, previous laparotomies, previous malignancy, primary site of disease, tumor grade and histology, preoperative serum CA-125, size and location of the tumor(s), amount of ascites, surgical procedure performed, amount of residual disease, estimated blood loss, number of units of blood transfusion, intraoperative complications, deep vein thrombosis prophylaxis, length of hospitalization, chemotherapy, morbidity and mortality within 30 days of surgery, and outcome. All analysis was of an exploratory nature.

All patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) system. All pathology specimens were reviewed in our institution, and tumors were classified according to WHO criteria. Medical comorbidities were classified into cardiovascular disease, endocrine disorders (diabetes mellitus and thyroid), pulmonary disease, and neurologic disorders. Optimal cytoreduction was defined as no residual tumor nodule measuring greater than 1 cm in maximal dimension at the end of the surgical procedure. Elderly patients were of age 65 years or older. The extent and aggressiveness of the debulking surgery was classified into standard, radical, and supraradical techniques. Standard debulking was defined as procedures limited to extrafascial abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, pelvic and paraaortic lymphadenectomy. Radical debulking procedures comprised components of standard technique with additional procedures of radical abdominal hysterectomy, and/or bowel resection, and/or gastrocolic ligament resection. Supraradical procedures included components of the standard and radical techniques with additional procedures of combined large and small bowel resection, and/or splenectomy, and/or diaphragm resection, and/or liver resection, and and/or exenteration.

All statistical analyses were performed using SPSS software (Chicago, IL). The chi-square or Fisher exact test were used to analyze the distribution of complications with surgical risk factors. Survival distributions were estimated by Kaplan-Meier method and statistical significance was determined by the log-rank test. No adjustments were made for multiple comparisons.

Results

A total of 140 patients underwent primary cytoreductive surgery for invasive epithelial ovarian cancer. The patient and tumor characteristics are shown in Table I. The median age of the entire cohort was 63 years (range 26-88 years). Sixty-three (45%) patients were age 65 or older. Sixty-nine (49%) patients had a major medical comorbidity. Cardiovascular disease was the most common comorbidity (39%). Twenty-seven (19%) patients had multiple comorbidities. Patients with significant cardiovascular comorbidities had preoperative clearance from a cardiologist; patients with pulmonary disease underwent pulmonary function tests and arterial blood gas evaluation. In general, if one of these patients had a comorbid condition and was being followed by a specialist preoperatively, then a clearance was obtained. Patients were admitted to the ICU if recommended in the clearance or for hemodynamic instability during the procedure. Nineteen (14%) patients had previous malignancies and 60 patients (43%) had a previous major laparotomy. The majority of the patients had an ovarian primary (80%), grade 3 tumors (83%), and papillary serous histology (69%). Eighty percent of the patients had advanced stage disease (stages III and IV). All patients were found to have received deep vein thrombosis prophylaxis, with either sequential compression devices, low-molecular-weight heparin, or both.

The intraoperative events for the entire cohort are listed in Table II. The median estimated blood loss was 500 mL. Nineteen of the patients required transfusion...
intraoperatively. One patient required 10 units and had a coagulopathy. The other intraoperative complication was a cystotomy, which was recognized and repaired. Majority of the patients underwent a radical procedure (57%) for cytoreduction. The debulking resulted in an 88% optimal debulking rate (defined as ≤1 cm residual disease at the end of the procedure). Majority of the patients had no macroscopic residual disease at the end of the procedure (60%). The median hospitalization was 8 days after the cytoreductive procedure.

The postoperative outcomes for the cohort are shown in Table III. Twenty-four percent of the patients required transfusion after the surgery. Twenty-one percent of patients had other postoperative complications, defined as within 30 days of surgery. Infectious (5%) and ileus (4%) were the most common complications. Two patients (1%) required reoperation within 30 days. Both of these patients developed an abscess that was not responsive to conservative management; 1 of them was found to have a fistula. There was 1 perioperative mortality in a patient that was found to have numerous liver metastases intraoperatively and only underwent biopsies. She subsequently died a few days later of overwhelming liver failure.

The median duration of follow-up for the cohort was 29 months (range 0.3-77 months). After cytoreductive surgery, the patients with stage IC disease and higher underwent adjuvant chemotherapy with platinum and a taxane for 6 to 8 cycles. There are some variations in the chemotherapy regimens depending on whether these patients were participating in clinical trials. As seen in Table IV, the majority of the patients (91%) showed response to treatment. Sixty-five percent of the patients were alive at the time of the review. The median survival for the patients was 51 months. The Kaplan-Meier curve for survival for the entire cohort is shown in Figure 1.

The distribution of the type of procedure and the associated need for transfusion, and postoperative complications were analyzed by the chi-square method. As shown in Table V, there was no significant relation between the type of procedure and occurrence of a postoperative complication. There was a statistically significant relation between the type of procedure and the need for transfusion (intraoperative or postoperative) \( (P = .05) \). There was a statistically significant
relation between the presence of comorbidities and the need for transfusion (intraoperative or postoperative) \( (P = .002) \). There was no difference in the need for transfusion and elderly age, or for the extent of procedure, elderly patients were equally likely to undergo extensive debulking as younger patients (Table VI).

Similarly, patients with medical comorbidities underwent extensive debulking at a similar rate to patients without comorbidities. There was no significant relation between the occurrence of postoperative complications and elderly age, comorbidity, and previous laparotomy (Table VI). Higher stage patients were not associated with more postoperative complications; however, there was a higher incidence of blood transfusion \( (P = .03) \). There was also a higher incidence of advanced stage disease in elderly patients \( (P = .04) \). The optimal cytoreduction rate was not significantly related to elderly age.

Comparison between the cohorts of residual disease showed that patients with no macroscopic tumor had a significantly higher survival than the patients with residual disease. Increasing size of residual disease indicated poorer survival. This is shown in Figure 2 \( (P < .001) \). Median survival for optimally debulked patients was 52 months versus 26 months for suboptimally debulked patients \( (P < .001) \). Univariate analysis also showed that advanced stage \( (P = .005) \), grade \( (P = .04) \), recurrence of disease \( (P < .001) \), and response to treatment \( (P < .001) \) were significant factors in overall survival.

Comparison between the cohort of patients who were defined as elderly age \( (\geq 65 \text{ years of age}) \) and overall survival is seen in Figure 3. The Kaplan-Meier survival distribution show that elderly patients have a similar overall survival as do younger patients \( (P = .11) \).

**Comment**

Aggressive surgical debulking is the cornerstone of initial therapy for epithelial ovarian cancer. In a meta-analysis by Bristow, he found that there was a statistically
significant positive correlation between survival and percent maximal cytoreduction. The study also showed that each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time. Our study also demonstrates that residual disease at the end of primary debulking correlates with survival. Patients with no residual macroscopic tumor had higher survival than patients with 0.5 to 1 cm residual disease. Similarly, patients with 1 to 2 cm residual disease had lower survival than the aforementioned cohorts, but had a higher survival than the greater than 2 cm residual disease group.

In this study, many of our patients were high-risk or complicated with advanced age, comorbidities, previous malignancies, and previous laparotomies. Despite the high-risk features in the study cohort, we were able to achieve a very high optimal cytoreductive rate that also translated into improved survival. This rate is higher than many of the other studies that have looked at cytoreductive rates in epithelial ovarian cancer. Our data also show that aggressive cytoreduction is safe and associated with a low complication rate. Our postoperative complication rate and overall transfusion rate of 18% and 37%, respectively, are similar to those reported by Chi and Wright in patients undergoing similarly aggressive cytoreduction. It should be noted that we did have a perioperative mortality in a patient that underwent a laparotomy and biopsies only; she was found to have numerous liver metastases and subsequently died in the ICU of liver failure.

Previous studies have shown that age is an independent indicator for poor prognosis in patients with epithelial ovarian cancer. Our study also confirms that elderly patients were more likely to present with higher stage disease. Previous studies have shown that elderly patients are less likely to be optimally debulked and treated less aggressively, which maybe a contributing factor to their overall poorer survival. Our data demonstrate that elderly women are able to tolerate equally radical procedures that lead to optimal cytoreduction without an increase in postoperative complications, and the need for transfusion. The optimal cytoreduction rate was equal in both age cohorts. Furthermore, there appears to be no significant difference in survival based on age alone.

Our study also looked at the major problem of comorbidity in these patients. As expected, we showed...
that elderly patients have a higher incidence of comorbidities. However, our data show these patients with comorbid conditions are able to tolerate radical procedures, without an increase in postoperative complications. These patients were more likely to receive blood transfusions, likely secondary to cardiovascular risk factors.

The majority of patients in our study cohort had multiple surgical risk factors, including advanced age, medical comorbidities, previous malignancies, and laparotomies. Despite the presence of these risk factors, we were able to achieve a highly respectable optimal cytoreductive rate in these patients. These procedures were tolerated well and were associated with a low complication rate. Our results reflect that once a patient was cleared for surgery, there was strong physician effort to optimize therapy that was not influenced by these risk factors. It can be stated that this aggressiveness of surgery also translated into improved survival for these high-risk patients. Although a retrospective study, our data suggest that age, medical comorbidities, previous surgical history, and advanced stage should not preclude patients from maximal surgical effort. Optimal cytoreduction continues to be a critical factor in survival.

References

Sacral neuromodulation for the treatment of refractory urinary urge incontinence after stress incontinence surgery

Neil D. Sherman, MD, Margaret G. Jamison, PhD, George D. Webster, MB, FRCS, Cindy L. Amundsen, MD

Objective: This study was undertaken to evaluate the response to sacral neuromodulation in women with refractory, nonobstructive urinary urge incontinence after stress incontinence surgery.

Study design: We reviewed the medical records of women in whom sacral neuromodulation was performed for worsening or de novo urinary urge incontinence after a stress incontinence procedure. All patients had undergone preliminary test stimulation. Demographics, surgical and urogynecologic history, including bladder diary and pad weight test, and urodynamic parameters were evaluated.

Results: Of 34 women, 22 (65%) responded to the test stimulation and underwent permanent lead implant. There was no difference between responders and nonresponders with respect to type of stress incontinence surgery. Incontinence or urodynamic parameters were not different between responders and nonresponders. Factors that were predictive of a positive response were women aged less than 55 years ($P = .01$), the test stimulation performed within 4 years of the stress incontinence procedure ($P = .01$), and evidence of pelvic floor muscle activity ($P = .03$).

Conclusion: Sacral neuromodulation is a viable option for the treatment of refractory urinary urge incontinence that occurs after stress urinary incontinence surgery. Older women with no pelvic floor activity who are remote from their incontinence surgery may have a suboptimal response.

A variety of surgical techniques report a greater than 80% cure rate in treating urinary stress incontinence. In addition, surgical intervention for stress incontinence may help the symptoms of the overactive bladder (OAB) in women with mixed incontinence. However, it is estimated that de novo urinary urge incontinence (UUI) occurs in 10% of women after stress urinary incontinence (SUI) surgery and up to 40% of women will have persistent UUI.

The accepted treatment algorithm for women with postsurgical urinary frequency, urgency, and urge incontinence is similar to that used in idiopathic OAB and includes behavioral therapy and pharmacotherapy. Although anticholinergic medication reduces urge...
incontinent episodes and voiding frequency, many are not improved significantly. In the past, those with refractory urgency, frequency, and urge incontinence either accepted their condition or underwent sling take-down or revision, augmentation cystoplasty, detrusor myectomy, or denervation procedures.

Recently, patients with intractable UUI, urgency-frequency, or nonobstructive urinary retention have been reported to show improvement after undergoing sacral neuromodulation (InterStim Continence Control System, Medtronic, Inc, Minneapolis, MN). To date, the efficacy of sacral neuromodulation has not been reported in women who underwent SUI surgery and who have de novo or worsening UUI develop.

In this study, we look at the use of sacral neuromodulation for the treatment of refractory UUI after stress incontinence surgery. We also examine whether demographic or pretest stimulation variables predict a positive response to sacral neuromodulation.

Material and methods

Institutional review board approval was obtained for this retrospective analysis. The medical records of all women undergoing sacral neuromodulation test-stimulation between October 2000 and September 2004 were reviewed. Those with severe OAB symptoms, which appeared de novo or persisted or worsened after their stress incontinence surgery, were eligible for this study. All had been referred to our Female Urology and Urogynecology clinic because of the severity of their OAB symptoms and having failed behavioral therapy, pelvic floor re-education, and anticholinergic treatment. Their evaluation included completion of a urogynecologic questionnaire, a pelvic examination with assessment of pelvic floor muscle strength based on a modified, validated pelvic floor muscle grading system, a 3-day bladder diary recording micturition frequency, voided volumes and incontinent episodes (IE) per day, a 24-hour pad weight test, cystoscopy, and a video-urodynamic study. Women with urethral obstruction, based on evidence of a retropted urethra on pelvic examination, poor sagital rotation of the urethra during cystoscopy, and/or obstruction on the micturition study underwent urethroylisis or incision and release of their sling. Nonobstructed women were candidates for a test stimulation because of the severity of their symptoms and unresponsiveness to medical and behavioral therapy.

Similar criteria were used for our study cohort as is used when offering sacral neuromodulation in previously studied InterStim groups. Before offering a test stimulation, all women underwent extensive pelvic floor re-education and had tried at least 2 anticholinergic medications to improve their symptoms. Those women with less than a 50% improvement in their symptoms and still requiring the use of multiple protective pads per day because of UUI were offered a test stimulation. The test stimulation period lasted between 5 and 7 days and was performed either as an outpatient procedure via a percutaneous electrode (PNE) or a 2-stage approach as previously described.

During the testing period, women completed a bladder diary recording voiding frequency, voided volumes, IE per day, severity of leakage, and number of pads used. In addition, a 24-hour pad weight test was collected the day before evaluation. A positive response was defined as a 50% or more improvement in baseline urge incontinent episodes or a 50% or more reduction in pad weight during the testing period. All positive responders were offered permanent implantation. Permanent implantation consisted of a tined lead placed in the S3 sacral foramen that was connected to a pulse generator implanted in the fatty tissue of the buttock.

Age, time since incontinence surgery, and urodynamic measurements, all continuous variables, were changed to categorical variables with 2 responses (age older than 55 years and age 55 years or less) that best discriminated between responders and nonresponders. Two-way $\chi^2$ tests were computed between these variables and responders and nonresponders, young responders and older responders, and older respondents and older nonresponders. A logistic regression model was created to find which independent variable(s) best predicted response or nonresponse in the older age group because there were no nonresponders in the younger age group.

Results

A total of 107 women underwent sacral neuromodulation test stimulation between October 2000 and September 2004. Of the 107 women tested whose OAB symptoms appeared de novo or persisted or worsened after their stress incontinence surgery, 34 (32%) were included in the study.

Of the 34 women in this study cohort, 22 (65%) responded to the sacral neuromodulation test stimulation and all had a permanent lead and pulse generator implanted. Twelve patients (35%) did not have greater than a 50% improvement in incontinent episodes or greater than 50% reduction in pad weights during the testing period and were classified as nonresponders, and therefore were not implanted. There were no other alternative therapies or surgical treatments offered to these 12 nonresponders.

The average age of the responders was 58 (range 35-82 years) and 66 (range 56-80 years) for the nonresponders (Figure). There was a difference between the responders and nonresponders with respect to age and length of time from incontinence surgery to the test stimulation. All the nonresponders were older than 55 years and 62% were 4 or more years from their incontinence surgery. Type of stress incontinence surgery and whether a sling incision
and release was performed were not statistically significant factors between responders and nonresponders (Table I).

Because a younger age has been previously shown to be an independent variable for success with sacral neuromodulation and this was reproduced in our study, we re-evaluated previously determined variables using the age of 55 as a cutoff between the 2 groups. The only parameter that was statistically significant between the 2 groups was that women older than 55, who responded to sacral neuromodulation, had more IE per day than the younger responders. All urodynamic and incontinence symptom parameters were similar. Interestingly, whether the woman was young or old, few responded to sacral neuromodulation if their surgery had been performed more than 4 years before the test stimulation procedure (Table II).

All the nonresponders were in the group of women older than 55 years. When one compared this older group of responders and nonresponders, lack of pelvic floor muscular activity best correlated with nonresponding to sacral neuromodulation (Table III). After logistic regression, if the woman is older than 55 years with no pelvic floor activity, she has a 100% chance of not responding to sacral neuromodulation in this cohort of women (Table IV).

Comment
The incidence of OAB symptoms after SUI surgery depends on the surgical technique used, and can be as high as 31%, although usually less than 10%. Even with the newer minimally invasive approaches for stress incontinence, the risk of OAB symptoms postoperatively persists. In this study, 7 of the 28 slings were placed by using a minimally invasive technique. Although SUI may be resolved, the presence of OAB symptoms proves to be a source of continued patient dissatisfaction after incontinence procedures.

It is not clear why OAB symptoms sometimes occur after stress incontinence procedures. Possible causes include undiscovered preexisting detrusor overactivity, a neurogenic dysfunction resulting from surgical interference with autonomic bladder innervation, increased striated urethral sphincter activity, or structural urethral obstruction. In the latter, sling incision and revision or other urethrolysis procedures are considered. In these cases, postoperative voiding symptoms (frequency, urgency, and urge incontinence) occur in conjunction with the finding of a retropexed urethra and/or an obstructive voiding pattern on urodynamics. One third of the women in our study group had undergone sling release that had relieved obstructive voiding symptoms but OAB symptoms had persisted. Interestingly, having had a sling incision and release did not affect response to neuromodulation.

The mechanism by which neuromodulation works is not completely understood, it has been shown to be efficacious in idiopathic refractory urge incontinence and nonobstructive urinary retention. It is believed that neuromodulation treats bladder overactivity by altering the activity and basal tone of the pelvic floor as well as modulating the afferent signals delivered to the spinal cord. The cause of nonobstructive urinary

<table>
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PVS, Pubovaginal sling.
Retention is believed to be due to a primary failure of relaxation of the striated urethral sphincter. The mechanism of action for neuromodulation in retention patients is believed to be an activation of somatic afferent axons in the sacral spinal roots causing an inhibition of reflex pathways to the urethral outlet. This ultimately relieves pelvic floor spasticity, releasing the detrusor from inhibition to allow for spontaneous voiding.

In this study, the overall response to sacral neuromodulation is similar to that which is reported by other groups treating refractory idiopathic urge incontinence with neuromodulation. There are no pretest stimulation urodynamic variables to predict success of sacral neuromodulation and similarly in this cohort no urodynamic variables seemed predictive of success. This study duplicates our earlier results, specifically, that younger women responded better to sacral neuromodulation. In addition, the presence of pelvic floor muscular activity, evaluated by voluntarily contracting the pelvic floor, was also found to predict a positive response to neuromodulation in our cohort. Because the believed mechanism of action of sacral neuromodulation relies on afferent input from the pelvic floor, this might explain the better response in these women compared with those who demonstrated no voluntary pelvic floor muscle contractile ability.

Our data show that a short duration between stress incontinence surgery and sacral neuromodulation was predictive of a positive response to neuromodulation in both the younger and older groups. There may be unidentified pathologic or neurologic bladder changes that occur and limit success when time to intervention is prolonged.

This is a small cohort study and findings regarding correlation with time from surgery, pelvic floor muscle denervation, and age need to be confirmed with a larger cohort. Our results have led us to offer test stimulation for sacral neuromodulation to women who have refractory OAB symptoms after a SUI procedure. Nevertheless, older women with no pelvic floor activity who are remote from their incontinence surgery may be counseled to a probable suboptimal response.

### Conclusion

Response to sacral neuromodulation for the treatment of refractory urge incontinence after SUI surgery is comparable to its use in idiopathic urge incontinence.
The type of stress incontinence surgery, incontinence parameters, and preimplantation urodynamics do not help predict response to neuromodulation. Our study suggests that a younger age, a shorter time from the incontinence surgery and evidence of pelvic floor muscular activity appear to predict a better response. Sacral neuromodulation should be considered in women with severe OAB symptoms after SUI surgery having failed medical and behavioral therapy and after urethral obstruction has been ruled out.

References


Factors associated with incontinence frequency in a surgical cohort of stress incontinent women

Holly E. Richter, PhD, MD, Kathryn L. Burgio, PhD, Linda Brubaker, MD, Pamela A. Moalli, MD, PhD, Alayne D. Markland, MD, Veronica Mallet, MD, Shawn A. Menefee, MD, Harry W. Johnson, MD, Muriel K. Boreham, MD, Kimberly J. Dandreo, MSc, Anne M. Stoddard, ScD, for the Urinary Incontinence Treatment Network (NIDDK, NICHD)

Department of Obstetrics and Gynecology, Division of Medical Surgical Gynecology, Birmingham/Atlanta Geriatric Research, Education, and Clinical Center (GRECC), Department of Veterans Affairs Medical Center, and Department of Medicine, Division of Gerontology and Geriatric Medicine, University of Alabama at Birmingham, Birmingham, AL; Loyola University Chicago, Maywood, IL; Division of Urogynecology and Pelvic Reconstructive Surgery, University of Pittsburgh, Pittsburgh, PA; University of Texas, San Antonio, TX; Oakwood Medical Center, Dearborn, MI; Kaiser Permanente, San Diego, CA; Department of Obstetrics and Gynecology, University of Maryland, Baltimore, MD; Department of Obstetrics and Gynecology, Division of Urogynecology and Pelvic Reconstructive Surgery, University of Texas Southwestern Medical Center, Dallas, TX; New England Research Institutes, Boston, MA

KEY WORDS
Incontinence severity
Risk factors
Surgery

Objective: The aim of this study was to identify factors associated with urinary incontinence severity at baseline in women undergoing surgery for stress incontinence.

Study design: Baseline data were obtained from 650 women (age 28 to 81 years) with stress incontinence participating in a randomized surgical trial. Severity of incontinence was defined by the mean number of incontinence episodes per day recorded in a 3-day bladder diary. The relationships between severity and several baseline variables were examined, including demographics, medical, obstetric, and gynecologic history, body mass index, smoking status, Q-tip displacement, and Pelvic Organ Prolapse Quantification stage (POP-Q).

Results: In a multivariable model, severity of incontinence was positively associated with body mass index ($P = .0003$) and current smoking ($P = .01$), and negatively associated with prolapse stage ($P < .0001$) and Q-tip displacement ($P = .042$).

Conclusion: Incontinence severity in a surgical population was independently associated with 2 modifiable factors, obesity and tobacco use, as well as pelvic support.

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Women are increasingly seeking definitive surgical therapy for symptoms of stress urinary incontinence (SUI). Numerous reports describe risk factors for presence of incontinence, including age and parity, body mass index (BMI), menopausal and estrogen status, etc.
smoking, and race. Few reports describe demographic and clinical factors that might influence or predict severity of incontinence.

The Urinary Incontinence Treatment Network is a group of 9 clinical sites and 1 biostatistical coordinating center with sponsorship through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institutes of Child Health and Human Development (NICHD). Its first research initiative was a randomized surgical trial of the modified Tanagho Burch procedure and the autologous rectus fascial sling procedure for the treatment of SUI (the SISTEr trial: Stress Incontinence Surgical Treatment Efficacy Trial). The primary aim of this trial was to compare the efficacy of these 2 procedures at 24 months postsurgery. The primary purpose of this secondary analysis was to identify demographic and clinical factors associated with severity of incontinence, as defined by the frequency of incontinence episodes in the 3-day voiding diary. It was hypothesized that incontinence severity would be associated with a number of demographic and clinical factors thought to adversely affect the bladder or pelvic floor.

Material and methods

Patients

A total of 904 women with pure or predominant SUI consented to participate in the SISTEr trial. The 650 eligible women who were subsequently randomly assigned to receive 1 of the study surgical procedures are the subjects of this report. The study was approved by the Institutional Review Boards at all participating clinical centers and the biostatistical coordinating center.

Inclusion and exclusion criteria

To be eligible for this trial, patients were diagnosed with predominant SUI on the basis of several self-reports and clinical measures. Predominant SUI was defined by symptoms reported on the Medical, Epidemiological, and Social Aspects of Aging (MESA) Questionnaire (percent of stress-type symptoms greater than the percent of urge-type symptoms). In addition, eligible patients described incontinence persisting for at least 3 months, frequency of urination less than 12 times per day, bladder capacity 200 mL or greater, postvoid residual urine volume 150 mL or less, and unobstructed voiding. In addition, there was evidence of urethral hypermobility on Q-tip testing (resting angle > 30 degrees or a maximum straining urethral angle > 30 degrees) and objective demonstration of urine loss during provocative bladder stress test at bladder volume 300 mL or less. Patients were clinically eligible for both surgical procedures, able to complete 24 months of clinical assessments, and provided informed consent to participate.

Patients were excluded if they were younger than 21 years, nonambulatory, pregnant, undergoing cancer treatment, less than 12 months postpartum, or if they had systemic disease known to affect bladder function, urethral diverticulum, prior augmentation cystoplasty or artificial sphincter, recent pelvic surgery, or were participating in another intervention trial that could affect the results of this trial.

Measures

Data for this report were derived from the baseline clinical assessment conducted before random assignment. This assessment included a 3-day bladder diary, medical, obstetric, and surgical history, physical examination, urodynamic evaluation, pelvic examination with a Q-tip test, and Pelvic Organ Prolapse Quantification (POP-Q). The MESA questionnaire was used to measure self-reported symptoms of incontinence. Quality of life was assessed by the Incontinence Impact Questionnaire (IIQ).

To select the most appropriate measure of incontinence severity from among the instruments used in this trial, a principal components analysis was conducted. Principal components analysis is an exploratory technique that is used to gain an understanding of the interrelationships among variables. Possible validated measures included number of incontinence episodes (on bladder diary), pad test weight, MESA stress score, and IIQ score. Although the several measures of incontinence severity were not perfectly correlated, we found that all were assessing a single dimension of SUI, with approximately equal weights (data not shown). Thus, any 1 of the 4 could be used to represent severity. We selected mean number of incontinence episodes because it had the highest coefficient in the principal components analysis (0.53), it is easy to interpret, it is more objective than the questionnaires, and it represents data collected over a longer period.

Several potential correlates of severity were selected for analysis, including: sociodemographic variables (age, ethnicity, socioeconomic status using Nam-Powers-Terrie Occupational Status Scores), medical history (diabetes, fecal incontinence, current smoking, urinary tract infections), obstetric history (number of pregnancies and vaginal deliveries, weight of largest baby), gynecologic history (menopausal status, current hormone therapy, hysterectomy), BMI, Q-tip displacement and POP-Q stage. We used occupation score to represent socioeconomic position as it includes both education and income in assigning a quantitative score to occupations.

Data analysis

The relationship between incontinence severity and each variable was explored using linear regression analysis.
To meet the normality assumption of this method, we transformed mean incontinence episodes per day to the logarithmic scale. Bivariate associations between each potential correlate and severity of incontinence were first evaluated by simple linear regression analysis. Variables with a relationship to severity on bivariate analysis \((P < .05)\) were then entered into a multiple linear regression model. Other selected variables thought to influence severity of incontinence were also included.

Statistical analyses were conducted using the personal computer version of SAS statistical software (SAS, Cary, NC).

### Results

Baseline characteristics of the cohort are presented in Table I. The age of the patients ranged from 28 to 81 years with a mean of 51.9 years (median = 50 years). The majority of patients (73.4%) were non-Hispanic white. The mean number of incontinence episodes per day ranged from 0 to 26 with a mean of 3.2. Fifty-nine percent of patients had stage II prolapse by POP-Q with 16.3% having severe prolapse, stage III or IV. Table II presents the antilog of the slope coefficients and the \(P\)-values for the bivariate association of each predictor variable alone in relation to incontinence episodes per day. The antilog of the slope is the measure of the strength of the association in the natural scale (number of episodes). For example, the coefficient for age, 0.92, indicates that as age increases 10 years, average episodes per day decrease by 8%.

#### Table I  Baseline characteristics of surgical cohort (N = 650)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N</th>
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<td>Race</td>
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<tr>
<td>Hispanic</td>
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<tr>
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<tr>
<td>Education</td>
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<td></td>
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<tr>
<td>&lt; High school</td>
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<td>High school/GED</td>
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<tr>
<td>Some college, vocational, junior college</td>
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<tr>
<td>College graduate/postcollege</td>
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<tr>
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<td>&lt; $20,000</td>
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<td>$20,000-$49,999</td>
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<td>$50,000-$79,999</td>
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<tr>
<td>&gt; $80,000</td>
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<tr>
<td>Age (y)</td>
<td>51.9</td>
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<tr>
<td>BMI</td>
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<td>Occupational score</td>
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<td>Post</td>
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<td>Weight largest infant (g)</td>
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<td>556</td>
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<tr>
<td>Current smoking status</td>
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<td>559</td>
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<td>91</td>
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#### Table I  (Continued)

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<th>Prior UI surgery</th>
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<td>556</td>
<td>85.8</td>
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<tr>
<td>Yes</td>
<td>92</td>
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<td>Prior UI treatment</td>
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<td>293</td>
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<td>Stage of prolapse</td>
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<td></td>
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<tr>
<td>0/I</td>
<td>160</td>
<td>24.6</td>
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<tr>
<td>II</td>
<td>384</td>
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<tr>
<td>III/IV</td>
<td>106</td>
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<tr>
<td>Mean (median)</td>
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<tr>
<td>IIQ Score</td>
<td>171.0 (156.9)</td>
<td>101.4</td>
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<tr>
<td>Stress score (MESA)</td>
<td>19.4 (20)</td>
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<tr>
<td>Stress index</td>
<td>71.6 (74)</td>
<td>17.0</td>
</tr>
<tr>
<td>Accidents/day</td>
<td>3.2 (2.3)</td>
<td>2.9</td>
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<tr>
<td>ΔPad weight (g)</td>
<td>43.7 (15.4)</td>
<td>79.6</td>
</tr>
<tr>
<td>ΔQ-tip resting angle (degrees)</td>
<td>15.5</td>
<td>17.7</td>
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<td>ΔQ-tip straining angle (degrees)</td>
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<tr>
<td>ΔQ-tip</td>
<td>44.8</td>
<td>18.2</td>
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</table>

IIQ, Incontinence Impact Questionnaire.
The factors significantly associated with severity on simple regression analysis were age, BMI, occupation score, current smoking, POP-Q stage, and Q-tip displacement. An increase of 10 years in age was associated with an 8% decrease in the number of incontinence episodes ($P = .04$), whereas an increase of 1 unit of BMI was associated with a 3% increase in episodes ($P < .0001$), and an increase of 10 units in occupation score was associated with a 4% decrease in incontinence episodes ($P = .02$). Current smokers had 56% more incontinence episodes than nonsmokers ($P = .0002$), whereas women at POP-Q stages 0/I and II had about twice as many episodes as those at stages III/IV ($P < .0001$). Finally, a 5-degree increase in Q-tip displacement was associated with a 3% decrease in episodes of incontinence ($P = .02$).

To explore the simultaneous associations of these measures with severity, we computed a multiple regression analysis including them all, controlling for Q-tip resting angle and previous hysterectomy. We believed it was important to control for these additional variables even though they had not been shown to be significantly associated with number of episodes (Table III). The associations of age and occupation score with incontinence episodes were no longer statistically significant when the other variables were controlled, indicating that these bivariate associations can be accounted for by the associations of BMI, POP-Q stage, or other factors. For the remaining factors, the slopes in the multivariable analysis were approximately the same as those in the bivariate analyses, indicating that the associations remained when the other variables were controlled.

**Comment**

The findings of this study indicate that the severity of urinary incontinence was positively associated with higher BMI, current smoking, lower POP-Q stage, and lower urethral mobility. We also found that factors previously reported to be associated with stress incontinence severity, such as greater age, low socioeconomic status, higher gravidity and parity, mode of delivery, high infant birth weight, and previous hysterectomy were not associated with severity in this analysis.
Prior reports have suggested that increased BMI is associated with presence of urinary incontinence, as well as incontinence severity. Weight loss techniques, including bariatric surgery suggest that weight reduction can improve symptoms of urinary incontinence. The findings of the SISTEr trial are consistent with these previous reports in showing that worsening urinary incontinence is yet another health consequence of excessive weight.

Smoking is another modifiable risk factor that has been weakly associated with more severe incontinence in some epidemiologic studies. Experts have postulated that the “smoker’s cough” is an exacerbating phenomenon that uncovers an otherwise quiescent disorder. We hope that by documenting the significant association of smoking with severity of incontinence, this study will provide additional impetus for an individual incontinent smoker to stop smoking. An observational study of smoking cessation and its effect on urinary incontinence may provide even stronger evidence of the benefit of smoking cessation.

General preventive health care includes recommendations about appropriate weight ranges and smoking cessation. On the basis of the current findings, we conclude that these recommendations are particularly important in the treatment of incontinent women, including those considering surgery. Further analysis of the SISTEr outcome data will allow us to determine whether these variables affect surgical outcomes.

The other significant associations detected in this study were between incontinence severity and a lower POP-Q stage (a reflection of point Aa on the anterior vaginal wall) and a lower Q-tip deflection. These findings corroborate previous case series supporting an association between the less mobile urethra and more severe incontinence. Indeed, a similar observation by McGuire et al led to the definition of the most severe form of urinary incontinence, “intrinsic urethral deficiency.” Although the patients in the current study were required to have some degree of hypermobility, the association of the less mobile urethra with more incontinent episodes on the voiding diary is consistent with earlier observations. It is also plausible that more severe incontinence with lower POP-Q stage is a reflection of a diminished kinking effect on the urethra, which may be present in women with advanced prolapse of the anterior vaginal wall.

The finding that incontinence was not more severe with increasing age and menopause is in contrast to previous findings in which decreased urethral mobility and increased severity of incontinence were associated with these variables. Similarly, prior hysterectomy, and more pregnancies, did not predict more severe stress incontinence, despite being identified risk factors in other studies.

The findings of this study are based on the frequency of incontinence episodes as recorded in a bladder diary as the measure of severity. There are several dimensions of severity, including frequency of episodes, volume of urine loss, and impact of incontinence on quality of life. In addition, there are several measurement methods, including the pad test, urodynamic testing, and patient self-report, for example, the Sandvik Severity Index, which combines the dimensions of frequency and volume of loss. The bladder diary is a reliable method for assessing frequency of involuntary urine loss. It has the advantage that the patient can document incontinence that occurs in her usual daily environment, it and minimizes recall error. Nevertheless, it is possible that other dimensions of severity or measurement methods could yield different results.

The major strength of this article is that the data were obtained from the preoperative evaluation of women with stress incontinence participating in a randomized clinical trial in which 2 surgical treatments were stringently evaluated. This is the largest randomized surgical trial to date, with a well-characterized study population using both objective and subjective variables. This study was also conducted across a wide geographic area, from coast to coast, with a broad socioeconomic representation. These features of the study allow generalizability of these findings to the majority of women undergoing surgery for urinary stress incontinence.

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References


Abdominal sacral suspensions: Analysis of complications using permanent mesh

Giti Bensinger, MD, Larry Lind, MD, Martin Lesser, PhD, Marsha Guess, MD, Harvey A. Winkler, MD

Objective: This study was undertaken to determine the complication rates of abdominal sacral suspensions (ASC) using polypropylene mesh and to compare the erosion rates in women who underwent ASC at the time of supracervical hysterectomy (SCH) versus total abdominal hysterectomy (TAH) versus ASC in women who had previously undergone TAH.

Study design: A retrospective analysis of patients from the urogynecology practice at North Shore University Hospital, who underwent ASC with polypropylene mesh between March 1997 and July 2004. Office and hospital charts were reviewed for patient demographics, preoperative history and physical examinations, intraoperative and postoperative findings, and complications. Women were stratified into 3 groups: group I: SCH with ASC; group II: TAH with ASC; and group III: ASC alone in women with a history of prior TAH.

Results: A total of 121 patients were analyzed and comprised group I, 30.6% (n = 37); group II, 40.5% (n = 49); and group III, 28.9% (n = 35). Four patients (3.3%) had mesh erosions develop. There were no significant differences in age, weight, parity, menopause status, estrogen therapy, previous surgery, or degree of preoperative prolapse between the patients with and without erosions. All the erosions occurred in group II (8.2%, 95% CI (2.3%-19.6%, P = .0389). The intraoperative complication rate was 2.5% and included a cystotomy (n = 2) and a small bowel laceration (n = 1). Immediate postoperative complications included partial SBO/Ileus (3.5%), febrile morbidity (9.6%), and autologous blood transfusions (1.7%). Long-term complications included persistent vaginal discharge (4.7%), vaginal bleeding (1.6%), dyspareunia (6.3%), and recurrent prolapse (2.5%). There were no significant differences in short- or long-term complications among the 3 groups (P > .05).

Conclusion: ASC with polypropylene mesh is a safe surgical procedure for vaginal vault prolapse with low complication rates. Mesh erosion occurred in 8.2% of patients who underwent TAH with concurrent ASC. Patients having ASC at the time of TAH had a 7-fold increased risk for mesh erosion compared with patients who underwent SCH with ASC.

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Urogenital prolapse affects a significant number of women in the United States. With the increase in the average life expectancy of women, the incidence of pelvic organ prolapse (POP) has also been increasing. Epidemiologic studies suggest that approximately 10% of women, who live 80 years or more, will have some type of pelvic reconstructive surgery. Purported causes of POP include childbirth, aging, congenital anomalies, denervation or weakness of the pelvic floor, and failure to suspend the vaginal vault when clinically indicated at the time of abdominal or vaginal hysterectomy. The purpose of pelvic reconstruction is to restore function to the pelvic floor by re-establishing normal anatomy. Abdominal sacral colpopexy (ASC), a procedure where a natural or synthetic graft is used as a bridge to attach the vaginal apex to the sacrum, is a highly effective procedure for treating uterine or vaginal prolapse. ASC has been estimated to have a 84% to 99% success rate for vaginal support, and restores the vaginal axis without compromising vaginal depth. Although the procedure boasts excellent success rates, minimizing complications remains a challenge.

Reported complications of sacral colpexies include hemorrhage from the presacral vessels and mesh erosion. Although uncommonly reported (3.4%-16%), mesh erosions at the vaginal apex typically occur 4 to 24 months after surgery and may require a return to the operating room to excise the piece of exposed mesh and to re-epithelialize the vaginal defect. Although the procedure boasts excellent success rates, minimizing complications remains a challenge.

Material and methods

After Institutional Review Board approval was obtained, we performed a retrospective analysis of patients from the urogynecology practice at North Shore University Hospital, who underwent ASC with polypropylene mesh between March 1997 and July 2004. Office and hospital charts were reviewed for patient demographics, preoperative history and physical examinations, intraoperative and postoperative findings, and complications. The presence or absence of complications were considered on the basis of chart documentation. Sample sizes vary because of missing data. POP was diagnosed using the Pelvic Organ Prolapse Quantification staging system (POPQ). Intraoperative complications, and procedure effectiveness were reviewed. The date of the last gynecologic examination relative to the date of the

<table>
<thead>
<tr>
<th>Table I</th>
<th>Patient characteristics among study groups</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Group I n</td>
</tr>
<tr>
<td>No. of subjects</td>
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<tr>
<td>Age (y)</td>
<td>49.3 ± 7.8</td>
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<tr>
<td>Weight</td>
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<tr>
<td>Parity</td>
<td>2.6 ± 1.3</td>
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<td>Postmenopausal</td>
<td>13 (35%)</td>
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<tr>
<td>HRT</td>
<td>2 (6%)</td>
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<tr>
<td>Follow-up (mo)</td>
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<td>Mean</td>
<td>10.5 ± 10.9</td>
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<tr>
<td>Median</td>
<td>8.1</td>
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<td>Mild (stage 1/2)</td>
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</tr>
<tr>
<td>Severe (stage 3/4)</td>
<td>37</td>
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</tbody>
</table>

Bensinger et al 2095
surgery was used to determine the follow-up interval. Patients with a previous suspension procedure or a sacral colpopereineopexy were not included in this study. Women were stratified into 3 groups: group I: SCH with ASC; group II: TAH with ASC; and group III: ASC alone. The selection of patients for the SCH or TAH groups was based on patient history of cervical dysplasia, and patient's informed decision after counseling with regard to current literature on female sexual dysfunction posthysterectomy. In all cases, separate pieces of polypropylene mesh were attached anteriorly to the pubocervical fascia and posteriorly to the rectovaginal fascia with broad base attachments. Patients were seen for follow-up postoperatively at 3 to 6 weeks, 3 months, and 6 months.

Essential features of the abdominal sacral suspension performed at North Shore are broad dissection along the anterior and posterior vaginal walls taking the bladder and rectum down, respectively. A generous area of mesh is incorporated by using a fine absorbable suture 2-0 or 3-0 of vicryl, or monofilament delayed or permanent suture. If the procedure is performed at time of hysterectomy, there are no sutures placed within 1.5 cm of the vaginal apex closure and the vaginal apex closure sutures are not incorporated into the mesh suspension. For the vaginal apex closure, we use fine absorbable interrupted edge-to-edge precise closure of the vaginal apex. The degree of dissection is individualized for each patient on the basis of the preoperative examination with respect to the extent of the anterior versus vaginal versus apical prolapse. Two separate pieces of mesh are used, 1 for the anterior and 1 for the posterior vaginal wall to allow minimal tension when attaching the mesh to the sacrum. The suspension is elevated to take the slack out of the vagina without tension. We avoid large caliber sutures and multiple figure of 8 sutures and multiple knots. We incorporate a fine, wide pore polyester monofilament mesh. All patients received 1 dose of prophylactic antibiotics preoperatively.

Statistical analysis was performed with the use of SAS software (SAS, Cary, NC). Descriptive statistics were computed using standard methods for means, medians, and proportions. Comparison of groups for categorical data were analyzed with the 2-tailed Fisher exact test. Mann-Whitney or Kruskal-Wallis tests were used to compare continuous variables across groups. (The results for these nonparametric tests were similar to those for t tests or analysis of variance.) On finding a significant difference among the 3 groups, Bonferroni-adjusted pairwise multiple comparisons (using P < .017) were carried out by using the Fisher exact test for categorical data and the Mann-Whitney test for continuous data. For computation of odds ratios in the presence of cells with zero frequency counts, the frequencies were corrected using a 0.5 correction in every cell. All analyses were considered statistically significant at P-values less than .05.

Results

Office and hospital records were reviewed for 121 women meeting the study criteria. Women were stratified into 3 groups: group I: SCH with ASC, 30.6% (n = 37); group II: TAH with ASC, 40.5% (n = 49); and group III: ASC alone, 28.9% (n = 35). Patients were followed up postoperatively for a mean of 12.5 ± 15.2 months (range 0.3-63.3). The demographics of the patients among study groups are shown in Table I. The mean age of the overall study population were 53.3 ± 9.6 years. The patients in group III were significantly older, more likely to be menopausal, and reported higher hormone replacement therapy (HRT) use than women in the other 2 groups (P < .0001). In addition, the women in group III had more advanced stages of prolapse compared with the other 2 groups (Table II).

Four patients (3.3%) had mesh erosions develop. All 4 erosions occurred in group II, the TAH-ASC group (8.2%, 95% C.I. (2.3%-19.6%) (Table III). There was a statistically significant increase in erosion rate for women in group II compared with women in groups I and III (P = .0389). There were no significant differences in age, weight, parity, estrogen status, or degree of preoperative prolapse between the patients with and without erosions.

Excluding hysterectomy, concomitant procedures performed at the time of sacral colpopexy are listed by frequency in Table IV. There was no evidence to indicate an association between erosions and concomitant procedures, although this study was not powered to address this question. Similarly, no significant difference in erosion rates was found in women with a positive estrogen status compared with those with a negative estrogen status (positive estrogen status defined as premenopausal women and postmenopausal women on HRT).

When patients were stratified according to their POPQ results, there was no significant difference in women with more pronounced prolapse when compared with women with lesser degrees of prolapse. To further explore this relationship, we grouped patients as mild and severe prolapse. Women with POP stage 0 and 1 were grouped as mild prolapse and those with stage 2 and 3 were grouped as severe prolapse. No significant difference was noted in erosion rates between women in these 2 groups.

Intraoperative and hospital-related complications are displayed in Table V. No statistically significant differences in complication rates were noted among the 3 groups. The intraoperative complication rate was 2.5% and included a cystotomy (n = 2), and a small bowel
laceration (n = 1). Immediate postoperative complications included partial SBO/Ileus (3.5%), febrile morbidity (9.6%), infection (1%), and autologous blood transfusions (1.7%). Short- and long-term complications included persistent vaginal discharge (4.7%), vaginal bleeding (1.6%), dyspareunia (6.3%), and erosions (4.8%). Overall, recurrent prolapse was noted in 3 women (2.5%).

**Comment**

ASC is a proven effective surgery for the treatment of POP. Our study, supports previous literature, in showing ASC with polypropylene mesh is an overall safe surgical therapy for vaginal vault prolapse with low complication rates.10,12

In our study, all 4 mesh erosions occurred in group II, the TAH concurrent to ASC group. This supports previous work performed by Culligan et al6 who reported a mesh erosion rate of 27% in 11 women who had an ASC with hysterectomy, compared with 1.3% in 234 women who underwent ASC alone and Imparato et al11 who reported a 14% erosion rate in 21 women who underwent sacrocolpopexy with a concurrent hysterectomy. In addition, our erosion rate of 3.3% (8.2% in ASC-TAH group) in this study falls within literature cited ranges for erosion (3.4% - 27%).10,12

Our review of the literature only identified 1 other study (abstract) that stratified patients according to the type of hysterectomy performed to evaluate the influence of SCH on mesh erosion in patients undergoing ASC. The results from this study also showed an increased rate of erosions in the group undergoing concomitant TAH (10.5%) compared with those who underwent a SCH (3.6%).15 However, this study lacked the power to detect a significant difference between the groups. Results from our study and previous studies support the role of cervical conservation in patients without contraindications to SCH in patients undergoing ASC.

An important limitation of our study relates to mesh erosion being a relatively uncommon event. Therefore, our failure to find other significant correlates with erosion might be due to the small number of cases with erosions, which generates an insufficient power to

---

**Table II** Preoperative prolapse among groups

<table>
<thead>
<tr>
<th>POPQ Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aa</td>
<td>N = 31</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Score</td>
<td>−0.23 ± 0.92</td>
<td>−0.019 ± 1.0</td>
<td>0.25 ± 1.2</td>
</tr>
<tr>
<td>P value</td>
<td>.16</td>
<td>&lt; .007</td>
<td>.09</td>
</tr>
<tr>
<td>Ba</td>
<td>N = 31</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Score</td>
<td>0.29 ± 1.6</td>
<td>0.42 ± 1.6</td>
<td>1.76 ± 2.4</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .007</td>
<td>.09</td>
<td>.09</td>
</tr>
<tr>
<td>C</td>
<td>N = 31</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Score</td>
<td>−1.7 ± 2.4</td>
<td>−1.3 ± 3.3</td>
<td>0.96 ± 4.4</td>
</tr>
<tr>
<td>P value</td>
<td>.09</td>
<td>&lt; .0001</td>
<td>.09</td>
</tr>
<tr>
<td>D</td>
<td>N = 28</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>Score</td>
<td>−5.1 ± 2.8</td>
<td>−4.7 ± 2.7</td>
<td>−0.9 ± 2.9</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Ap</td>
<td>N = 31</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Score</td>
<td>−1.4 ± 0.8</td>
<td>−1.42 ± 1.1</td>
<td>−0.29 ± 1.4</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0009</td>
<td>&lt; .0009</td>
<td>&lt; .0009</td>
</tr>
<tr>
<td>Bp</td>
<td>N = 31</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Score</td>
<td>−1.2 ± 1.2</td>
<td>−1.5 ± 1.2</td>
<td>0.7 ± 2.5</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0002</td>
<td>&lt; .0002</td>
<td>&lt; .0002</td>
</tr>
</tbody>
</table>

**Table III** Erosion by hysterectomy type

<table>
<thead>
<tr>
<th>Erosion</th>
<th>Group I (n = 37)</th>
<th>Group II (n = 49)</th>
<th>Group III (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>%</td>
<td>0</td>
<td>8.16</td>
<td>0</td>
</tr>
<tr>
<td>P value</td>
<td>.0389</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

who had an ASC with hysterectomy, compared with 1.3% in 234 women who underwent ASC alone and Imparato et al11 who reported a 14% erosion rate in 21 women who underwent sacrocolpopexy with a concurrent hysterectomy. In addition, our erosion rate of 3.3% (8.2% in ASC-TAH group) in this study falls within literature cited ranges for erosion (3.4% - 27%).10,12

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An important limitation of our study relates to mesh erosion being a relatively uncommon event. Therefore, our failure to find other significant correlates with erosion might be due to the small number of cases with erosions, which generates an insufficient power to

---

**Table IV** Concomitant procedures (n = 121)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Group I %</th>
<th>Group II %</th>
<th>Group III %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burch urethropexy</td>
<td>68</td>
<td>76</td>
<td>66</td>
<td>.5742</td>
</tr>
<tr>
<td>Paravaginal repair</td>
<td>62</td>
<td>29</td>
<td>29</td>
<td>.0029</td>
</tr>
<tr>
<td>Enterocele repair</td>
<td>43</td>
<td>37</td>
<td>80</td>
<td>&lt; .0002</td>
</tr>
<tr>
<td>Posterior repair</td>
<td>32</td>
<td>35</td>
<td>31</td>
<td>.9698</td>
</tr>
<tr>
<td>Anterior repair</td>
<td>3</td>
<td>8</td>
<td>6</td>
<td>.5595</td>
</tr>
<tr>
<td>Sting</td>
<td>14</td>
<td>4</td>
<td>9</td>
<td>.2670</td>
</tr>
</tbody>
</table>

**Table V** Overall complications

<table>
<thead>
<tr>
<th>N (n)*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-operative injury</td>
<td>3 (121)</td>
</tr>
<tr>
<td>Hospital: Febrile morbidity</td>
<td>11 (115)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2 (115)</td>
</tr>
<tr>
<td>Ileus/SBO</td>
<td>4 (115)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (115)</td>
</tr>
<tr>
<td>3-mo follow-up: Discharge</td>
<td>5 (117)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (116)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>5 (116)</td>
</tr>
<tr>
<td>Erosion</td>
<td>0 (117)</td>
</tr>
<tr>
<td>6 mo follow-up: Discharge</td>
<td>3 (64)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (64)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>4 (64)</td>
</tr>
<tr>
<td>Erosion</td>
<td>3 (62)</td>
</tr>
</tbody>
</table>

* Sample sizes vary because of missing data.
detect reasonable differences, and an increased chance of accepting the null hypothesis when it is false.

Of the 4 erosions, 3 occurred between 5 to 10 months postoperatively, with patient complaints of pain, discharge, and dyspareunia. The fourth patient presented with an erosion at approximately 2 years postoperatively. Review of the patients complicated by mesh erosions did not point to any common variables or special features that might increase erosion risk. One patient had a history of a leep and 2 previous cone biopsies, perhaps making her vaginal cuff uniquely vulnerable to problems. This patient failed multiple attempts to locally excise the mesh and is now scheduled for an abdominal resection of the mesh. The other 3 patients with mesh erosion resolved with simple excision in an ambulatory surgery setting.

Although we hypothesized that a positive estrogen status would help maintain better tissue condition and potentially decrease the rate of erosion, this factor did not prove statistical significance in our cohort. Similarly, the degree of preoperative prolapse, potentially a marker of poorer quality tissue, did not prove statistically significant.

Analysis of the patient characteristics across the 3 groups showed that group III had a patient population that was older, with a greater number of postmenopausal women on HRT. This is intuitive, as these patients were returning with a prolapse later in life after having had a hysterectomy at a prior time. These women also had more severe prolapse preoperatively and a statistically significant higher rate of enterocele repairs. One can extrapolate the importance of doing some type of vault suspension procedure on patients when performing a hysterectomy for other indications, to prevent a reoperation for vault prolapse.

Mesh erosion may occur many years postoperatively, and patients should be followed long-term for that possibility. Our follow-up time may not accurately reflect the erosion-free period from the date of surgery in our population. The unique setup at North Shore allows for these patients to be monitored by general gynecologists within the North Shore system with referral back to the urogynecologist for suspension-related complications. These patients were not lost to follow-up after brief intervals as the data might suggest, rather they remain in our system likely without any complications.

We conclude from this study that sacral colpopexy is a safe procedure with overall low complication rates. Furthermore, our work supports the role for cervical conservation to reduce the incidence of mesh erosion when concomitant hysterectomies are indicated in women undergoing ASC. Given the 7-fold increase in erosion rates found in women undergoing an ASC with TAH, this method should be reserved for women with contraindications for SCHs.

References

Anatomic relationships of infracoccygeal sacropexy (posterior intravaginal slingplasty) trocar insertion

John E. Jelovsek, MD,* Andrew I. Sokol, MD, Matthew D. Barber, MD, MHS, Marie Fidela R. Paraiso, MD, Mark D. Walters, MD

Division of Urogynecology and Pelvic Reconstructive Surgery, Department of Gynecology and Obstetrics, The Cleveland Clinic Foundation, Cleveland, OH

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KEY WORDS
Anatomy
Vaginal vault suspension
Pelvic organ prolapse
Infracoccygeal sacropexy
Posterior intravaginal slingplasty

Objective: The purpose of this study was to describe the distances of the major bony, vascular, neurologic, and visceral structures to the path of the infracoccygeal sacropexy trocar and to determine the point of trocar entry into the vagina.

Study design: Infracoccygeal sacropexy trocars were inserted bilaterally into 6 fresh frozen cadavers. Dissection was performed and the maximal length of the vagina, ischiorectal fossa, and pararectal spaces were measured bilaterally. Mean distances with 95% CIs to important anatomic structures were made from fixed points along the trocar’s path.

Results: The path of the trocar began dorsal and lateral to the anus, passed through the ischiorectal fossa, iliococcygeus muscle, into the pararectal space, and into the posteriolateral vagina. Along this course, the mean distance (95% CI) to the pudendal vessels at the exit of Alcock’s canal was 2.8 cm (2.1 to 3.4 cm) and rectum was 0.5 cm (0.2 to 0.9 cm). The closest inferior rectal vessel was 0.1 cm (0 to 0.3 cm). In the pararectal space, the mean distance to the ischial spine was 2.6 cm (1.7 to 3.5 cm). In 12 of 12 trocar passages, the inferior rectal branches of the pudendal artery and the rectum were within 1 cm or less of the trocar. The mean distance of trocar entry into the vagina was only 4.8 cm (4.3 to 5.4 cm) proximal to the hymenal ring compared with a mean total vaginal length of 8.7 cm (8.0 to 9.3 cm).

Conclusion: This anatomic study suggests that the rectum and the inferior rectal branches of the pudendal neurovascular bundle may be at risk of injury during infracoccygeal sacropexy trocar placement. Additionally, this procedure appears to provide support to the mid-posterior vaginal wall, not the vaginal apex.

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In 1997, Petros described the infracoccygeal sacropexy (posterior intravaginal slingplasty) as a minimally invasive surgical option to restore vaginal vault support. The first prospective study using this procedure reported cure rates of 94% for vault prolapse, with a 5.3% tape erosion rate. In 2002, Farnsworth reported on 93 infracoccygeal sacropexy procedures performed on patients with advanced vaginal vault prolapse. Out of 56 patients who were followed-up at 12 to 24 months, 49/56 (87%) were cured of prolapse. Cure of prolapse was not explicitly defined. Complications included 1 rectal perforation and 1 mesh erosion into the rectum. The author concluded that this procedure has similar efficacy to other surgical techniques for vaginal vault prolapse and that the procedure “has built in safety, as it avoids pudendal nerves and vessels and surface rectal veins.”

The posterior infracoccygeal sacropexy mesh placement is unique. Subjects undergo placement of a ‘U’-shaped mesh using a tunneler (trocar) device in an effort to establish artificial uterosacral neoligaments. The trocar is introduced through 2 small buttoc incisions, into the ischiorectal fossa, and through the levator ani muscles towards the ischial spine. The trocar tip is then deviated medially, where it briefly passes through the pararectal space and into the posteriolateral aspect of the vagina, beneath the vaginal epithelium. A mesh tape is introduced onto the trocar tip and pulled back through the trocar’s path. A similar passage is performed on the opposite side, completing the ‘U’ shape.

The intravaginal mesh is sutured to the apex of the “atrophied” uterosacral ligaments bilaterally, in an effort to reestablish support for the vaginal apex. The vaginal epithelium is then closed. The 2 ends of the tape are “gently stretched” at the buttoc incisions and are left in a “tension-free” fashion. It is unclear what guidelines are used to adjust tension on the tape. Given this unique surgical approach to vault prolapse, we undertook a descriptive study of the relevant anatomy of this region. Our objectives were to describe the distances of the major bony, vascular, and visceral structures to the path of the infracoccygeal sacropexy trocar and to determine the point of trocar entry into the vagina.

**Material and methods**

Infracoccygeal sacropexy trocars (American Medical Systems, Minnetonka, Minn) were inserted bilaterally using the technique described by Petros into 6 fresh frozen cadavers with a surgically absent uterus. Institutional Review Board exemption was obtained. Cadavers were placed in the high dorsal lithotomy position with the legs in candy cane stirrups. Before beginning, total vaginal length was measured using the pelvic organ prolapse quantification system method. Bilateral skin incisions were made 3 cm lateral and 3 cm dorsal to the midanus. Neither vaginal dissection nor placement of an examining finger within the rectum was performed in an effort to avoid disrupting adjacent anatomy in the paravaginal and pararectal spaces during passage.

With 1 finger in the vagina, the ischial spine was identified. The infracoccygeal sacropexy trocar was advanced through the buttock skin, into the ischiorectal fossa, and through the levator muscles. The tip was aimed toward the ischial spine until it was felt at the level of the ischial spine by the vaginal finger. An attempt was made to pass the trocar tip in the plane between the lateral rectovaginal tissue to reach as close to the vaginal apex as possible. The needle was passed medially through the vaginal epithelium at a point 1 to 2 cm below the hysterectomy scar. The distance from the 6 o’clock position on the hymenal ring to the point of trocar entry into the vagina was measured using a ruler.

After trocar placement, dissection began abdominally by removing the anterior abdominal wall. The retroperitoneal space was dissected revealing the ureter, ureter artery, and internal and external iliac arteries. The internal iliac artery was injected with latex to identify the pudendal vessels and its associated branches. The space of Retzius was opened, revealing the arcus tendineus fascia pelvis, ischial spine, and obturator artery. The pararectal space was opened caudal to the level of the levator ani muscles. Dissection then proceeded from the perineum, identifying the ischial tuberosity, glutaeus maximus, and sacrotuberous ligament. The ischiorectal fossa was dissected with the objective to identify the pudendal vessels as they exited Alcock’s canal, the inferior rectal branches of the pudendal artery, external anal sphincter, rectum, and the levator ani muscles. The trocar was left in situ as dissection was performed.

Measurements were made from fixed points along the trocar’s path. These fixed points were in the following planes: the perineal surface, ischiorectal fossa including the plane from the exit of Alcock’s canal to the external anal sphincter, and pararectal space including the plane from the ischial spine to the rectal-levator junction. Distances of the trocar within the ischiorectal fossa, pararectal spaces, and vagina were also measured. Once all measurements were obtained, we repeated the passage of the trocar on the opposite side and similar distances were measured.

Measurements were taken using calipers. We then placed the calipers on a measuring tape and recorded the distances. Distances are reported using centimeters and taken from the lateral edge of the trocar to the lateral edge of the vessel, viscera, or other anatomic structures. Mean distances with 95% CIs were calculated. Statistical analysis was performed using JMP 5.1 (SAS Corp, Cary, NC).
Results

The boundaries of the ischiorectal fossa include the ischial tuberosity and obturator internus muscle laterally. The external anal sphincter, pubococcygeus, and iliococcygeus portions of the levator ani muscle make up the medial border. The lateral and medial portions of this space converge toward the ischial spine. The sacrotuberous ligament and deep portions the gluteus maximus lie posteriorly. Connective tissue along the inferior border of the pelvic diaphragm lie anteriorly. The ischiorectal fossa is largely filled with adipose tissue, allowing for expansion of the rectal wall and incorporating branches of the inferior rectal (hemorroidal) neurovascular bundle. These vessels originate as branches of the pudendal neurovascular bundle. The connective tissue surrounding the obturator internus laterally helps form the pudendal (Alcock’s) canal beginning at the lesser sciatic notch. The neurovascular bundle within the canal courses inferiorly along the medial surface of the ischium and ends by branching into the lateral portion of the ischiorectal fossa. The pudendal neurovascular bundle sends branches both anteriorly towards the labia, clitoris, and muscles of the urogenital diaphragm and posteriorly towards the rectum and external anal sphincter. These are referred to as the inferior rectal (hemorrhoidal) arteries, veins, and nerves. These neurovascular branches course from

Figure 1  Lithotomy view demonstrating the infracoccygeal sacroplexy trocar passing from the skin surface into the ischiorectal fossa directly through the inferior rectal branches of the pudendal vessels. It is bordered medially by the external anal sphincter, pubococcygeus, iliococcygeus, and rectum; laterally by the ischial tuberosity and obturator internus; and inferiorly by the gluteus maximus and sacrotuberous ligament (not shown). Reprinted with the permission of The Cleveland Clinic Foundation.
lateral to medial and from deep (from Alcock’s canal) to superficial towards the rectum and external anal sphincter. As shown in Figure 1, the infracoccygeal sacropexy trocar runs directly through this area.

The path of the trocar began dorsal and lateral to the anus, passed through the ischiorectal fossa, iliooccygeus muscle, into the pararectal space, and into the posteriolarateral vagina. Mean distances from important vasculature structures are shown in Table I. In 12 of 12 trocar passages, the inferior rectal branches of the pudendal artery and the rectum were within 1 cm or less of the trocar. In the majority of passages, a branch of the inferior rectal artery rested immediately adjacent to the trocar. The mean distance from the trocar to the pudendal artery as it exited Alcock’s canal was 2.8 cm (CI 2.1 to 3.4; range 1 to 4 cm).

The mean distances from important bony, soft tissue, and visceral organs are shown in Table II. All infracoccygeal trocar passages were lateral to the rectum. The mean distance of the trocar starting at the skin surface, through the ischiorectal fossa, to the levator ani was 5.9 cm (CI 4.9 to 6.9 cm). In the pararectal space the distance from the levator surface where the trocar exited to the entry into the inferio-lateral vagina was 1.6 cm (CI 0.7 to 2.4 cm). The mean distance of the trocar from the ischial spine was 2.6 cm (CI 1.7 to 3.5 cm; range 0 to 4 cm).

The mean total vaginal length from the hymen was 8.7 cm (CI 8.0 to 9.3 cm) before insertion of the trocar. Trocar entry into the inferolateral vagina was only 4.8 cm (CI 4.3 to 5.4 cm) proximal to the hymenal ring or approximately 55% of total vaginal length, as shown in Figure 2.

### Table I

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Mean distance in cm (95% CI) from trocar to vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pudendal vessels at exit of Alcock's canal</td>
<td>2.8 (2.1–3.4)</td>
</tr>
<tr>
<td>Inferior rectal artery (closest)</td>
<td>0.1 (0–0.3)</td>
</tr>
<tr>
<td>Uterine artery</td>
<td>3.5 (2.7–4.4)</td>
</tr>
<tr>
<td>Internal iliac artery</td>
<td>6.4 (4.9–7.9)</td>
</tr>
<tr>
<td>External iliac artery</td>
<td>8.9 (7.5–10.3)</td>
</tr>
<tr>
<td>Obturator artery</td>
<td>6.5 (5.2–7.7)</td>
</tr>
</tbody>
</table>

### Table II

<table>
<thead>
<tr>
<th>Structure</th>
<th>Mean distance in cm (95% CI) from trocar to structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td></td>
</tr>
<tr>
<td>Ischial tuberosity</td>
<td>4.8 (4.0–5.6)</td>
</tr>
<tr>
<td>Sacrotuberous ligament</td>
<td>3.6 (2.3–4.8)</td>
</tr>
<tr>
<td>Coccyx</td>
<td>5.3 (4.2–6.3)</td>
</tr>
<tr>
<td>Ischial spine</td>
<td>2.6 (1.8–3.5)</td>
</tr>
<tr>
<td>Muscle and ligaments</td>
<td></td>
</tr>
<tr>
<td>Gluteus maximus</td>
<td>0.6 (0–1.4)</td>
</tr>
<tr>
<td>External anal sphincter</td>
<td>2.1 (1.7–2.5)</td>
</tr>
<tr>
<td>Arcus tendineus fascia pelvis</td>
<td>3.4 (2.6–4.3)</td>
</tr>
<tr>
<td>Viscera</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>0.5 (0.2–0.9)</td>
</tr>
<tr>
<td>Ureter</td>
<td>3.5 (2.8–4.2)</td>
</tr>
</tbody>
</table>

### Comment

The Manufacturer and User Friendly Device Experience Database and Medical Device Reporting (MDR) databases managed by the United States Food and Drug Administration include complications from medical devices that have occurred in the United States. A search for complications reported using the infracoccygeal sacropexy for vaginal prolapse included hematomas requiring evacuation in the pararectal space, pararectal abscess, and tape erosions in the vagina and rectum. Published complications include erosion into the vagina and rectum, as well as rectal perforation.5,6,3

Our study demonstrates that there are 3 anatomic concerns with passage of the infracoccygeal sacropexy trocar: 1) proximity of the trocar to the inferior rectal (hemorrhoidal) neurovascular bundle in the ischiorectal fossa; 2) the low margin of error for medial trocar deviation caused by the proximity of the rectum; and 3) limitations on the extent of vaginal length.

Many advocates of the infracoccygeal sacropexy insist that there is no risk of “major” vascular injury during trocar insertion. Our data support this finding regarding main branches of the pudendal artery as it exits Alcock’s canal. We found that, on average, the trocar lay 2 to 3 cm medial to the artery at this point. If insertion is more lateral than 2 to 3 cm from the midanus, this vessel may be at risk of damage. However, there have been no reports of this in the literature to date. Nonetheless, our study does suggest that the inferior rectal branches of the pudendal artery may be at risk of injury. Branches of this artery were immediately adjacent to the trocar in all passes.

Proponents of the infracoccygeal sacropexy do not consider the inferior rectal branches of the pudendal at risk because of the blunt design in some trocar tips and the mobility of the vessels in the adipose tissue of the ischiorectal fossa. The needle “tunnels” through the tissue and pushes the vascular structures aside. Although the actual risk of laceration of these vessels is currently unknown, bleeding in the ischiorectal fossa may be clinically difficult to detect until significant blood loss has resulted. If significant anemia occurs, a thorough vaginal and rectal exam, as well as palpation of the
area between the anus and ischial tuberosity, should be considered to rule out hematoma formation after placement of the infracoccygeal sacropexy.

Other potential concerns include possible neurologic damage to the external anal sphincter. Although we did not specifically dissect the nerves of the external anal sphincter in this study, nerves usually follow their vascular counterparts. Given the higher prevalence of fecal incontinence in patients with pelvic floor disorders, physicians should be aware of any new onset soiling or gross incontinence should it develop. Currently, data are lacking regarding fecal incontinence or functional bowel disorders in patients undergoing this procedure. A study evaluating sphincter neurologic function with electromyography before and after this procedure seems warranted.

Our study suggests that the risk of injury to the rectum is high when the trocar is medially deviated. In 12 of 12 trocar passages, the rectum was within a centimeter or less of the trocar. Efforts to reduce injury or “button holes” of the rectum include medial deviation of the rectum after dissection of the rectovaginal and pararectal spaces along with strict adherence to a parallel insertion path until the tip of the trocar is palpated as it penetrates the levator ani muscles. Much like insertion of the tension free vaginal tape where there is a significant distance of “blind passage,” the surgeon should not lose control of the trocar after penetration.
into the ischiorectal fossa. Use of an external bony landmark to guide the axis of the trocar (similar to using the ipsilateral shoulder as a guide during the tension-free vaginal tape procedure) would be helpful for surgeons who choose to perform this procedure.

The infracoccygeal sacropexy was originally described to repair level I support. Delancey previously described level I support to include both vertical and dorsal fibers from the sacrum that attach to the most cephalic portion of the vagina. Level II support involves attachment of the vagina to the lateral pelvis, specifically the arcus tendineus fasciae pelvis and arcus tendineus levator ani. Based on our study, the infracoccygeal sacropexy trocar appears to enter the mid-posterior-lateral vaginal wall; this is closer to level II than level I support.

In our study, the trocar entered the vagina at a mean length of 4.8 cm from the hymen. This is likely caused by anatomic limitations of the pelvis given the location of the ischial spine. This limitation raises several concerns. If mesh is attached across the top of the vagina to repair the defect (ie, enterocoele) at the vaginal apex, functional vaginal length may be compromised as healing of vaginal tissue within the mesh occurs. Also, given the path of trocar entry into the vagina, the direction of force applied to the attached vaginal tissue may place abnormal caudal tension on the posteriolateral portion of the vagina towards the tip of the coccyx. This could potentially predispose the anterior vaginal wall to prolapse as in the sacrospinous ligament vault suspension or iliococcygeal vault suspension. In a series of 75 cases of infracoccygeal sacropexy performed by Petros, the recurrence rate of anterior vaginal wall prolapse was consistent at 16% (12/64 and 12/40) at 2 to 5 years, respectively. Given the anatomy of the pelvis, location of the ischial spine, sacrospinous ligament, and pudendal neurovascular bundle, the maximum theoretical distance of trocar entry into the vagina is only as far as the ischial spine. Even if this were attainable, the vagina would still be shortened similar to performing an iliococcygeal vault suspension.

Based on our anatomic findings, differences in technique are unlikely to result in less vascular or neurologic injury to the inferior rectal branches of the pudendal artery and nerve. Placing the needle more laterally could potentially place the main branches of the pudendal artery at higher risk, while more medial placement places the rectum at risk. Increased vaginal length will be difficult to achieve using this technique given the anatomic limitations of the bony pelvis and the normal vaginal axis. An “inside-out” technique is likely to be similarly limited by the bony pelvis, as well as a significant distance of blind passage.

Before adopting a new surgical technique there are several things to consider. The technique should either be 1) more effective, 2) equally effective but safer, 3) equally safe and effective, but cheaper, or 4) more easily performed compared with the established procedure without compromising safety and efficacy. So far, no comparative trials of efficacy have been performed using the infracoccygeal sacropexy.

Advocates of the infracoccygeal sacropexy argue that the mesh is placed “tension free.” However, the benefits of this technique are not yet proven, and the procedure introduces the risk of needle insertion into the ischiorectal fossa bilaterally when placing the mesh. Technique generalizability (a type of external validity in surgery) is a concern because the approach through the ischiorectal fossa is novel to gynecologic and urologic surgeons. Techniques that avoid blind trocar passage through the ischiorectal fossa seem preferred.

Industry often times precedes science in the development of creative medical devices. Properly designed, descriptive anatomic studies, as well as efficacy studies, should be paramount before widespread application of new medical technology. The infracoccygeal sacropexy is a unique, minimally invasive approach purported to repair vaginal vault prolapse. The surgeon performing the infracoccygeal sacropexy should have a thorough knowledge of the anatomy of the perineum, ischiorectal fossa, and pararectal space to avoid potential complications when performing this procedure.

Acknowledgments

Trocars were provided by American Medical Systems (Minnetonka, MN).

References

Objective: The purpose of this study was 1) to determine the prevalence of functional bowel and anorectal disorders as defined by the Rome II criteria in patients with advanced pelvic organ prolapse (POP) and urinary incontinence (UI), and (2) to determine if the extent of prolapse on gynecologic examination is related to the subtypes of constipation or any functional anorectal pain disorder.

Study design: Three hundred and two consecutive female subjects presenting to a tertiary urogynecology clinic were enrolled. Demographic, general medical, and physical examination information, including POPQ measurements and a standardized sacral neurologic evaluation, were collected. The prevalence of functional disorders of the bowel, rectum, and anus as defined by the Rome II criteria were collected using the Rome II Modular questionnaire. Relationships of functional disorders to various components of the vaginal examination were reviewed.

Results: Thirty-six percent (108/302) met the criteria for constipation, including the following subtypes: 19% outlet constipation, 5% functional constipation, 5% constipation predominant irritable bowel syndrome (IBS), and 7% IBS-outlet. Nineteen percent (56/302) of subjects had IBS or 1 of its subtypes. Functional diarrhea was seen in 6% (17/302), fecal incontinence in 19% (58/302), and anorectal pain disorders in 25% (77/302). After controlling for age, parity, diabetes, constipating medications, and previous pelvic surgery, there were no differences in the prevalence of constipation or any of its subtypes between patients with UI and those with stage 3 or 4 POP. Fecal incontinence was independently associated with UI (adjusted odds ratio [OR] 6.3; 95% CI 2.6–19.1), but not advanced POP. Neither overall stage of POP nor stage of posterior vaginal prolapse was significantly associated with any of the functional bowel disorders, including constipation and its subtypes. Perineal body measurement was significantly longer in patients with outlet type constipation (mean 3.5 ± 0.6 cm vs 3.1 ± 0.9 cm, P < .01) and in those with proctalgia fugax (mean 3.4 ± 1.0 vs 3.1 ± 0.8, P < .05).
Conclusion: There is a high prevalence of constipation and anorectal pain disorders in women with urinary incontinence and pelvic organ prolapse. However, patients with stage 3 or 4 pelvic organ prolapse have similar rates of constipation compared with those with urinary incontinence. Constipation and its subtypes are not related to the stage of pelvic organ prolapse. It appears that either constipation is not a significant contributor to prolapse, or constipation contributes equally to the development of both urinary incontinence and pelvic organ prolapse.

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Symptoms of constipation are commonly reported in patients with pelvic floor disorders, particularly posterior vaginal prolapse. These include excessive straining, a need to splint or push on the vagina or perineum to complete a bowel movement, and the trapping of stool upon evacuation. The ability to predict which patients will have an improvement in such symptoms after surgical repair requires an understanding of anatomy and pathophysiology of disorders of the bowel, rectum, and anus. There is a paucity of literature evaluating these disorders in gynecologic populations. Furthermore, disorders that are commonly encountered in clinical practice, such as functional diarrhea, proctalgia fugax, levator ani syndrome, and pelvic floor dyssynergia, are frequently ignored in gynecologic clinical practice and research.

The Rome II criteria are a set of consensus agreed upon criteria to describe disorders of the bowel, rectum, and anus used by our gastroenterology and colorectal colleagues. These criteria have been established to standardize communication regarding disorders of the bowel, rectum, and anus. To our knowledge, these definitions and their relationships have not been described in subjects presenting with prolapse or incontinence. By using standardized terminology regarding these disorders, we may have a better understanding of the disorders, their effects on pathophysiology, and the treatment of pelvic floor disorders.

We sought to determine the prevalence of functional bowel, rectal, and anal disorders in women with urinary incontinence (UI) and pelvic organ prolapse (POP) using the definitions set forth in the Rome II criteria. Because the overwhelming majority of gynecologic literature reports on the relationship between constipation and pelvic organ prolapse, we attempted to determine the prevalence of subtypes of constipation in this population. Our hypotheses were that: 1) patients with pelvic organ prolapse and urinary incontinence would have a higher overall prevalence of constipation compared with the US population; 2) the predominate subtype in our population would be attributed to the outlet subtype; and 3) the degree of prolapse would be higher in subjects with constipation, particularly those with the outlet subtype.

Material and methods

This study was approved by the Cleveland Clinic Foundation Institutional Review Board. This was a cross-sectional study design. Three hundred and two consecutive female subjects presenting to a tertiary referral, urogynecology clinic were prospectively recruited between December 2003 and July 2004. Subjects were eligible for recruitment if the reason for consultation was either pelvic organ prolapse or lower urinary tract symptoms, including urinary incontinence. Exclusion criteria included age less than 18, refusal of the patient to participate, inability to complete the questionnaire, and inability to speak or read English. All 302 potential subjects agreed to participate. Subjects were given a routine questionnaire in the waiting room before being seen by the nurse or physician. Demographic, general medical, and physical exam information were collected. Subjects were classified as having any urinary incontinence by subjective response. Examiners were blinded to results from the bowel questionnaire. Each subject underwent a standardized evaluation, including assessment of prolapse using the POPQ staging system in the lithotomy position. A screening sacral neurologic examination was performed, including testing for anal and bulbocavernous reflexes, testing for ability to discriminate sharp and dull sensation to perineal pin-prick, subjective rating of squeeze anal sphincter tone, and a modified pelvic muscle rating as outlined by Worth et al. The pelvic or circumvaginal muscle rating scale, which assesses the patient’s ability to contract the muscles of the pelvic floor with the examiner’s fingers in the vagina, subjectively evaluates strength and duration of the contraction.

The prevalence of functional bowel and anorectal disorders as defined by the Rome II criteria were determined by the subject’s responses to the Rome II Modular questionnaire, a symptom-based questionnaire developed by clinical consensus. Functional bowel disorders included: 1) irritable bowel syndrome (IBS) and its subtypes: diarrhea predominant, constipation predominant, and IBS-outlet type; 2) functional constipation; and 3) functional diarrhea. Subjects were defined as having outlet type constipation if subjects met both the criteria for functional constipation and had 1 or more of the following outlet symptoms at least 25% of the time during bowel movements over the past 3 months: 1) a sensation that the stool cannot be passed (ie, blocked) when having a bowel movement; 2) a need to press on or around your bottom or vagina to try to remove stool in order to complete the bowel movement;
or 3) having difficulty relaxing or letting go to allow the stool to come out at least one quarter of the time. IBS-outlet type constipation was defined as subjects who met both the criteria for IBS and had 1 or more of the aforementioned outlet symptoms. Subjects who met the criteria for functional type were only classified in this group if they did not meet the criteria for IBS, outlet, or IBS-outlet type. Overall, constipation was grouped together with subjects who met criteria for the mutually exclusive subgroups: 1) functional constipation; 2) functional constipation with outlet delay or obstruction; 3) constipation predominant IBS; and 4) IBS-outlet type.

Functional disorders of the anus and rectum included functional fecal incontinence (and its subtypes of soiling and gross incontinence), and functional anorectal pain (including levator ani syndrome, proctalgia fugax, and pelvic floor dyssynergia). Incontinence of flatus was not assessed because it is not recognized by the Rome II criteria as a disorder. Rome II defines proctalgia fugax as having more than 1 episode of aching pain or pressure in the anal canal or rectum over the last year that lasts from seconds to minutes and disappears completely. Levator ani syndrome includes the same pain; however, the pain can last more than 20 minutes up to several days or longer and has occurred frequently or continuously in the last 3 months.

Univariate analysis was conducted using the Pearson $\chi^2$ statistic or Fisher exact test for categorical data, the Student $t$ test for continuous parametric data, and the Wilcoxon rank sum test for continuous nonparametric data. Multiple logistic regression analysis was performed to identify factors associated with functional bowel and anorectal disorders, including constipation and its subtypes. Data are reported using odds ratios (OR) and 95% CI. All statistical tests were 2-tailed and $P < .05$ was considered statistically significant. Statistical analysis was performed using JMP 5.0.1 (SAS Institute, Cary, NC).

Results

Table I summarizes the demographics in the sample population. This was a healthy, multiparous population with a mean age of 60 ± 14 years. Forty-one percent (123/302) had a previous hysterectomy, and previous surgery for prolapse was reported in 21% (62/302) of subjects. Overall, 13% (39/302) of subjects had stage 3 or 4 POP without urinary incontinence, 50% (152/302) had urinary incontinence without stage 3 or 4 POP, and 20% (60/302) had both stage 3 or 4 POP and urinary incontinence. The remaining 53 subjects did not have either urinary incontinence or stage 3 or 4 prolapse. They had lesser degrees of prolapse without urinary incontinence or other lower urinary tract symptoms (ie, dysuria). Subjects with stage 3 or 4 POP were older (66 vs 56 years, $P < .0001$), had higher vaginal parity (3 vs 2, $P < .0001$), and were more likely to have had a previous hysterectomy (56% vs 34%, $P < .001$). Patients with urinary incontinence were more likely to be taking antidepressants (27% vs 5%, $P < .0001$).

Table II summarizes the overall prevalence of functional bowel and anorectal disorders in this population. Of the 302 subjects, 36% (95% CI 31–41) had constipation. The majority of constipation was caused by the outlet subtype. We observed 19% (58/302) of subjects who met the criteria for fecal incontinence, with 35 (12%) of these subjects reporting loss of a “small amount” of stool and 22 (7%) who complained of a loss of “moderate or large amount” compared with 22 (7%) who complained of a loss of “moderate or large amount.” One subject did not quantify the amount of fecal incontinence. Functional anorectal pain was seen in 77 (25%) of subjects, with 20% (61/302) meeting the criteria for proctalgia fugax and 5% (16/302) having levator ani syndrome. Four percent (11/302) of subjects met questionnaire criteria for pelvic floor dyssynergia. We did not confirm this diagnosis with physiologic testing.

On physical exam, an abnormal anal wink was associated with diarrhea-predominate IBS ($P < .005$). Subjects with constipation were more likely than those without constipation to have an anal wink present on exam. The majority of these subjects were those with outlet type constipation ($P < .05$). Anal resting tone, squeeze strength, and levator ani contraction and genital hiatus measurement were not significantly different...
among different groups of functional bowel disorders. The presence of a sphincter defect on physical exam was associated with fecal incontinence ($P < 0.01$). Perineal body was statistically longer in patients with outlet type constipation (mean 3.5 ± 0.6 vs 3.1 ± 0.9 cm, $P < .01$) and proctalgia fugax (mean 3.4 ± 1.0 vs 3.1 ± 0.8 cm, $P < .05$).

Table III summarizes the frequency of selected bowel and anorectal symptoms seen in patients with prolapse and incontinence. On univariate analysis, hard or lumpy stools were associated with the stage of posterior vaginal wall prolapse ($P < .05$) and passing mucous (slime) during a bowel movement was associated with total stage of POP ($P < .01$). There was no association between number of bowel movements reported and both stage of posterior wall and total POPQ stage ($P = .4$ and $P = .7$, respectively).

After controlling for age, parity, antidepressant use, and previous hysterectomy, neither overall stage of POP nor stage of posterior vaginal prolapse was significantly associated with any of the functional bowel disorders, including constipation or its subtypes. There was no difference in the prevalence of constipation or any of its subtypes between patients with UI and those with stage 3 or 4 POP. Fecal incontinence was independently associated with UI (adjusted OR 6.3; 95% CI 2.6–19.1), but not advanced pelvic organ prolapse.

**Comment**

Our understanding of the pathogenesis of pelvic organ prolapse is limited. Risk factors cited in the literature range from childbirth, hysterectomy, age, ethnicity, genetics, constipation, and chronic intrabdominal pressure. Although frequent straining associated with constipation is often mentioned as an etiology of prolapse, the relationship remains unclear.

Snooks et al compared 24 women with chronic constipation for a mean duration of constipation of 19.4 years with 20 age- and parity-matched controls. Their results showed that damage to the nerve supply of both the puborectalis and external anal sphincter occurred in chronic constipation. This was attributed to straining during defecation, resulting in perineal descent and resultant pudendal neuropathy. Lubowski et al described a relationship between perineal descent produced by a simulated defecation effort and pudendal nerve damage. In 1994, Spence-Jones et al concluded that straining at stool as a young adult before the development of urogynecologic symptoms was significantly more common in women with prolapse than in controls (61% vs 4%, $P < .001$). A bowel frequency of less than twice per week as a young adult was also more common (48% vs 8%).

However, several authors have found no association between various bowel complaints and prolapse. Weber et al described 143 women who completed a questionnaire assessment of bowel function with standardized exams using the POPQ method. Straining to have a bowel movement was required rarely in 26.6%, sometimes in 49.6%, usually in 14%, and always in 9.8%. In their sample, severity of prolapse was not related to bowel dysfunction. Among 491 Swedish women, when a rectocele was present, 18% reported problems with emptying the bowel at defecation compared with 13% in the nonrectocele group, a nonsignificant difference. Constipation was not related to prolapse in this population sample. Additionally, Hendrix et al found that self-reported constipation in subjects in the Women’s Health Initiative was not a risk factor for pelvic organ prolapse.

<table>
<thead>
<tr>
<th>Functional disorder</th>
<th>Prevalence per 100 (95% CI) in UI group</th>
<th>Prevalence per 100 (95% CI) in stage 3 or 4 POP group</th>
<th>Overall prevalence per 100 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS</td>
<td>18 (13 to 25)</td>
<td>18 (9 to 33)</td>
<td>19 (15-23)</td>
</tr>
<tr>
<td>Diarrhea predominate</td>
<td>3 (1 to 7)</td>
<td>5 (1 to 17)</td>
<td>5 (3 to 8)</td>
</tr>
<tr>
<td>Constipation predominate</td>
<td>5 (2 to 9)</td>
<td>5 (1 to 17)</td>
<td>5 (3 to 8)</td>
</tr>
<tr>
<td>IBS-outlet</td>
<td>7 (4 to 12)</td>
<td>3 (0.4 to 13)</td>
<td>7 (5 to 11)</td>
</tr>
<tr>
<td>Functional constipation</td>
<td>3 (1 to 7)</td>
<td>5 (1 to 14)</td>
<td>5 (3 to 8)</td>
</tr>
<tr>
<td>Outlet type</td>
<td>17 (12 to 24)</td>
<td>23 (13 to 38)</td>
<td>19 (15 to 24)</td>
</tr>
<tr>
<td>Functional diarrhea</td>
<td>5 (3 to 10)</td>
<td>5 (1 to 17)</td>
<td>6 (4 to 9)</td>
</tr>
<tr>
<td>Functional fecal incontinence</td>
<td>22 (16 to 29)</td>
<td>5 (1 to 17)</td>
<td>19 (15 to 24)</td>
</tr>
<tr>
<td>Soiling</td>
<td>11 (7 to 17)</td>
<td>3 (0.4 to 13)</td>
<td>12 (8 to 16)</td>
</tr>
<tr>
<td>Gross</td>
<td>10 (6 to 16)</td>
<td>3 (0.4 to 13)</td>
<td>7 (5 to 11)</td>
</tr>
<tr>
<td><strong>Anorectal pain disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctalgia fugax</td>
<td>17 (12 to 24)</td>
<td>36 (23 to 52)</td>
<td>20 (16 to 25)</td>
</tr>
<tr>
<td>Levator ani syndrome</td>
<td>8 (5 to 13)</td>
<td>0</td>
<td>5 (3 to 8)</td>
</tr>
<tr>
<td>Pelvic floor dyssynergia</td>
<td>3 (1 to 7)</td>
<td>0</td>
<td>4 (2 to 6)</td>
</tr>
</tbody>
</table>

Table II Prevalence of functional disorders of the bowel, rectum, and anus as defined by the Rome II criteria in patients presenting to a tertiary urogynecology clinic (n = 302)
All of these studies used various definitions of constipation. Using the more standardized Rome II definitions, our findings confirm that the symptom-definition of constipation is not associated with the degree of prolapse in patients presenting to a tertiary care urogynecology clinic. Also, we were unable to show a significant difference in the prevalence of constipation between patients with advanced pelvic organ prolapse only versus those with urinary incontinence only. If constipation were a significant cause of prolapse we would suspect this would not be the case, unless it is also a significant cause of urinary incontinence. Our data suggest, like that of other authors, that it is unlikely that prolapse is a significant contributor to constipation. Additionally, it appears that either constipation is not a significant contributor to prolapse, or that constipation contributes equally to development of both urinary incontinence and pelvic organ prolapse.

A logical reason for our inability to elucidate that constipation seems to be a confounding factor and not necessarily a true contributor of prolapse may be attributed to the lack of use of standardized definitions of functional bowel and anorectal disorders in the field of gynecology. Gynecologists often limit patient inquiries regarding bowel function to “are you constipated,” “how often do you have a bowel movement,” “do you strain during bowel movements,” “or do you press in or around the vagina to have a bowel movement?” Important items that are not routinely asked include aching pain or pressure in the rectum, having difficulty relaxing or letting go to allow stool to come out, or the feeling of not completely emptying the rectum after a bowel movement. Although all of these symptoms are decidedly relevant to these areas it illustrates why we are unable to formally group patients as having or not having a disorder and possibly determining cause and effect.1 For example, straining has been strongly associated (OR 66.7) with self-report of constipation.11 However, self-reported constipation is neither sensitive nor specific compared with symptom-based criteria.2 Self-reported frequency of bowel movements is poorly correlated with self-reported constipation.11-13

### Table III

<table>
<thead>
<tr>
<th>Symptom</th>
<th>UI group (n = 152)</th>
<th>Stage 3 or 4 POP group (n = 39)</th>
<th>Both UI and stage 3 or 4 POP (n = 60)</th>
<th>Neither UI or stage 3 or 4 POP (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort or pain in your abdomen</td>
<td>58 (38)</td>
<td>11 (28)</td>
<td>19 (32)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>Fewer than 3 bowel movements a week (0-2)</td>
<td>31 (20)</td>
<td>5 (13)</td>
<td>5 (8)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Hard or lumpy stools</td>
<td>52 (34)</td>
<td>14 (36)</td>
<td>25 (42)</td>
<td>21 (41)</td>
</tr>
<tr>
<td>Straining during a bowel movement</td>
<td>60 (39)</td>
<td>13 (33)</td>
<td>24 (40)</td>
<td>21 (41)</td>
</tr>
<tr>
<td>Feeling of incomplete emptying</td>
<td>56 (37)</td>
<td>16 (41)</td>
<td>22 (37)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>A sensation that the stool cannot be passed (ie, blocked) when having a bowel movement</td>
<td>52 (34)</td>
<td>11 (28)</td>
<td>17 (28)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>A need to press on or around your bottom or vagina to try to remove stool in order to complete the bowel movement</td>
<td>43 (28)</td>
<td>10 (26)</td>
<td>17 (28)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Accidentally leak or pass stool</td>
<td>34 (22)</td>
<td>2 (5)</td>
<td>19 (32)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Small amount (it stains underwear)</td>
<td>20 (57)</td>
<td>1 (50)</td>
<td>13 (68)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Moderate or large amount (2 teaspoons or more)*</td>
<td>15 (43)</td>
<td>1 (50)</td>
<td>5 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>More than 1 episode of aching pain or pressure in the anal canal or rectum</td>
<td>40 (26)</td>
<td>14 (36)</td>
<td>14 (23)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Lasts from seconds to minutes and disappears completely</td>
<td>26 (70)</td>
<td>14 (100)</td>
<td>10 (77)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Lasts more than 20 minutes and up to several days or longer</td>
<td>12 (31)</td>
<td>0 (0)</td>
<td>3 (23)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Feel as if you had to strain to pass your stool at least one quarter of the time</td>
<td>68 (45)</td>
<td>13 (33)</td>
<td>25 (42)</td>
<td>19 (37)</td>
</tr>
<tr>
<td>Feel as if you were unable to empty the rectum at least one quarter of the time</td>
<td>39 (26)</td>
<td>10 (26)</td>
<td>23 (38)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Have difficulty relaxing or letting go to allow the stool to come out at least one quarter of the time</td>
<td>23 (15)</td>
<td>4 (10)</td>
<td>10 (17)</td>
<td>7 (13)</td>
</tr>
</tbody>
</table>

* One patient did not specify the quantity in subjects with both UI and stage 3 or 4 POP.

† One patient did not specify the time period in the UI and stage 3 or 4 POP.
individuals with fewer than 3 bowel movements per week do not consider themselves constipated. This highlights the need to better assess functional bowel disorders using consensus-agreed upon criteria in the gynecologic literature. Using such definitions allows us to make more formalized diagnoses of disease and improves our ability to investigate how certain disorders affect or are affected by disorders of the pelvic floor.

Little effort has been made to using the standardized definitions that are available. The International Continence Society (ICS) has been responsible for standardization of terminology of lower urinary tract and validated definitions of pelvic organ prolapse. The purpose of such definitions is to facilitate comparisons of published series from different institutions and longitudinal evaluations of individual patients. Clinicians and investigators of the pelvic floor are becoming increasingly aware of the relationships between gynecologic disorders of the pelvic floor and those of the lower bowel, rectum, and anus. This awareness necessitates the urgent need to standardize these areas in the gynecologic literature.

Based on our data, between 31% and 41% of patients presenting with pelvic organ prolapse or incontinence will meet formal standardized definitions of constipation. This is higher than estimates from a recent meta-analysis of constipation in North America that were between 12% and 19%. Overall, outlet type and IBS-outlet type accounted for 73% of all cases of constipation in our population. This is slightly higher than the 60% of outlet type constipation and IBS-outlet reported in US women who have a diagnosis of constipation. It also illustrates why constipation is presumed to be a either a contributing cause or a result of prolapse. This may be because of the abundance of overlapping symptoms in patients with both outlet type constipation and those we typically associate with pelvic organ prolapse. We speculate that the combination of symptoms results from pelvic organ prolapse, urinary incontinence, and constipation sharing a common etiology and that one may not necessarily cause the other. This could be studied prospectively by identifying women with constipation and its subtypes along with pelvic floor disorders at the onset of the study and determining which ones develop each of the disorders through time. A case-control study of bowel function comparing women with advanced stage prolapse to appropriate controls without prolapse or urinary incontinence would also be useful.

The association of fecal incontinence and urinary incontinence has been previously demonstrated. Jackson et al found a significant association between urinary incontinence and fecal incontinence (adjusted OR 4.6, 95% CI 1.9–11.2) in 247 patients with pelvic floor disorders. Nichols et al found that patients with both pelvic organ prolapse and urinary incontinence were significantly more likely to have anal incontinence (OR 2.72, 95% CI 1.2–6.1) than patients with urinary incontinence only or pelvic organ prolapse only. Cystometry in these women with and without anal incontinence (including flatal incontinence) showed no difference among stress, urge, and mixed urinary incontinence between the 2 groups. Interestingly, these data contradict our findings that fecal incontinence, as defined by the Rome II criteria, was independently associated with subjective urinary incontinence and not with stage 3 or 4 prolapse.

Surprisingly, we also found that a significant percentage of our patients suffer from some form of anorectal pain disorder. Proctalgia fugax may be seen in 16% to 25% of patients. This disorder seems to be moderately elevated in patients with advanced stage prolapse compared with those with incontinence. This association is unclear given the limited understanding of causes of proctalgia fugax. We speculate that the way the Rome II criteria asks the questions “over the last year, did you have more than one episode of aching pain or pressure in the anal canal or rectum” and “does it last from seconds to minutes and disappears completely” may be inaccurate in patients with advanced stage prolapse. These patients may interpret pressure resulting from a prolapsed vagina and not necessarily a distinct pain disorder. Levator ani syndrome was found in 3% to 8% of patients. This disorder, previously known as tenesmus, involves spasm of the levator ani muscles, making defecation painful. There were no cases of levator ani syndrome and pelvic floor dyssynergia in subjects with stage 3 or 4 prolapse. This is not surprising given that these disorders are associated with pain or spasm of the puborectalis, and patients with stage 3 or 4 prolapse often have atonic levator muscles.

The relationship between anorectal pain disorders and pelvic floor dyssynergia, as possible contributors of pain during sexual intercourse, is also unclear. In our population, we were unable to show a significant relationship between dyspareunia and proctalgia fugax (P = .65), levator ani syndrome (P = .05), and pelvic floor dyssynergia (P = .21). Although there is a trend towards an association between levator ani syndrome, pelvic floor dyssynergia, and dyspareunia, we lacked statistical power to show a difference. A larger study comparing patients with dyspareunia using the Rome II criteria for levator ani syndrome and pelvic floor dyssynergia is warranted.

The limitations of this study include the lack of appropriate control subjects. The ideal control subjects would be age-equivalent females without pelvic organ prolapse or urinary incontinence. This limitation prevents us from drawing definitive conclusions about the impact of constipation or any of the functional bowel disorders on pelvic organ prolapse or urinary incontinence. A second limitation is the lack of differentiation between the types of urinary incontinence. Knowledge of the types...
of urinary incontinence would be useful in drawing conclusions about their relationship to bowel and ano-
rectal dysfunction because the pathogenesis of stress urinary incontinence is largely attributed to a disruption of anatomic support of the bladder neck, while that of urge incontinence is believed to be neurogenic in origin.

Another limitation includes the lack of anorectal physiology studies in our subjects. Such testing is useful in documenting the presence and/or cause of certain anorectal disorders. Endoanal ultrasound may identify the presence of anatomic sphincter disruption. Defecography may identify intussusception as a cause of constipation. The Rome II criteria require the presence of abnormal relaxation or paradoxic contraction of the puborectalis muscle based on physiologic testing to verify the diagnosis of pelvic floor dyssynergia. Anorectal physiologic testing would provide better objective evidence of the presence of disorders.

In order to improve outcomes in women suffering from pelvic floor disorders, we must have a thorough understanding of the pathophysiology of the pelvic floor. This includes disorders of the lower bowel, rectum, and anus. These disorders are key contributors to the symptom complex reported by women in this population. Identification of such disorders may allow gynecologists to offer improved nonsurgical and surgical treatments to selected women.

References

Suburethral sling materials: Best outcome with autologous tissue

Amanda J. Simsiman, MD,a,b,c Curt R. Powell, MD, b Ryan R. Stratford, MD, c Shawn A. Menefee, MDa,c,*

Division of Female Pelvic Medicine and Reconstructive Surgery, Kaiser Permanente Medical Centera; Department of Urology, Naval Medical Centerb; Department of Reproductive Medicine, University of California San Diego,c San Diego, CA

Objective: This study was undertaken to assess the outcome of suburethral slings by type of sling material.

Study design: A retrospective review of women who underwent a suburethral sling between January 1997 and January 2003 with autograft, allograft or xenograft materials. Objective failure was defined as urinary leakage with cough stress testing at any time after 3 months, postoperatively. Objective cure was defined as no leakage with a standing cough stress test with at least 200 mL bladder volume at a minimum of 12 months postoperatively. Data were analyzed using Student t, Wilcoxon rank sum, and Kaplan-Meier survival tests.

Results: A total of 241 women were included in this study: 78 received autograft, 80 received allograft, and 83 received xenograft. Objective failure was 36% and 46% for allograft and xenograft, respectively compared with 13% for autograft (P < .001).

Conclusion: Autograft has a significantly higher cure rate when used for suburethral slings.

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The best long-term results for urinary stress incontinence surgery are observed with the retropubic urethropexy or suburethral sling procedures.1 Once considered only for recurrent incontinence or intrinsic sphincter deficiency, slings are now accepted as a primary procedure. Materials used in performance of slings have included autologous rectus fascia or fascia lata, allograft, or xenograft. There is extensive evidence in the literature supporting the use of native tissue with cure rates ranging from 80% to 93%.2 The use of non-autologous materials is popular and attractive because it decreases operative time and avoids the possible morbidity associated with a second surgical site.3 However, the efficacy of these materials for use as a sling has yet to be determined. There have been conflicting reports in the literature on whether outcomes are compromised with the use of cadaveric fascia, and there is a paucity of data on the use of porcine dermis for slings.4 The aim of this study is to report on our experience using autograft, cadaveric fascia, and porcine dermis as sling material for the treatment of stress incontinence.
Materials and methods

The Institutional Review Boards approved the study. Data were extracted from the San Diego Pelvic Floor Consortium database on all women who underwent a suburethral sling from January 1997 to January 2003 at Naval Medical Center San Diego and Kaiser Permanente Medical Center. Sling material consisted of autograft (rectus fascia or fascia lata), allograft (cadaveric fascia lata), and xenograft (porcine dermis). Cadaveric fascia was freeze-dried and irradiated (Allosource, Denver, CO). The porcine dermis used was Pelvicol, a cross-linked acellular collagen matrix (Bard, Covington, GA). The selection of the sling material for surgery was made by the patient after the study surgeon reviewed with her the options for materials. Of note, autologous tissue was uniformly offered throughout the study period. Allograft was initially offered during the early years of the study period; however, as data was published suggesting decreased efficacy with this material, we then transitioned to offering porcine dermis.

Preoperative evaluation included history, standardized written questionnaire, urogenital examination (including pelvic organ prolapse quantification [POP-Q] assessment), Q-tip angle, stress test, and multichannel urodynamics.5 All patients had demonstrated stress urinary incontinence on filling cystometry and stress testing.

Surgies were performed primarily by a resident surgeon under the supervision of 1 of 3 attending surgeons (A.J.S., C.R.P., S.A.M.). The senior surgeon (S.A.M.) had proctored the other 2 attendings over a 2- to 3-year period therefore techniques were similar. The slings were secured abdominally by tying the polypropylene attachment sutures across the rectus muscle, as described by McGuire, or by directly attaching the sling to Cooper's ligament, as described by Koduri.6,7 Each of the surgeons performed the different attachment methods. Autologous tissue sling varied in length from 8 to 12 cm, and in width from 1.5 to 2 cm. Cadaveric tissue was standardized at 10 cm length \(\times\) 2 cm width. Porcine dermis sling length was 12 cm and the width ranged 1.5 cm to 2 cm. The ends of the autologous and cadaveric tissue were folded over before suture placement to reduce risk of suture pull-through. In all cases, suture material for sling attachment was permanent 0-gauge.

Postoperative assessment was performed at 3, 6, and 12 months and annually thereafter. The evaluation included a history via standardized written questionnaire, physical examination, cough stress test, and Q-tip test. Objective failure was defined as any leakage of urine with cough stress test. Objective cure was defined as no leakage with standing cough stress test with a minimum of 200 mL bladder volume. Subjective failure was defined as a positive response to the question “do you ever leak with activity, cough or sneeze?” on a standardized written pelvic floor questionnaire, which had undergone face validation. A patient was not considered objectively cured until they were followed at least 12 months postoperatively; failures could be reported at any postoperative time period after 3 months with last observation carried forward (LOCF) as a failure.

Statistical analysis was performed with the use of \(t\) tests and Wilcoxon rank sum tests to compare the groups with respect to age, BMI, parity and concomitant surgery, and failure. Logistic regression analysis was used to determine the confounding effects of age, parity, body mass index (BMI), prior surgery, or sling material. Kaplan-Meier analysis was performed to assess sling “survival” over time on the basis of material group.

Results

Three hundred fifty-four patients underwent suburethral slings, with nonsynthetic material, for stress urinary incontinence from January 1997 to January 2003 at Naval Medical Center San Diego and Kaiser Permanente San Diego. Two hundred forty-one patients (68%) had a minimum of 12 months postoperative follow-up, or had failed before 1-year assessment thus qualifying them to be included in the outcome as LOCF.

Of the 241 patients, 78 received autograft, 80 received allograft, and 83 received xenograft. Of the 241 patients, 10 underwent sling takedown (4 autograft, 4 allograft, 2 xenograft).

<table>
<thead>
<tr>
<th>Table I</th>
<th>Demographics</th>
<th>Autograft</th>
<th>Allograft</th>
<th>Xenograft</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>55 ± 10</td>
<td>59 ± 11</td>
<td>57 ± 10</td>
<td>&lt; .05 autograft vs allograft</td>
<td></td>
</tr>
<tr>
<td>Mean BMI</td>
<td>28 ± 6</td>
<td>30 ± 6</td>
<td>30 ± 6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Median parity</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Prior surgery</td>
<td>24%</td>
<td>25%</td>
<td>14%</td>
<td>&lt; .05 xenograft vs autograft and allograft</td>
<td></td>
</tr>
<tr>
<td>Attachment to rectus</td>
<td>74%</td>
<td>84%</td>
<td>57%</td>
<td>&lt; .05 xenograft vs allograft and autograft</td>
<td></td>
</tr>
<tr>
<td>Concomitant surgery</td>
<td>77%</td>
<td>82%</td>
<td>81%</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
and 2 xenograft) for prolonged postoperative voiding dysfunction or persistent irritative symptoms and their data will be presented separately. Therefore, the outcomes analysis is reported for 231 patients.

Patients had a mean age of 56 years, median parity of 3 and mean BMI of 30 kg/m$^2$ (Table I). The autograft and xenograft groups were similar for these characteristics, with the only exception being that the allograft group tended to be slightly older ($P < .05$). Of the xenograft group, 12% had undergone prior pelvic reconstructive surgery compared with 24% in the other groups ($P < .05$). Preoperative straining Q-tip angles ranged from 0 degrees to 90 degrees, with just 9 patients whose angle was less than 30 degrees. There were no differences between groups in concomitant surgery rates (81% of the autograft group vs 84% in the other 2 groups). There were more slings attached to Cooper’s in the xenograft group ($P < .05$). Preoperative straining Q-tip angles ranged from 0 degrees to 90 degrees, with just 9 patients whose angle was less than 30 degrees. There were no differences between groups in concomitant surgery rates (81% of the autograft group vs 84% in the other 2 groups). There were more slings attached to Cooper’s in the xenograft group ($P < .05$). Logistic regression, performed as a forward conditional analysis, with BMI, age, parity, prior surgery, sling material, and attachment site as independent variables, revealed that attachment site was not an independent predictor of continence.

Objective and subjective continence outcomes outlined in Table II indicate that patients undergoing sling with allograft or xenograft were more likely to experience failure to correct their incontinence than women undergoing the same procedure with autograft. The Figure illustrates sling survival by group. The Kaplan-Meier curve by group. 3 = xenograft; 2 = allograft; 1 = autograft.

Two of the 9 (22%) failures in the autologous group, 10 of 25 (40%) in the allograft group, and 12 of 34 (35%) in the xenograft group have undergone retreatment for stress incontinence. Of those 24 who underwent retreatment, 17 received bulking agents. There was no statistical difference with respect to retreatment between the groups.

Ten patients underwent vaginal urethrolysis (4 autograft, 4 allograft, and 2 xenograft) for persistent voiding dysfunction or worsened irritative symptoms (NS). Before urethrolysis, these patients had been managed with clean intermittent catheterization and anticholinergics, respectively. Of these 10 patients, 9 had follow-up and 6 remained continent with resolution of voiding difficulties (2 autograft, 2 allograft, and 2 xenograft).

Postoperatively, the range of straining Q-tip angles for the cured group was −20 degrees to 80 degrees, with 110 of 134 (82%) being less than 30 degrees. For the failure group, the range was 0 to 80 degrees, with 40 of 60 (66%) being less than 30 degrees. There was no difference between the material groups with respect to postoperative straining angles.

Intraoperative complications were rare. One ureteral injury required reimplantation in the autograft group but was likely related to an uterosacral ligament suspension. Four cystotomies occurred: 3 in the autograft group and 1 in the allograft group. Immediately postoperatively, there was 1 deep venous thrombosis (autograft). We did not reliably note minor postoperative complications such as lower urinary tract infections and wound seromas and therefore cannot comment on any group differences.

Comment

Women in this series undergoing suburethral sling with either allograft or xenograft were more likely to experience recurrence of their incontinence than women undergoing the same procedure with autograft. Given that it is estimated that more than 200,000 women undergo surgery for incontinence annually in the United States, understanding how different materials behave is critically important.

The failure rates, particularly subjective, in this study may seem high. We attempted to strive for stringent criteria, requiring cure to mean dry, not merely improved. This is supported by the finding that only 35% (24/68) of the total objective failures sought retreatment; thus many
of the “failures” may have been minimally bothered. Other studies, when using stringent criteria, have found similar rates. Hilton and Ward reported 43% cure for tension-free vaginal tape (TVT) and 37% for Burch when considering subjective cure for stress incontinence.

There is significant evidence in the literature to support the use of autologous tissue for slings. However, the use of autologous tissue adds an operative site, increases surgical time, may increase hospitalization time, and may not provide a graft of adequate size or strength. For these reasons, alternatives such as allograft or xenograft materials have become popular options.

Allografts have been used for several years for other surgical procedures, most notably in orthopedics. There is significant literature to support its safety and lack of antigenicity. Data on surgical outcomes for its use in incontinence surgery, however, are conflicting. Fitzgerald et al concluded that allograft should not be used for slings on the basis of several early failures they noted with use of solvent-dehydrated cadaveric fascia. O’Reilly and Govier reported on 8 women who had received fresh frozen cadaveric fascial slings and had recurrent stress urinary incontinence at a mean of 6.5 months. Alternatively, other authors have found more favorable results. Handa et al reported on a 79% objective cure rate. Flynn and Yap, also in a retrospective review, found similar cure rates in comparison to autologous tissue, however, with less postoperative pain and disability.

The literature is just as unclear regarding the outcomes with porcine dermis slings. Arunkalaivanan and Barrington prospectively randomly assigned 142 women to receive either Pelvicol (Bard) or TVT (Gynecare) and followed them by postal questionnaire. At a mean follow-up period of 12 months, patients in the Pelvicol group reported an 89% cure rate versus 85% in the TVT group (NS). At 3 years, the same group of patients had similar self-reported cure rates. Dikranian et al reported on 20 male patients who underwent porcine dermal slings and found just a 56% cure rate.

Failures of these tissues may be explained by their biomechanical properties. Dora et al implanted several materials into the rabbit, then harvested and compared them with baseline. They found that human cadaveric fascia and porcine graft decreased markedly in tensile strength and stiffness (60%-89%) from baseline. In contrast, autologous tissue did not differ from baseline. Although the contribution of tensile strength to success has not been established, it is credible that it would be a significant factor. However, it does not appear to be the only factor, as we would have expected to see more urethral hypermobility in the allograft and xenograft groups were that true.

There are limitations to this study, particularly its retrospective nature that may impart bias in the results. However, statistical analysis revealed that the groups were similar, except for age. Although a randomized controlled trial would be the preferred method to evaluate these materials, we do not believe embarking on that would be appropriate on the basis of these findings. In addition, the failure to assess postoperative satisfaction with a validated questionnaire limits our ability to comment on the amount of bother in those objective failures. Finally, the postoperative examiner may have been the patient’s surgeon, and thus was not always blinded.

In a recent editorial, Walters questioned the use of allograft and xenograft given the paucity of available data. He called for more studies to be performed. This study adds to the body of literature on sling materials. Of the nonsynthetic material options, autologous tissue appears to offer the only acceptable cure rates in our patient population.

References

14. Arunkalaivanan AS, Barrington JW. Randomized trial of porcine dermal sling (Pelvicol implant) vs. tension-free vaginal tape (TVT)


Removal of the retained cervical stump

Wesley S. Hilger, MD, a,* Antonio R. Pizarro, MD, b Javier F. Magrina, MD a

Department of Gynecology, Mayo Clinic, Scottsdale, AZ a; Shreveport, LA b

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Objective: The purpose of this study was to identify indications for and complications of abdominal or vaginal surgical removal of the cervical stump after previous supracervical hysterectomy.

Study design: This was a retrospective chart review of trachelectomy patients at Mayo Clinic, Rochester, Minnesota, or Mayo Clinic, Scottsdale, Arizona, between January 1974 and December 2003.

Results: Of 335 patients with a history of supracervical hysterectomy who subsequently required trachelectomy, 25 were excluded from study. Half of the remaining 310 patients had trachelectomy between 1974 and 1983, an average of 26 years after hysterectomy. The indication in three quarters of trachelectomies performed vaginally was prolapse. The vaginal approach had significantly fewer complications than the abdominal approach.

Conclusion: Removal of the cervical stump is infrequent and has declined over a 30-year period. The decline in trachelectomy may be because of a decreasing number of supracervical hysterectomies performed. When trachelectomy is performed vaginally, prolapse is the most common indication, and there are few complications.

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In recent years, there has been a renewed interest in supracervical hysterectomy and the rate of patients having this procedure has tripled. 1-3 Advocates of supracervical hysterectomy hypothesize that removing the entire cervix may diminish sexual response, urinary function, and pelvic support while increasing operative complications and time. 2,3 However, some studies contradict these claims. 4,5

Hysterectomy patients should be counseled about the risks and benefits of removing or retaining the cervix before the procedure. One study found that only 17% of physicians provide such counsel to their patients. 6 Operative time, blood loss, and recovery time are substantially reduced in patients who undergo supracervical hysterectomy compared with total hysterectomy. 5,7,8 The use of medical care resources at 12 months or 24 months is comparable between patients undergoing either procedure. 9 Studies which have randomly assigned patients to total hysterectomy or supracervical hysterectomy have found no differences in bladder, bowel, or sexual function. 5,7,10

The definitive difference between a supracervical and a total hysterectomy is the retained cervical stump. Okaro et al 11 recently reported that 22.8% of patients...
who had laparoscopic supracervical hysterectomy for pain later required removal of the cervical stump (trachelectomy). Although the benefit of maintaining the cervical stump is debatable, little data exist on the adverse consequences of its removal.

The purpose of our study was to identify and analyze the indications for abdominal or vaginal trachelectomy, and to identify any complications of these procedures conducted at our tertiary-care medical clinic during a 30-year period.

### Material and methods

After approval by the Mayo Foundation Institutional Review Board, a retrospective chart review was undertaken of all patients who underwent trachelectomy by the abdominal or vaginal route at Mayo Clinic, Rochester, Minnesota, or Mayo Clinic, Scottsdale, AZ, for the 30-year period between January 1974 and December 2003. A total of 335 patients were identified, 25 of whom were excluded for various reasons (19 because the uterus was left intact, 4 because removal was by laparoscopy, and 2 because the records were unavailable).

Data abstracted from the 310 cases reviewed included the date of the trachelectomy; patient age, parity, height, and weight at the time of surgery; year and indication of supracervical hysterectomy; indication and route of trachelectomy; estimated blood loss; length of postoperative stay; concomitant procedures; cervical histology; extracervical histology; and complications.

### Results

Table I summarizes the age, parity, body mass index, estimated blood loss (EBL), hospital stay, and years since the supracervical hysterectomy for all 310 patients, both those who had the cervix removed vaginally and those who had it removed abdominally. Those who had the cervix removed vaginally were older, had less blood loss, a shorter hospital stay, and a longer interval between supracervical hysterectomy and trachelectomy. The indication for supracervical hysterectomy was documented for 64% (197/310) of the patients. The reasons indicated for supracervical hysterectomy included fibroids 44% (87/197), bleeding 24% (48/197), cancer 11% (21/197), cesarean hysterectomy 9% (18/197), pelvic mass 9% (18/197), endometriosis 8% (16/197), pain 7% (14/197), other 6% (12/197).

The number of trachelectomies performed either abdominally or vaginally over 5-year intervals showed a decline over time (Table II). The indications for trachelectomy were noted in Table III. Prolapse was the most common indication overall 52% (161/310) and for the vaginal group 74% (150/202), while pelvic mass was the most common indication in the abdominal group 65% (70/108).

The average time elapsed between a supracervical hysterectomy and trachelectomy for patients with prolapse as an indication was 31.1 years (SD 12.9 years) compared with 20.7 years (SD 16.3 years) for patients with other indications ($P < .001$). The time interval from a supracervical hysterectomy to trachelectomy in

### Table I  Characteristics of trachelectomy patients by surgical approach

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abdominal (n=108)</th>
<th>Vaginal (n=202)</th>
<th>Total (n=310)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58.4 (15.1)</td>
<td>67.2 (11.3)</td>
<td>64.1 (13.4)</td>
</tr>
<tr>
<td>Parity (no.)</td>
<td>2.2 (2)</td>
<td>2.3 (1.9)</td>
<td>2.3 (2)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.7 (7.4)</td>
<td>26.6 (6.3)</td>
<td>26.7 (6.7)</td>
</tr>
<tr>
<td>EBL (mL)</td>
<td>605.6 (689.5)</td>
<td>193.2 (156)</td>
<td>338.7 (470.5)</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>8.2 (3.5)</td>
<td>6.4 (4.6)</td>
<td>7 (4.4)</td>
</tr>
<tr>
<td>Interval since hysterectomy (y)</td>
<td>19 (16.3)</td>
<td>29.9 (13.6)</td>
<td>26.1 (15.5)</td>
</tr>
</tbody>
</table>

* Values are mean (SD).

### Table II  Trachelectomies over time (5-year intervals)

<table>
<thead>
<tr>
<th>Time period</th>
<th>Abdominal (n=108)</th>
<th>Vaginal (n=202)</th>
<th>Total (n=310)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974 to 1978</td>
<td>28 (26)</td>
<td>62 (31)</td>
<td>90 (29)</td>
</tr>
<tr>
<td>1979 to 1983</td>
<td>19 (18)</td>
<td>43 (21)</td>
<td>62 (20)</td>
</tr>
<tr>
<td>1984 to 1988</td>
<td>20 (19)</td>
<td>24 (12)</td>
<td>44 (14)</td>
</tr>
<tr>
<td>1989 to 1993</td>
<td>13 (12)</td>
<td>27 (13)</td>
<td>40 (13)</td>
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<tr>
<td>1994 to 1998</td>
<td>16 (15)</td>
<td>28 (14)</td>
<td>44 (14)</td>
</tr>
<tr>
<td>1999 to 2003</td>
<td>2 (2)</td>
<td>9 (4)</td>
<td>11 (4)</td>
</tr>
</tbody>
</table>

* Values are number (percentage).

### Table III  Indications for trachelectomy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Abdominal (n=108)</th>
<th>Vaginal (n=202)</th>
<th>Total (n=310)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolapse</td>
<td>11 (10)</td>
<td>150 (74)</td>
<td>161 (52)</td>
</tr>
<tr>
<td>Pelvic mass</td>
<td>70 (65)</td>
<td>8 (4)</td>
<td>78 (25)</td>
</tr>
<tr>
<td>Abnormal Pap</td>
<td>7 (6)</td>
<td>29 (14)</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>9 (8)</td>
<td>19 (9)</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (13)</td>
<td>9 (4)</td>
<td>23 (7)</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>13 (12)</td>
<td>9 (4)</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Noncervical cancer</td>
<td>18 (17)</td>
<td>1 (0)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>5 (5)</td>
<td>4 (2)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Multiple indications</td>
<td>33 (31)</td>
<td>23 (11)</td>
<td>56 (18)</td>
</tr>
</tbody>
</table>

* Values are number (percentage).
patients with cancer of the cervix as a diagnosis was 20.7 years (SD 16.2 years) versus 26.8 years (SD 15.3 years) in patients without that diagnosis ($P = .03$).

Concomitant procedures were performed in 85% (263/310) of all patients, in 79% (159/202) of patients who had a vaginal approach, and in 96% (104/108) of patients who had an abdominal approach. The 3 most common concomitant procedures performed in the 202 patients who had vaginal removal were rectocele repair (62%), cystocele repair (60%), or enterocele repair (45%). The 3 most common concomitant procedures for the 108 patients who had abdominal removal were oophorectomy (61%), bowel resection (27%), or a non-gynecologic operation (25%).

Two thirds of the available 309 cervical specimens, whether removed vaginally or abdominally, were found to be abnormal (Table IV). Extracervical disease was found in 73% of the 108 abdominal cases. The 3 most common extracervical histologic findings were cancer (25%), benign cyst (24%), or other (7%). Less than 6% of vaginal cases had extracervical pathologic findings and included benign cyst (2%), endometriosis (1%), noncervical cancer (1%), and other (1%).

Intraoperative and perioperative complications (Table V) were more common when the cervical stump was removed by an abdominal approach than a vaginal approach (43% vs 20%; $P < .001$). Of the 47 patients who only had a trachelectomy and no additional procedure, 93% (44/47) had no complication, 4% (2/47) developed an infection, and 2% (1/47) had perioperative bleeding.

**Comment**

At our clinic, trachelectomy is performed infrequently, and the number of procedures has declined during the past 30 years. Almost half of all 310 patients who were identified had a trachelectomy between 1974 and 1983. This decline may reflect the decrease in the number of supracervical hysterectomies performed in the decades before 1974 and has been noted in other studies of that era. The mean time between a hysterectomy and removal of the cervical stump has been reported to be 30 years, which is consistent with our findings.

The most common indication for trachelectomy was prolapse but indications varied considerably, depending on the surgical approach. Our finding that abdominal trachelectomy was generally an incidental procedure is consistent with other reports. We found that vaginal removal was associated in most cases with pelvic floor relaxation. This rate of occurrence is in agreement with other studies that identified prolapse as an indication for trachelectomy in 45% to 85% of patients.

Even after supracervical hysterectomy and the best efforts to remove or cauterize the endocervical canal, cyclical bleeding may continue in 6.8% to 19% of patients. Vaginal bleeding was an indication in 9% of our patients, although we could not assess which percentage was cyclical. Some authors have reported that patients with persistent cyclical bleeding after supracervical hysterectomy required subsequent trachelectomy because the bleeding continued or extent of bleeding was not acceptable. Thus, patients who are contemplating a supracervical hysterectomy to eliminate vaginal bleeding should be counseled that cyclical bleeding may persist and may necessitate another procedure.

Trachelectomy appears to have few complications. The fewer procedures performed during trachelectomy, and those removed vaginally, resulted in fewer complications in our population. This low complication rate is consistent with what has been described in other studies. Of note is that in 202 vaginal trachelectomies only 1 subject sustained an injury to the bowel, which was repaired intraoperatively. All operative reports were reviewed and the technique for removal was consistent over time. It appears that careful dissection of the cervix and identification of the ureters by visualization or palpation are essential for avoiding damage to

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Histologic characteristics of cervical stumps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finding</strong></td>
<td><strong>Abdominal</strong> (n=107)</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>55 (51)</td>
</tr>
<tr>
<td>Normal</td>
<td>34 (32)</td>
</tr>
<tr>
<td>Squamous dysplasia</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fibroids</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

* Values are number (percentage).

<table>
<thead>
<tr>
<th>Table V</th>
<th>Surgical or postoperative complications for trachelectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complication</strong></td>
<td><strong>Abdominal</strong> (n=108)</td>
</tr>
<tr>
<td>None</td>
<td>62 (57)</td>
</tr>
<tr>
<td>Infection</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Perioperative bleeding</td>
<td>24 (22)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>4 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Intraoperative injury</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

* Values are number (percentage).
surrounding structures. Urinary retention occurred in 6% of patients but all had a concomitant anterior colporrhaphy and Kelly-Kennedy plication, which was more likely the cause of this complication. The length of stay for patients in our vaginal group was longer than current lengths of stay for similar patients, which may reflect the nature of medical practice over the past 30 years or the fact that our institution is a tertiary-care clinic receiving most patients by referral.

Most of the cervical stump specimens had abnormal pathologic findings. However, cervicitis was the most common histologic diagnosis (more than 50% of patients), and it was most likely of little clinical consequence. Cervical dysplasia or cancer accounted for 12% of our cases, much less than the 27% reported in a previous series, probably because of better surveillance for cervical cancer. This estimated risk of cancer of the cervical stump is equivalent to that of vaginal cuff carcinoma in a screened population. The time interval between supracervical hysterectomy and cervical stump cancer was 20.7 years in our group of patients, which is somewhat longer than the 17.6 years noted by others. Patients treated for cervical stump carcinoma are typically 10 years older or have a higher rate of complications after radiotherapy or surgery than those treated for cervical cancer of the intact uterus; however, survival is equal. Thus, vigilance in screening for cervical cancer is essential in patients who have had a supracervical hysterectomy.

In our patients, pelvic relaxation was the most common reason for removing the cervical stump. No studies have examined whether retaining the cervix will prevent prolapse. One randomized trial noted that 2% of patients in the supracervical group had prolapse, whereas none in the total abdominal hysterectomy group had prolapse 1 year after surgery. Whether retaining the cervical stump helps prevent prolapse cannot be ascertained from our study. Prolapse was not an indication for supracervical hysterectomy in any of the patients, and this may indicate that prolapse can develop overtime even in patients who appear to have a well-supported cervix at the time of the hysterectomy. Because of the long interval (average, 31 years) between hysterectomy and removal of the cervical stump for prolapse in our patient population, this would be difficult to ascertain in a prospective study.

Subsequent trachelectomy should be considered a complication of supracervical hysterectomy. Some patients should not have a supracervical hysterectomy because of the greater likelihood they will require further surgery. In an effort to avoid this complication, some authors have advocated avoiding supracervical hysterectomy in patients with a history of pelvic pain, endometriosis, or cervical dysplasia. Similarly, patients with menorrhagia should be counseled about the possibility of persistent spotting or cyclical bleeding despite removal of the uterus. Because this bleeding may be unacceptable for some patients, acknowledging the possibility may help avoid the need for future removal of a retained cervical stump.

The deficiencies of our study are what might be expected from a retrospective chart review, which only allows observations rather than definitive statements. Changes over time in surgical practice and in practitioners could also alter the findings of our study. Nonetheless, the strengths of the study are the large number of cases for an uncommon procedure at a single institution.

Trachelectomy is performed infrequently but appears to be a safe procedure, especially when performed for the most common indication, prolapse of the cervical stump. Current data do not support many of the proposed benefits for retaining the cervical stump at the time of a hysterectomy. Future data should be accumulated and analyzed to determine whether a retained cervix does aid pelvic support and prevent pelvic prolapse. In the meantime, practitioners should counsel patients about the risks and benefits of retaining the cervix during a hysterectomy and then removing it later if necessary.

References

Predicting uterine weight before hysterectomy: Ultrasound measurements versus clinical assessment

Tarek S. Harb, MD, Rony A. Adam, MD

Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, GA

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Objective: The purpose of this study was to determine the most accurate method in estimating the preoperative uterine weight of enlarged nongravid uteri.

Study design: We performed a retrospective review of 1238 patients who were premenopausal and underwent hysterectomy for benign indications between January 1993 and July 1999. Eight hundred and sixty-four patients were selected to include only those that had both a reported bimanual assessment of preoperative uterine size and an ultrasonography report with all 3 estimated uterine dimensions. Reported uterine sizes on bimanual examination were converted to clinical weight (CWT). Two different calculations were used to estimate uterine weight from ultrasound measurements (UWT 1 and 2). Actual uterine weights (AWT) in pathology reports were then compared with the findings of bimanual assessment and the calculated weights to determine which method is the best predictor of AWT. Simple linear regression analysis was used to measure and compare how closely the estimated weights predicted the actual weight. Predictive residuals sum of squares (PRESS) was then used to determine the best predictor of actual weight.

Results: After exploring the data using linear modeling, all 3 estimated weights were significantly correlated to the actual weight when compared, but PRESS scores showed that the clinical weight estimate was superior by far compared with the other 2.

Conclusion: In this study, bimanual assessment was shown to be the most accurate method of preoperative uterine weight estimation. Ultrasound examination may not be routinely needed when deciding the route of hysterectomy based on estimated weight.

KEY WORDS
Uterine weight
Ultrasound estimation
Clinical evaluation

Every year more than 590,000 American women undergo hysterectomies, making the procedure the second most common major surgery among reproductive age women in the United States, resulting in an estimated cost exceeding $5 billion. The vast majority of these surgeries are performed for benign conditions. Increased uterine size has been shown to increase the risk for complications among women undergoing hysterectomy. The size or estimated weight of the uterus is also a major determinant of the choice of surgical procedure, which also affects the risk for complications. The traditional assessment of uterine size relies on bimanual examination. Ultrasound examination is commonly used to confirm bimanual assessments, but it is not clear if ultrasound studies add to clinical information. In most cases, the ultrasound confirms the clinical findings and adds cost.
The purpose of this study is 4-fold: 1) to assess the accuracy of a preoperative bimanual examination in estimating the uterine weight of enlarged nongravid uteri; 2) to determine the accuracy of preoperative ultrasound in estimation of the uterine weight of clinically enlarged nongravid uteri using a previously published formula; 3) to determine the validity of its simplified version; and 4) to determine the most accurate method of preoperative estimation of uterine weight.

Material and methods

Setting

Grady Memorial Hospital is a community-based teaching hospital with one of the largest gynecologic surgical services in Georgia. Senior residents perform all hysterectomies under direct supervision of the attending physicians.

Selection of patients

Using the hospital Star database for surgical procedures and logs, all hysterectomies performed at Grady Memorial Hospital (GMH) between January 1993 and July 1999 were identified. A retrospective chart review of the 1898 patients identified was performed. Of these patients, 1238 were premenopausal and had benign indications for hysterectomy, including symptomatic fibroids, pain, abnormal bleeding, and anemia. All of these patients met the selection criteria of having had a Pap smear and an endometrial biopsy (EMB) within 1 year of surgery with no evidence of invasive carcinoma. A total of 864 patients had a clinical assessment of uterine size and all 3 ultrasound measurements documented in the chart, and were therefore available for analysis.

Techniques and methods

Bimanual examinations were performed by a senior resident and the findings confirmed by an attending physician. For uterine sizes estimated to be within a range, the mean was used (eg, 10-12 weeks was used 11 weeks). The uterine size estimates were then converted to weights. The clinical weights (CWT) were derived from the most recently published study allowing for conversion from “weeks” to estimated uterine weights. Because all previously published data used only week numbers that were even, all the odd week numbers were converted to the closest higher even number in the data analysis (eg, 9 weeks was considered to be 10 weeks).

A transabdominal ultrasound was performed with a 3.5 mHz linear and sector transducer to determine all 3 uterine dimensions. A transvaginal ultrasound, using a multifrequency 5.0 to 9.5 mHz transducer, was only performed when deemed necessary by the ultrasonogra-

The uterine length (L) was the distance between the external cervical os to the dome of the fundus; the maximum width (W) and anteroposterior (AP) diameter were taken perpendicular to the axis of the uterine length. The ultrasound estimated uterine weight (UWT) was derived from the algebraic formula by Kung and Chang expressed in weights and measurements: weight (g) = 50 + (4/3 × π × L/2 × W/2 × AP/2), which will be designated in this study as UWT 1. This formula was further simplified to: weight (g) = L × W × AP × 0.52, which will be referred to as UWT 2. Estimated weights using these 2 formulas were then compared separately to the actual weights (AWT) to determine their accuracy.

Actual uterine weights and dimensions were obtained from the pathology reports. All uteri were weighed after the adnexal structures were removed.

Statistical analysis

Simple linear regression analysis was used after logarithmic transformation to measure and compare how closely the estimated weights, by clinical exam and ultrasound, predicted the actual weight. Predictive residuals sum of squares (PRESS) was used to determine the best predictor of actual weight. PRESS statistics looks at the effectiveness of a predictive model for predicting unobserved results. A low PRESS score indicates that the model is very good at predicting future events.

Results

Of the 1238 women who underwent hysterectomies for benign indication over the 6 and a half year period at GMH, 92.2% (n = 1141) were African American, 4.5% (n = 56) were Caucasian, 0.9% (n = 11) were Hispanic, and 0.3% (n = 4) were Asian. Of those, 864 patients had ultrasound measurements of all 3 uterine parameters (L, W, AP). The number was further reduced to 718 to only include patients with clinical uterine size between 9 and 20 weeks of estimated gestational size. There are no reliable data available to convert the other uterine sizes (≤8 and >20 weeks) to weights in the literature used. When compared, there was a significant correlation (r = .72, P<.0001). The second estimated weight, UWT2, obtained using: weight (g) = L × W × AP × 0.52, is the simplified version of the formula used above, and is commonly used at GMH. This formula was used in our study to test for its validity. There was also a
significant correlation between the estimated and actual weight ($r = .71, P < .0001$). The estimated clinical weight (CWT) was obtained through preoperative bimanual assessment after converting the clinical size in weeks of gestation to weights using previously published data. A somewhat better significant correlation was obtained when comparing the clinically estimated weight to the actual weight ($r = .76, P < .0001$).

All 3 weight estimations indicated a strong, positive, linear association with the actual weight (Table I). PRESS scores revealed that all 3 models are very good at predicting future events but the CWT model with a PRESS score of 29.65 was superior compared with the other 2 (Table I).

Comment

The role of preoperative ultrasonography in patients undergoing hysterectomy for benign indication is controversial. In some practices, an ultrasound examination is commonly used to determine preoperative uterine weight to assist physicians in deciding the route of hysterectomy. Although common, the validity of such an evaluation has not been established.

Few studies in the literature have compared bimanual examination with other diagnostic methods with regard to predicting preoperative uterine weight in the nongravid uterus. Enlarged nongravid uterine size is estimated clinically by comparison with uteri of equivalent gestational size in pregnant women. Bimanual examination, uterine sounding, and ultrasonography were used to determine uterine size before hysterectomy in a previous study done by Flickinger et al in 1986. The estimated uterine weights were then compared with the actual uterine weight after hysterectomy. The use of bimanual examination and uterine sounding yielded greater error in estimation. However, the study only included 66 patients and assumed that all the uteri studied were ellipsoid in shape.

In 1989, the American College of Obstetrics and Gynecology (ACOG) published a conversion table between uterine weight and gestational size. This table has limited clinical value because the weights were derived from hysterectomies performed on gravid uteri after delivery. The derived weights do not correspond to uterine weights of nongravid patients.

In 1996, Kung and Chang in Taiwan studied the relationship between ultrasonic volume and the actual weight of the uterine specimen. Using linear regression analysis, they were able to derive a formula that converts volume to weight. This formula has been simplified and is commonly used. Knowing that the original formula gives among the best estimation of uterine weight, it was used in our study to assess its accuracy in comparison with bimanual examination. The simplified version was also tested in our study for its accuracy.

Cantuarria et al compared bimanual examination with ultrasound examination in determining the size of leiomyomatous uterus. They found a strong correlation between bimanual and ultrasound examinations with regard to determining the size, but weight estimation was not assessed. Mean uterine weights for uterine sizes between 10 and 20 weeks were measured from actual specimen weights. These measured weights were used in our study to convert clinical size into clinical weights. These conversion values were used in our study because these are the most recent published data.

Our study showed that all 3 weight estimates showed a high correlation when compared with the actual weight. PRESS statistics showed that clinical weight estimation was the best predictor of the actual weight, which was also confirmed by a validation test. The strengths of this study are its large sample size and the good correlation of the weight means to previously published data. It expands the data available to correlate uterine weights with uterine size estimates to encompass gestational sizes from 6 weeks to 26 weeks (Table II). The clinical estimates quoted for the purpose of the study were at the initial preoperative evaluation, at which time an ultrasound is routinely ordered. In rare situations, an ultrasound has been ordered before the preoperative evaluation for a different purpose. In such rare cases, the retrospective nature of the data collection precludes completely ruling out the possibility that

<table>
<thead>
<tr>
<th>Table I</th>
<th>Correlation analysis of outcome (AWT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r$</td>
<td>$r^2$</td>
</tr>
<tr>
<td>UWT1</td>
<td>0.72</td>
</tr>
<tr>
<td>UWT2</td>
<td>0.71</td>
</tr>
<tr>
<td>CWT</td>
<td>0.76</td>
</tr>
</tbody>
</table>

PRESS, Predictive residuals sum of squares.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Preoperative clinical uterine size along with mean uterine weight of specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Nongravid uterine size (wk)</td>
</tr>
<tr>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td>119</td>
<td>10</td>
</tr>
<tr>
<td>151</td>
<td>12</td>
</tr>
<tr>
<td>176</td>
<td>14</td>
</tr>
<tr>
<td>123</td>
<td>16</td>
</tr>
<tr>
<td>82</td>
<td>18</td>
</tr>
<tr>
<td>67</td>
<td>20</td>
</tr>
<tr>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>26</td>
</tr>
</tbody>
</table>

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clinical estimates were influenced by ultrasound reports that may have been noted at the time of the clinical evaluation. This remains the primary limitation of this study.

Although ultrasonography has proven valuable in many gynecologic situations such as assessment of adnexal masses, evaluation of endometrial lining, as well as estimation of uterine size in obese patients, its routine use to confirm the uterine size is questionable.

This study suggests that clinical evaluation of uterine size is at least as accurate as ultrasound evaluation when compared with actual uterine specimen weight. Because estimation of uterine size is often considered when determining the route of hysterectomy, careful consideration to the teaching of clinical skills allowing residents to accurately assess uterine weight is strongly encouraged.

References


Outcomes of vaginal reconstructive surgery with and without graft material

Babak Vakili, MD, a Trang Huynh, MD, b Holly Loesch, MD, b Nicholas Franco, MD, b Ralph R. Chesson, MD b

Department of Obstetrics and Gynecology, Division of Female Pelvic Medicine and Reconstructive Surgery, Cooper University Hospital, University of Medicine and Dentistry of New Jersey—Robert Wood Johnson School of Medicine, a Camden, NJ; Department of Obstetrics and Gynecology, Division of Urogynecology and Reconstructive Pelvic Surgery, Louisiana State University Health Sciences Center, b New Orleans, LA

Objective: This study was undertaken to evaluate the outcomes of vaginal surgery for pelvic organ prolapse, comparing cases implementing graft augmentation to those without graft augmentation.

Study design: This was a retrospective cohort study of 312 patients who underwent vaginal surgery for prolapse from February 1998 to January 2004.

Results: Of the 312 patients, 98 (31.4%) had graft augmentation. The median follow-up was 9 months (3-67 months). Graft use was not associated with reduction in recurrent prolapse, recurrent stage 3 prolapse, recurrent incontinence, or additional surgery for prolapse. After controlling for confounders, there was still no difference in surgical outcomes. Complications such as vaginal/graft infection (18.4% vs 4.7%; \( P < .001 \)) and granulation tissue (38.8% vs 17.3%; \( P < .001 \)) were more common after cases in which graft was used.

Conclusion: In the early postoperative period, there was no benefit in using graft for prolapse repair. Graft use leads to a higher rate of postoperative complications.

Pelvic organ prolapse (POP) is a very common condition that will affect as many as 50% of women in the United States. Approximately 11% of women will undergo surgery for POP at least once in their lifetimes.

When a patient elects to have surgery for POP, the route of surgery is often at the discretion of the operating surgeon. Advocates of abdominal surgery, who normally perform abdominal sacrocolpopexy (ASC) using mesh, contend that their repair is more durable because it is a compensatory surgery. A compensatory surgery is one that does not rely on the patient’s own tissue (ie, using graft to bolster the repair). Although there is some support for this contention, the topic remains controversial.

With few comparative trials assessing surgical outcomes, recommendations on surgical route are often based on preference. Advocates of vaginal surgery tout the advantages of diminished pain and quicker recovery. Patients may prefer vaginal surgery for cosmetics. Consequently, most surgical modifications for correction of prolapse have focused on vaginal procedures.

A rapidly evolving technique involves augmentation of vaginal repair by using graft material. There are many

Keywords: Pelvic organ prolapse, Vaginal surgery, Graft, Complications, Surgical outcome
different materials available, including both synthetic and biologic. The graft can be used to augment repair in the anterior or posterior vaginal wall. Although techniques may vary, graft is generally attached bilaterally to the pelvic sidewall (eg, arcus tendineus), creating a hammock to reinforce the native support tissue. This technique is therefore a compensatory repair. Results have been favorable, with anatomic success rates ranging from 59% to 94%.\textsuperscript{6-8} Unfavorable consequences do occur with reports of worsening dyspareunia\textsuperscript{8} and a higher incidence of recurrence in other vaginal compartments.\textsuperscript{9} The lack of comparative data and anticipated higher incidence of graft-related complications (ie, graft erosion and infection) has led to some debate among vaginal surgeons about the necessity of graft use. The purpose of this study is to see if graft augmentation improves surgical outcomes in vaginal surgery when compared with more traditional repair.

Materials and methods

Data were collected retrospectively from the office charts of patients having undergone surgery for POP from February 1997 to January 2004. The Institutional Review Board of the Louisiana State University Health Sciences Center granted approval for the study. Charts were systematically reviewed in all patients who underwent vaginal reconstructive surgery for prolapse during the indicated time interval by the 2 senior authors (R.R.C, N.F.).

Cases in which graft was used to support the anterior vaginal wall, posterior vaginal wall, or both defined the graft-augmented cases. These cases were compared with those in which restorative repairs (ie, no graft) were performed during the same interval. The choice of procedure (compensatory or restorative) as well as of graft material had been at the discretion of the primary surgeon. Patients were excluded if the procedure was oblitative (ie, colpocleisis). Cases were excluded from analysis if the operative report was not available. Only patients with at least 3 months of follow-up were included in the study.

The technique for anterior vaginal wall fixation involved fashioning a trapezoid shape from the graft to cover the entire vaginal wall. After opening the entire anterior vaginal wall through a midline incision, the graft was fixed bilaterally to the arcus tendineus fascia pelvis by using at least 3 permanent sutures on each side. The graft was fixed apically either to the vaginal apex or bilaterally to the uterosacral or sacrospinous ligaments if a concurrent vault suspension was performed. The technique was similar for posterior grafts, with lateral fixation to the arcus tendineus fascia rectovaginalis.

Data collected included demographic and background data, such as previous surgical history. The initial visit, operative report, and all postoperative visits were reviewed. Staging was by the Baden-Walker Halfway (BWH) system\textsuperscript{10} in most patients and the Pelvic Organ Prolapse-Quantification (POP-Q)\textsuperscript{11} system in some during this interval. Because it is easier to convert the POP-Q to the BWH and not vice versa, for the purpose of this article, all staging will be described according to the BWH system.

Patients were evaluated at each postoperative visit for recurrent pelvic floor disorders. Recurrent prolapse, defined as any descent of any compartment of the vagina below the normal anatomic position (greater than stage zero by the BWH system), was the primary outcome variable. Recurrent stage 3 prolapse was defined as any prolapse beyond the hymen. Recurrent incontinence was defined as any subjective incontinence recorded in the chart during the postoperative visits. Patients requiring additional surgery for POP or incontinence were identified only if the additional surgery was performed by 1 of the 2 primary surgeons.

Secondary outcome variables included graft-related complications such as granulation tissue, vaginal infection, and the need for surgical treatment of these complications. Follow-up interval was defined as the time interval (months) from surgery to the last postoperative visit. In the case of those patients who had additional surgery, the follow-up interval was defined as the time from initial surgery to the second surgery.

Statistics usage

Data were recorded in a paper database before compilation into a computer database (Microsoft Access, Microsoft Corp, Redmond, WA). Statistical analysis was performed with the use of Statistical Package for Social Sciences 11.0 for Windows (SPSS Inc, Chicago, IL). Student \textit{t} test was used to compare means for continuous variables. The \textit{\chi}^2 test was used to compare categorical data. Fisher exact test was performed when the assumptions for the \textit{\chi}^2 distribution were violated. The Mann-Whitney \textit{U} test was used to compare means when normality assumptions were violated. Logistic regression was used to create both univariate and multivariate models. A \textit{P} value less than .05 was considered significant.

Results

Of 502 patients undergoing surgery during this time frame, 441 had at least 1 postoperative visit. Another 34 patients who had abdominal surgery were also excluded from analysis. After excluding another 95 patients who had less than 3 months of follow-up, 312 patients were available for analysis. Demographic data for the cohort are described in Table I. Women in whom graft was used were older (and consequently menopausal), more parous, and more likely to have had posterior repairs.
and perineorrhaphies performed, while also having longer follow-up.

There were 98 patients who had 100 graft-augmented procedures as part of the vaginal repair. One surgeon (N.F.) performed the majority (n = 88) of the graft-augmented cases. All the procedures performed in this cohort are listed in Table II. The numerous different biomaterials used for graft augmentation are listed in Table III. Comparison of the numerous different graft materials used during this interval revealed no significant differences in any outcome or other variable. Analysis was limited because of the relatively small numbers in each group.

Comparison of recurrence rates based on location of graft use is provided in Table IV. There was a trend toward a decreased incidence of recurrent prolapse (18.2% vs 40.5%; \(P = .054\)) when a posterior graft was used, mainly because of a decrease in recurrent posterior vaginal prolapse (4.5% vs 23.0%; \(P = .064\)). Subanalysis comparing biologic (n = 92) with synthetic (n = 6) graft revealed no difference in surgical outcomes or complication rates.

Because there was no difference between graft materials used, all cases in which graft was used for prolapse repair were grouped together and compared with those undergoing restorative repair. The results are shown in Table V. There was no difference in any of the primary outcome measures assessing surgical outcome, even after controlling for confounders such as age, parity, follow-up interval, and surgical procedures. However, graft use was associated with more complications such as tissue granulation (38.8% vs 17.3%; \(P < .001\)) and

### Table I  Demographic data for the cohort

<table>
<thead>
<tr>
<th>Category</th>
<th>Graft (n = 98)</th>
<th>No Graft (n = 214)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65.4</td>
<td>60.7</td>
<td>.003</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.3</td>
<td>26.1</td>
<td>.892</td>
</tr>
<tr>
<td>Gravidity</td>
<td>3.6</td>
<td>3.4</td>
<td>.224</td>
</tr>
<tr>
<td>Parity</td>
<td>3.3</td>
<td>2.9</td>
<td>.018</td>
</tr>
<tr>
<td>POP-Q measurements (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aa</td>
<td>1.0</td>
<td>0.6</td>
<td>.508</td>
</tr>
<tr>
<td>Ba</td>
<td>3.2</td>
<td>2.7</td>
<td>.709</td>
</tr>
<tr>
<td>C</td>
<td>1.6</td>
<td>0.2</td>
<td>.828</td>
</tr>
<tr>
<td>GH</td>
<td>6.0</td>
<td>5.2</td>
<td>.265</td>
</tr>
<tr>
<td>PB</td>
<td>3.3</td>
<td>3.9</td>
<td>.639</td>
</tr>
<tr>
<td>TVL</td>
<td>7.5</td>
<td>8.3</td>
<td>.213</td>
</tr>
<tr>
<td>Ap</td>
<td>−0.4</td>
<td>−0.6</td>
<td>.403</td>
</tr>
<tr>
<td>Bp</td>
<td>1.2</td>
<td>0.7</td>
<td>.434</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td>.456</td>
</tr>
<tr>
<td>White</td>
<td>72 (73.5%)</td>
<td>147 (68.7%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>5 (5.1%)</td>
<td>6 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (3.1%)</td>
<td>7 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (18.4%)</td>
<td>54 (25.2%)</td>
<td></td>
</tr>
<tr>
<td>Previous hysterectomy</td>
<td>82 (83.7%)</td>
<td>163 (76.9%)</td>
<td>.172</td>
</tr>
<tr>
<td>Prior reconstructive</td>
<td>48 (49.0%)</td>
<td>80 (37.6%)</td>
<td>.057</td>
</tr>
<tr>
<td>tobacco use (n = 305)</td>
<td>8 (8.3%)</td>
<td>20 (9.6%)</td>
<td>.728</td>
</tr>
<tr>
<td>If yes, packs per day</td>
<td>1.0</td>
<td>1.0</td>
<td>.855</td>
</tr>
<tr>
<td>Menopausal</td>
<td>89 (92.7%)</td>
<td>173 (83.2%)</td>
<td>.025</td>
</tr>
<tr>
<td>If menopausal, % on HRT</td>
<td>61 (70.1%)</td>
<td>131 (76.6%)</td>
<td>.258</td>
</tr>
<tr>
<td>Concurrent anti-incontinence surgery procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>7 (7.1%)</td>
<td>23 (10.7%)</td>
<td>.316</td>
</tr>
<tr>
<td>Uterosacral ligament</td>
<td>45 (45.9%)</td>
<td>106 (49.5%)</td>
<td>.553</td>
</tr>
<tr>
<td>suspension</td>
<td>17 (17.3%)</td>
<td>18 (8.4%)</td>
<td>.020</td>
</tr>
<tr>
<td>Sacrospinous ligament</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior repair</td>
<td>37 (37.8%)</td>
<td>31 (14.5%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Perineorrhaphy</td>
<td>28 (28.6%)</td>
<td>30 (14.0%)</td>
<td>.002</td>
</tr>
<tr>
<td>Follow-up interval (mo)</td>
<td>11.6</td>
<td>15.0</td>
<td>.027</td>
</tr>
</tbody>
</table>

Means were compared by using independent sample t test, except where noted. Categorical data were compared with the use of χ² test. HRT, Hormone replacement therapy.

* Point D was not included in analysis because it was measured in only 1 case with graft use.

\(^{1}\) Mann-Whitney U test.

### Table II  Reconstructive procedures performed

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number performed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal hysterectomy</td>
<td>30 (9.6%)</td>
</tr>
<tr>
<td>Uterosacral ligament suspension</td>
<td>151 (48.2%)</td>
</tr>
<tr>
<td>Sacrospinous ligament suspension (bilateral)</td>
<td>35 (11.2%)</td>
</tr>
<tr>
<td>Vaginal paravaginal repair</td>
<td>123 (39.3%)</td>
</tr>
<tr>
<td>Graft-augmented anterior repair (hammock)</td>
<td>76 (24.2%)</td>
</tr>
<tr>
<td>Graft-augmented posterior repair (hammock)</td>
<td>24 (7.6%)</td>
</tr>
<tr>
<td>Posterior repair (site-specific)</td>
<td>68 (21.7%)</td>
</tr>
<tr>
<td>Perineorrhaphy</td>
<td>58 (18.5%)</td>
</tr>
<tr>
<td>Sphincteroplasty</td>
<td>8 (2.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (2.6%)</td>
</tr>
<tr>
<td>Anti-incontinence surgery</td>
<td></td>
</tr>
<tr>
<td>Pubovaginal sling—bone anchor</td>
<td>169 (54.0%)</td>
</tr>
<tr>
<td>Pubovaginal sling—traditional or Cooper’s ligament sling</td>
<td>19 (6.1%)</td>
</tr>
<tr>
<td>Midurethral sling</td>
<td>19 (6.1%)</td>
</tr>
<tr>
<td>Retropubic urethropexy</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Needle suspension</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>
vaginal infection (18.4% vs 4.7%; \( P < .001 \)), requiring more intervention and more office visits. These complications were most commonly managed by cautery, suture removal, and operative surgical intervention. In the cases in which graft was used, there were 25 (28.4%) cases of graft erosion, with 18 (72%) requiring debridement. The remaining 7 erosions were treated successfully with topical estrogen alone.

A regression model was created to define independent risk factors for granulation tissue and infection postoperatively. Initially, univariate analysis was performed to identify individual risk factors for postoperative complications. Having identified those outcomes, a logistic regression model was built incorporating all variables identified as significant on univariate analysis. With the use of a stepwise, backward technique, insignificant variables were sequentially removed until all variables were found to be significant. Outcomes of univariate and multivariate analysis are described in Table VI. Graft use (odds ratio [OR] 3.397 [1.878-6.145]) and use of braided suture (OR 2.853 [1.488-5.469]) were most associated with granulation, whereas women older than 70 years (OR 0.412 [0.206-0.787]) tended to be less likely to have granulation tissue (\( r = 0.404 \)). Infection was associated with graft use (5.871 [2.058-16.745]), performance of a sacrospinous ligament fixation (OR 3.853 [1.220-12.175]), and black race (OR 14.907 [3.470-64.040]) (\( r = 0.519 \)).

**Comment**

Improving surgical outcomes is the driving force for the many newer procedures being developed for reconstructive surgery. Because patients recover more quickly and

<table>
<thead>
<tr>
<th>Table III</th>
<th>Different graft materials used and site of use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Graft material</strong></td>
<td><strong>Anterior</strong></td>
</tr>
<tr>
<td>Freeze-dried cadaveric fascia lata (banked)</td>
<td>27</td>
</tr>
<tr>
<td>Solvent-dried cadaveric fascia lata (Tutoplast, Mentor, Santa Barbara, CA)</td>
<td>13</td>
</tr>
<tr>
<td>(Intaxen, American Medical Systems, Inc, Minnetonka, MN)</td>
<td>10</td>
</tr>
<tr>
<td>Porcine small subintestinal submucosa (SIS, Cook Biotechnology Inc, West Lafayette, IN)</td>
<td>10</td>
</tr>
<tr>
<td>Acellular porcine dermis (Pelvicol, Bard, Covington, GA)</td>
<td>7</td>
</tr>
<tr>
<td>Autologous fascia lata</td>
<td>4</td>
</tr>
<tr>
<td>Polypropylene (Gynemesh, Gynecare Worldwide, New Brunswick, NJ)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>74</td>
</tr>
</tbody>
</table>

Table IV | Location of recurrence that is based on the location of graft placement |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location of recurrence</strong></td>
<td><strong>Location of Graft Placement</strong></td>
</tr>
<tr>
<td>None</td>
<td>(n = 74)</td>
</tr>
<tr>
<td>Anterior</td>
<td>(n = 22)</td>
</tr>
<tr>
<td>Posterior</td>
<td>17 (23.0%)</td>
</tr>
<tr>
<td>Apex</td>
<td>1 (1.4%)</td>
</tr>
</tbody>
</table>

\( ^1 \chi^2 \) test.

Comparisons are made using the Fisher exact test, except where noted. Because there were only 2 cases involving multiple grafts, these were excluded from analysis.

* In 2 cases involving anterior vaginal grafts, the recurrence occurred with both the anterior and the posterior vaginal wall. In these cases, the recurrence is listed in both the anterior and posterior recurrence category. Therefore, the sum for the column equals 76.

**Table V** | Graft vs no graft in vaginal reconstructive surgery |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
<td><strong>Graft</strong> (n = 98)</td>
</tr>
<tr>
<td>Recurrent prolapse</td>
<td>34 (34.7%)</td>
</tr>
<tr>
<td>Recurrent stage 3 prolapse</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>Recurrent urinary incontinence</td>
<td>25 (25.5%)</td>
</tr>
<tr>
<td>Further surgery for prolapse</td>
<td>8 (8.2%)</td>
</tr>
<tr>
<td>Further surgery for prolapse or incontinence</td>
<td>13 (13.3%)</td>
</tr>
<tr>
<td><strong>Postoperative complications</strong></td>
<td><strong>Granulation</strong></td>
</tr>
<tr>
<td>Infection</td>
<td>18 (18.4%)</td>
</tr>
<tr>
<td>Management of complications (n = 75)</td>
<td><strong>Was patient symptomatic</strong></td>
</tr>
<tr>
<td>Cautery used</td>
<td>24 (63.2%)</td>
</tr>
<tr>
<td>Cut suture</td>
<td>12 (31.6%)</td>
</tr>
<tr>
<td>Surgery (in operating room)</td>
<td>8 (21.6%)</td>
</tr>
<tr>
<td>Interval from surgery (mo)</td>
<td>2.8</td>
</tr>
<tr>
<td>Interval to resolution (mo)</td>
<td>4.7</td>
</tr>
<tr>
<td>Number of office visits</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Means were compared using independent sample t test. Categorical data was compared by using \( \chi^2 \), except where noted.

* Fisher exact test.
have fewer complications with vaginal surgery, most of these innovations in technique have focused on the vaginal route.

When Benson et al found that ASC was superior to vaginal sacrospinous ligament fixation (SSLF), reconstructive surgeons began to favor abdominal repair of the vaginal vault. Many proponents of abdominal surgery argue that compensatory repairs such as the ASC are more durable. Consequently, advances in surgical technique have focused on achieving the results of abdominal compensatory repair while still using the vaginal route favored by many.

With the resurgence of the site-specific defect repair in POP, surgical procedure choice has evolved toward defect-directed repairs, such as the paravaginal repair and site-specific posterior repair. Unfortunately, the few comparative studies have showed little benefit of these “newer” procedures, leading to a continued search for a superior procedure.

Developed as a compensatory procedure, graft-augmented vaginal repair is 1 of the most recent innovations in surgical technique. Proponents of graft use in vaginal surgery have justified its use by extrapolating from hernia data that describe a more durable repair with less postoperative discomfort. Critics of graft use argue that the pathophysiology of prolapse and of abdominal hernias differs. Despite the controversy, an overabundance of biomaterials has become available for use in vaginal repair.

Many studies have described favorable results of graft augmentation. In the only trial comparing graft with no graft, Julian described the results of using polypropylene mesh in the anterior vaginal wall of 24 patients with recurrent prolapse. After nonrandomized allocation of 12 patients to site-specific repair and 12 patients to the same procedure with graft augmentation, the author concluded that graft use was more effective in preventing recurrent prolapse (0% vs 33%; \( P < .05 \)). There were 3 graft complications (25%) easily managed on an outpatient basis.

In a review of anterior vaginal graft using autologous fascia lata, Chesson et al found a recurrence rate of 31.3% for which only 1 patient (3.1%) required surgery. The graft complication rate was 18.8%. In a similar series fascia lata, Kobashi et al found a recurrence rate of 23.2% with a graft complication rate of 15.2%. Many other series have reported a wide range of success rates (59%-100%) with graft-augmented anterior repair.

The results with graft augmentation of the posterior vaginal wall have been slightly better in the few published case series. Miklos et al reported a 95% success rate in 57 patients using a dermal matrix. Milani et al found a high (94%) success rate for prolapse in 31 patients undergoing polypropylene mesh-augmented posterior repair. Unfortunately, there was a high rate of dyspareunia (69% compared with 6% preoperatively; \( P < .05 \)) and vaginal erosion (6.5%). Using only functional outcomes, Mercer-Jones et al demonstrated improvement in symptoms of straining and incomplete evacuation, although 27.2% still complained of a vaginal bulge. No objective assessment was described.

Unfortunately, the paucity of comparative data analyzing graft use has been disappointing. It is also difficult to compare the results of the various case series for many reasons. Differences in surgical technique, graft material, patient selection, and performance of concomitant procedures influences any comparison of results. Outcome measures vary between series with a lack of functional measures.

The comparative data presented here contradict the theory that graft use results in better outcomes. With regard to our main surgical outcome variables, in the early postoperative period there was no improvement when

<table>
<thead>
<tr>
<th>Table VI</th>
<th>Univariate and multivariate analysis that used granulation as primary endpoint (only variables found significant on univariate analysis are listed in this table)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Granulation</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Univariate</td>
<td></td>
</tr>
<tr>
<td>Graft use</td>
<td>3.029</td>
</tr>
<tr>
<td>Braided suture</td>
<td>2.704</td>
</tr>
<tr>
<td>Age &gt; 70 y</td>
<td>0.507</td>
</tr>
<tr>
<td>Black race</td>
<td>NS</td>
</tr>
<tr>
<td>Sacrospinous</td>
<td>NS</td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Graft use</td>
<td>3.397</td>
</tr>
<tr>
<td>Braided suture</td>
<td>2.853</td>
</tr>
<tr>
<td>Age &gt; 70 y</td>
<td>0.402</td>
</tr>
<tr>
<td>Sacrospinous</td>
<td>NS</td>
</tr>
<tr>
<td>Black race</td>
<td>NS</td>
</tr>
</tbody>
</table>
Biologic grafts can be acellular, cross-linked, and per-forested. All these characteristics could certainly affect outcomes. No difference existed among the different graft materials leading to the decision to combine the cases. In the early postoperative period, graft-augmented vaginal surgery appears to confer no added benefit over more traditional vaginal procedures for POP. The high rate of complications, although mild and easily treated, calls the routine use of graft into question.

References

Chronic urinary retention and pelvic floor hypertonicity after surgery for endometriosis: A case series

Alan P. Gehrich, MD,* John N. Aseff, MD, Cheryl B. Iglesia, MD, John R. Fischer, MD, Jerome L. Buller, MD

Washington Continence Center/Institute for Pelvic Floor Disorders, Washington Hospital Center, Washington, DC

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**KEY WORDS**
Urinary retention
Endometriosis
Hypertonicity
Pelvic floor hypertonicity
Urethral spasm
Chronic pelvic pain

**Objective:** The purpose of this study was to evaluate 4 cases of chronic urinary retention and pelvic floor muscle spasms after surgery for endometriosis.

**Study design:** These patients underwent a complete history, physical exam, and diagnostic work-up. The results were analyzed with regards to type and extent of inciting surgery, diagnostic findings, postoperative recovery, and treatment success.

**Results:** The patients’ mean age was 39.5 years and all had undergone various surgical interventions for endometriosis. In addition to urinary retention, all developed debilitating pelvic floor muscle spasm postoperatively. Physical exam revealed pelvic floor hypertonicity and urodynamics indicated hypoactive detrusor contractility. Neurodiagnostic testing gave evidence of neuropathy in all subjects.

**Conclusion:** Extensive endometriosis surgery may pose a risk for postoperative bladder dysfunction and pelvic floor muscle spasm.

Chronic postoperative urinary retention is an uncommon occurrence with benign gynecologic surgery, which has been effectively documented by numerous prospective studies. Simple hysterectomy preserves the parametrium and the dissection generally does not extend deeply into the cardinal-uterosacral ligament complex. The bladder pillars, which form the terminal pathway for bladder parasympathetic innervation, are also spared. In contrast, oncologic pelvic surgery, particularly radical hysterectomy, involves a high risk of bladder denervation injury with subsequent bladder dysfunction, ranging from 20% to 80%. This injury leads to chronic urinary retention in 2% to 3% of cases. The increased incidence results from the extensive surgical dissection into the lateral and posterior pelvic sidewall and parametrium. This dissection can disrupt the finely arborized and poorly defined branches of the hypogastric nerve, as well as pelvic and sacral plexi. This can lead to visceral and pelvic floor dysfunction. Excision of endometriotic lesions may require dissection as extensive as that seen in radical hysterectomy.

The mechanism of injury in postoperative non-obstructive urinary retention results from either a decreased sensory output from the bladder, a decreased parasympathetic input into the bladder, or a combination of both. This leads to a decreased sensation of
bladder filling or decreased intensity of detrusor contraction, resulting in urinary retention.

In this series, we present 4 patients who were referred to the urogynecologic service at Washington Hospital Center with the diagnosis of chronic nonobstructive urinary retention after surgery for endometriosis. In addition, these patients presented with debilitating spastic activity of the pelvic floor and urethral sphincter. The goal of this paper was to compile the individual histories, diagnostic evaluations, and treatments that these patients underwent in an effort to better understand these atypical postoperative complications. We will conclude with theoretical considerations regarding the association of pelvic floor muscle spasm with nonobstructive urinary retention in the postoperative patient.

Material and methods

Four female patients were referred to the urogynecologic clinic at a large metropolitan teaching hospital with the diagnosis of postoperative nonobstructive urinary retention and exacerbated pelvic pain after surgery for endometriosis. Operative reports from the 4 outside referring surgeons were reviewed. Patients underwent a complete history, physical exam, and diagnostic workup, including urodynamics, cystoscopy, radiographic imaging, and neurophysiologic testing. Each patient underwent multiple treatment modalities. These cases were compared with regards to type and extent of inciting surgery, neurologic findings, postoperative recovery, and treatment. Approval for this case review was obtained from the Institutional Review Board at Washington Hospital Center, Washington, DC.

Results

The mean patient age was 39.5 years. All had the diagnosis of endometriosis (see Table I). Although all patients had preoperative complaints of pelvic pain, none of the patients complained of voiding dysfunction or pelvic floor spasms. The patients underwent various surgeries, which documented adhesiolysis or excision of endometriotic lesions involving the pelvic side wall. None of the surgeries involved parametrial dissection (see Table II).

These patients presented with various postoperative symptoms (see Table III). Patients 1, 2, and 3 left the hospital after surgery requiring continuous bladder drainage. Patient 4 had a delayed diagnosis of urinary retention 6 months after surgery. All of these women developed increasing pain postoperatively, which we attributed to the spasticity of either the pelvic floor musculature or urethral sphincter. The patients with urethral spasm had difficulties performing chronic intermittent self-catheterization because of pain, which was severe enough to require placement of a suprapubic catheter in patient 2. All 4 patients developed severe dyspareunia postoperatively and, interestingly, 3 of the

<table>
<thead>
<tr>
<th>Table I</th>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient 1</td>
</tr>
<tr>
<td>Age at presentation</td>
<td>44</td>
</tr>
<tr>
<td>Parity</td>
<td>0</td>
</tr>
<tr>
<td>Endometriosis stage</td>
<td>4</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td>Pelvic pain</td>
</tr>
<tr>
<td>Symptom onset</td>
<td>Immediately postoperatively</td>
</tr>
<tr>
<td>Elapsed time before evaluation at WHC*</td>
<td>2 months</td>
</tr>
</tbody>
</table>

* Washington Hospital Center.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Inciting surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Patient 1</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>+</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>+</td>
</tr>
<tr>
<td>Adhesiolysis</td>
<td>Minor</td>
</tr>
<tr>
<td>Deep infiltrative endometriosis excision</td>
<td>+</td>
</tr>
</tbody>
</table>

lsc, Laparoscopic; +, positive; –, negative.

<table>
<thead>
<tr>
<th>Table III</th>
<th>Postoperative symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>Patient 1</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Complete</td>
</tr>
<tr>
<td>Pelvic floor muscle spasm</td>
<td>–</td>
</tr>
<tr>
<td>Urethral spasm</td>
<td>+</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>+</td>
</tr>
<tr>
<td>Constipation</td>
<td>–</td>
</tr>
<tr>
<td>Dyschezia</td>
<td>–</td>
</tr>
</tbody>
</table>

+, positive; –, negative.
4 patients also complained of increased constipation and dyschezia in the postoperative period.

Pelvic physical exam findings were equivocal (see Table IV). Pelvic floor muscle strength was assessed using the Modified Oxford Scale from 0 to 5 with all patients showing minimal pelvic floor muscle movement.7 This exam was compromised by the pain and palpable spasm over the levator ani, which did not allow the patients to effectively relax during the exam. On lower extremity exam, patient 1 had deficits involving the right obturator nerve and sensory L5-S1 distribution. Patient 3 had decreased sensation over bilateral the right obturator nerve and sensory L5-S1 distribution. Patient 1 had deficits involving the right obturator nerve and sensory L5-S1 distribution. Patient 3 had decreased sensation over bilateral the right obturator nerve and sensory L5-S1 distribution.

Evaluation proceeded with multichannel urodynamic testing (see Table V). Three patients had abnormal storage phases and could only sense bladder filling at approximately 500 mL. All patients had abnormalities on voiding phase studies. Three patients had elevated postvoid residual ranging from 150 to 275 mL. Patient 2 was unable to initiate spontaneous voids during her initial presentation to the urogynecology clinic. None of the patients developed detrusor pressures > 20 cm H2O during voiding, but urine flow was intermittent, requiring abdominal pressures often greater than 80 cm H2O to initiate flow. Maximum urethral closure pressure was greater than 100 cm H2O in patients 1 and 3.

The history and exam findings prompted a neurologic evaluation in all 4 of these patients, with results listed in Table VI. Neurophysiologic testing demonstrated both sensory and motor pathway abnormalities. Three of the 4 patients demonstrated prolonged pudendal nerve terminal motor latency values. Two of the 3 patients were nulliparous, which eliminates vaginal delivery as a potential confounding factor. The absence of bladder anal reflexes in all 4 patients signifies a potential loss of bladder afferent innervation. Two of the 4 patients had abnormalities of the clitoral/urethral anal reflex, indicating a potential loss of somatic innervation as well.

Table IV: Physical exam findings

<table>
<thead>
<tr>
<th>PE finding</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacral reflexes*</td>
<td>WNL</td>
<td>WNL</td>
<td>Diminished</td>
<td>WNL</td>
</tr>
<tr>
<td>Pelvic floor strength&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
</tr>
<tr>
<td>Pelvic pain on exam</td>
<td>Mild</td>
<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>Limb strength</td>
<td>Right</td>
<td>WNL</td>
<td>WNL</td>
<td>WNL</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>Right</td>
<td>None</td>
<td>Bilateral</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>lateral leg</td>
<td>S2-S4 dermatome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bulbocavernous reflex, anal wink.
<sup>1</sup> Modified Oxford Scale 0–5.

Table V: Complex urodynamics at time of presentation

<table>
<thead>
<tr>
<th>Urodynamic findings</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filling sensation</td>
<td>Intact</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Compliance</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Postvoid residual</td>
<td>↑</td>
<td>Complete</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Detrusor instability</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

↑, Increased; ↓, decreased.

Abbreviations: WNL, Within normal limits; ↓, weak; 5, sacral.

Monopolar needle electromyographic studies of the urethral and anal sphincter muscles demonstrated fibrillation potentials, which indicate acute or ongoing neurogenic compromise consistent with denervation. The additional presence of polyphasic motor unit action potentials in the same muscles indicated a subacute reinervation process. These studies define the presence of a neurogenic lesion within or proximal to the level of the pelvis in all 4 patients. Furthermore, a urethral EMG abnormality known as Fowler’s syndrome, which is associated with voiding dysfunction, was documented in patients 3 and 4.

These patients underwent further diagnostic evaluation with magnetic resonance imaging (MRI) and cystoscopy. MRI did not reveal any evidence of central nervous system involvement, such as multiple sclerosis. Cystoscopy ruled out mechanical bladder outlet obstruction, as well as intrinsic bladder or urethral lesions, which could have contributed to the patients’ condition.

With the acute presentation of patients 1, 2, and 3 after surgery, muscle relaxants and narcotic therapy were instituted as the first line of therapy. We targeted detrusor hypoactivity and outlet resistance using parasympathomimetics, α-blockers, calcium channel blockers, as well as β-agonists, without success. Physical therapy for a 6- to 12-month period aided in the treatment of pelvic pain and spasm but did not cure voiding dysfunction. After 6 months, patients 1 and 2 were able to adequately empty their bladder using Valsalva and Credé maneuvers. After exhausting conservative measures, patients 3 and 4 underwent sacral neuromodulation therapy with Interstim (Medtronic Corporation, Minneapolis, MN), resulting in marginal success after multiple revisions. Unfortunately, with the exception of patient 1, the patients are still requiring intermittent narcotic therapy for their pelvic floor muscle spasms.

Comment

This case series illustrates 2 severe morbidities after pelvic surgery for endometriosis: 1) detrusor hypoactivity leading to retention, and 2) pelvic floor muscle spasm resulting in severe pelvic pain. The neuropathology in our 4 patients stems from the compromise of multiple neural pathways originating in the pelvis. These pathways comprise...
the autonomic parasympathetic inflow to the bladder, visceral sensory outflow from the bladder, and the somatic innervation of the pelvic floor musculature. Previous studies indicate a convergence of various neuropathies in the development of postoperative urinary retention. Using animal models, Koyanagi documented an increase in alpha-adrenergic receptor function within the urethra after parasympathectomy. Martin concluded that a lesion in the sacral pathway may lead to detrusor hyperreflexia and a nonrelaxing sphincter. According to Wein, the pattern of postoperative voiding dysfunction in patients who have undergone radical pelvic surgery is a combination of impaired bladder contractility along with a fixed striated sphincter tone. Our series of patients illustrate this combination of findings. They exhibited interruption of bladder afferent and efferent pathways based on urodynamic and neurologic testing and suffered with hypertonicity of the pelvic floor. We suspect that the pelvic floor muscle spasm in combination with urethral sphincter dysfunction contributed to the urinary retention by raising outlet resistance. The International Continence Society has delineated the term nonrelaxing urethral sphincter obstruction to help define the pathology seen in this patient population but has not defined clear clinical or urodynamic parameters.

This theory combining hypoactive detrusor function and urethral obstruction does not, however, explain why these patients presented with acute and chronic pelvic floor pain. We believe that the pain these patients experienced is primarily neuropathic in origin. The nociceptive pathways, activated by preexisting endometriosis, may have been further up-regulated by the surgery and led to pelvic floor dysfunction. This windup phenomenon is well documented in the pain literature. The pelvic floor could also have been injured in the pursuit of deeply infiltrative endometriosis and, in turn, led to a compensatory response of the surrounding muscle tissue, involving spastic activity. Although less likely, surgery may have caused direct injury to the innervation of the pelvic floor, leading to a dysfunctional contraction pattern culminating in fatigue and spasm-like activity of the pelvic floor.

The evaluation of these patients is extremely complex. Urodynamic studies can demonstrate detrusor hypoactivity and obstruction but cannot determine the etiology. Neurophysiologic testing is a necessary adjunct to help delineate the source of voiding dysfunction. In our case series, we had evidence of detrusor hypoactivity based on maximum detrusor pressures, as well as evidence of urethral hypertonicity based on elevated urethral closure pressures. Denervation injury to the bladder has been clearly associated with detrusor hyporeflexia, and neurogenic abnormalities of the urethral sphincter, such as seen with Fowler’s syndrome, have been associated with elevated urethral pressure profilometry.

As a follow-up to urodynamic testing, electromyographic studies of the pelvic floor musculature, including external urethral sphincter (EUS), should be performed. Among 15 women with idiopathic urinary retention, Deindl found inappropriate pelvic floor muscle activation during voiding in 11 and inappropriate EUS activation in 4 women. EMG studies can also be used to evaluate appropriate urethral relaxation with voiding. Our neurophysiologic testing showed signs of neurologic compromise involving the EUS in all of our patients, but we did not assess urethral needle EMG with voiding and, therefore, cannot comment on urethral relaxation. Everaert theorized that urethral sphincter contractions, in particular, Fowler’s syndrome, could cause detrusor relaxation, as well as obstructive voiding. At the time of the initial evaluation of our patients, we did not perform EMG studies on the pubococcygeus muscle, which may have confirmed our physical exam findings of pelvic floor spasticity. This case series illustrates how neurophysiologic testing in combination with MRI, complex urodynamics, cystoscopy, and physical exam can be utilized to help better define neurologic lesions.

Treatment of urinary retention in the context of pelvic floor muscle spasm is challenging and should not be delayed. Self-catheterization should be instituted to prevent upper urinary tract injury, but the critical aspect of treatment is to reduce the hypertonicity of the pelvic floor. This is a major contributor to the pain symptoms and may be contributing to the voiding dysfunction, as well. All patients should be started in pelvic floor physical therapy as soon as the diagnosis of pelvic floor muscle spasm is made. Detrusor hypoactivity...
is poorly responsive to medical therapy. Antispasmodic therapy may decrease pelvic floor and urethral hypotonicity, but it was not effective in eliminating urinary retention in our case series. This was likely because of the hypothetic detrusor seen in our patients. Botulinum toxin in experimental trials has also been injected both into the external urethral sphincter for dysfunctional voiding, and into the pubococcygeus for pelvic floor muscle spasm. This was attempted in patient 3 with short-term effect on her voiding dysfunction but, because of discomfort, she refused to continue therapy. Sacral neuromodulation has been approved for the treatment of urinary retention. Success rates, based on retrospective analysis, have been higher in patients with a diagnosis of urethral spasm. This therapy has also been evaluated for refractory pelvic floor dysfunction. Neuromodulation provided 2 of our patients with modest improvement.

Urinary retention and chronic pelvic floor dysfunction can arise as 2 distinct complications from benign gynecologic surgery. The association of detrusor hypoactivity with pelvic floor hypotonicity has proved difficult to manage. The suspected etiologies involve postsurgical autonomic dysfunction and neuropathic pain coupled with pelvic floor muscle spasm. This case series highlights the close interconnection among the pelvic floor musculature and visceral organs and their functioning as an integrated neuromuscular unit. Further research into this complex relationship will ultimately identify the root causes and help develop more effective treatments for complex pelvic floor disorders. This case series also serves as a reminder that pelvic surgery can potentially aggravate preexisting pelvic floor disorders, and that any pelvic floor muscle pathology should be addressed aggressively preoperatively.

References

Suburethral sling using the transobturator approach: A quality-of-life analysis

James Chivian Lukban, DO*

Urogynecology Associates of Colorado, Denver, CO

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KEY WORDS
Transobturator sling
Stress urinary incontinence
Quality of life
Outcome analysis

Objective: The objective of the study was to determine the degree of benefit of a transobturator midurethral polypropylene sling in patients with stress urinary incontinence through a quality-of-life instrument and outcome analysis.

Study design: Forty-seven patients completed the validated Individual Incontinence Impact Questionnaire both before and after treatment. Subjects also completed the validated Patient Satisfaction Questionnaire postoperatively to complete outcome analysis. Statistical analyses included a paired Student t test for intrapair comparisons and 2-sample t tests to compare mean differences between groups.

Results: Individual Incontinence Impact Questionnaire scores for the entire sample declined from a preoperative mean of 43.0 ± 27.0% to a postoperative mean of 11.8 ± 16.4 (P < .0001). On review of Patient Satisfaction Questionnaire responses, 45 patients (95.7%) were completely satisfied or somewhat satisfied, and 42 subjects (89.4%) stated their leakage was much better or better.

Conclusion: The transobturator midurethral sling provides a significant improvement in quality-of-life and high postoperative patient satisfaction.

Quality-of-life instruments have recently been given a greater measure of consideration in the evaluation of urinary incontinence treatment because traditional objective and subjective definitions of cure are consistently variable. Additionally, the benefit or detriment of a particular intervention on one’s ability to perform activities of daily living is not represented in traditional definitions of cure. In a study of 105 women who underwent either a Burch colposuspension or Raz bladder neck suspension, Filbeck et al1 reported an improved quality of life by validated questionnaires, even in women with persistent or recurrent urinary incontinence. Alternatively, a patient who exhibits an objective cure, but experiences postoperative voiding dysfunction from surgical overcorrection, may report a significant reduction in quality of life.

Outcome analysis has also seen greater utilization of late, and complements quality-of-life assessment, giving consideration to patient satisfaction in the context of overall postoperative lower urinary tract function.2

The midurethral sling was introduced as the tension-free tape (TVT) in 1997 and has shown significant
efficacy with excellent long-term durability. More recently a transobturator approach to midurethral sling placement was introduced as an alternative to retropubic needle passage, with initial studies showing efficacy comparable with that of the TVT in addition to the suggestion of a reduction in operative morbidity. A sling placed through the transobturator route is thought also to better mimic normal anatomic midurethral support, with scarce early data showing less short-term postoperative voiding dysfunction.

Our objective was to assess the benefit of the transobturator sling procedure in patients with stress urinary incontinence (SUI) through change in a quality-of-life assessment in addition to postoperative outcome analysis.

Material and methods

Patients

A retrospective chart review of patients who underwent treatment with the Monarc subfascial hammock (American Medical Systems, Inc, Minnetonka, MN) was performed by the author between July 2003 and June 2004. Demographic data were extracted, with patient characteristics listed in Table I. This study was approved by our medical center’s institutional research review board.

Preoperative evaluation

Clinical evaluation of each patient included a full history with completion of a genitourinary symptom questionnaire, physical examination, empty supine stress test, measurement of postvoid residual through sterile catheterization, urinalysis, cotton swab assessment of urethral mobility, assessment of pelvic organ prolapse, and a local neurologic evaluation.

Urodynamic testing was performed in all surgical candidates with the patient in the standing or sitting positions and included measurement of urine flow, filling cystometry, assessment of urethral function in the form of maximum urethral closure pressure and/or vesical leak point pressure, and a pressure flow study as appropriate. Intrinsic sphincter deficiency (ISD) was diagnosed in subjects with a maximum urethral closure pressure of 20 cm or less of H2O or in those with a vesical leak point pressure of 60 cm or less of H2O. Patients with urodynamic stress incontinence were considered candidates for surgical treatment after having been given the option of a trial of conservative therapy. All definitions conform to the International Continence Society Standardization of Terminology.

Sling material and operative procedure

The Monarc subfascial hammock uses a woven polypropylene tape 11 mm in width, with each monofilament measuring 0.15 mm in diameter and the cross-sectional area of each major pore measuring approximately 1 mm².

Transobturator sling placement was carried out in the manner as described by Delorme under general anesthesia with a Foley catheter in place. Sling tensioning was achieved with a Kelly clamp used as a spacer to allow the sling to rest against the midurethra without tension. Cystoscopy was performed on all patients to rule out trauma to the bladder or urethra in addition to ensuring ureteral patency.

Outcome measures

At the time of initial presentation, all subjects were asked to complete the Individual Incontinence Impact Questionnaire (IIIQ) as seen in the Figure. The IIIQ is a validated instrument designed to assess the effect of urinary incontinence on activities of daily living. The following number of points were assigned to each question response: 0, not at all; 1, rarely; 2, frequently; and 3, all the time. The total number of accumulated points (total points) is then divided by the total number of possible points (total possible points) in the determination of a final percentage: the higher the percentage, the more bothersome the urinary incontinence. If a question is not applicable, 3 is subtracted from the total possible points prior to score calculation.

Postoperatively, patients were asked to fill out a second IIIQ in addition to an outcome analysis instrument in the form of the Patient Satisfaction Questionnaire (PSQ). The PSQ is a validated questionnaire used previously in the postintervention evaluation of patients with urinary incontinence, providing an assessment of patient satisfaction, degree of improvement, and the persistence or appearance of postoperative lower urinary tract symptoms.

Subjects were sent questionnaires by mail in addition to a cover letter explaining the nature of the study and...
My bladder control problem affects my … (place an "X" in the appropriate box after each question)

1) Ability to do household chores (washing dishes, cleaning house, etc.)?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

2) Ability to socialize and interact with friends and colleagues?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

3) Quality and quantity of sleep?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

4) Performance of routine exercise or participation in sports (walking, aerobics, tennis, swimming, jogging, etc.)?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

5) Personal and intimate relationships (including hugging and sexual intercourse)?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

6) Ability to participate in entertainment activities (sitting through the movies, playing cards, watching T.V. program)?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

7) Ability to perform my job?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

8) Ability to wear clothes you want?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

9) Ability to go places you want?
   □ not at all □ rarely □ frequently □ all of the time □ not applicable

10) List an activity (not listed above) which is particularly affected by your urine loss.

□ not at all □ rarely □ frequently □ all of the time □ not applicable

Scoring: Total points: _____ Total possible points: _____ Score: _____ %
absolving them of any responsibility to participate. Return of completed questionnaires served as study consent. Patients who did not return a data set within 2 weeks were contacted by phone by 1 of 2 clinical research coordinators to complete data verbally. Such contact by telephone was taken from an approved script in which patients were again informed of a choice not to participate. Those with persistent leakage as per PSQ were asked also by a scripted phone follow-up to characterize their urine loss as “leakage associated with an urge (sudden and compelling need to void)” or “following physical activity (cough, sneeze, laugh, exercise).”

Subjective cure was defined as a response of “no leakage” or “a drop or two” to question 5 of the PSQ. Patients were considered to have persistent leakage if they answered with “pad or clothing damp” or “pad or clothing soaked” to question 5 of the PSQ.

Statistical analyses

Descriptive statistics were used in the reporting of demographic data and PSQ responses. Statistical analyses included a paired t test for intrapair comparisons and 2 sample t tests to compare mean differences between groups for quality-of-life data. Significance was set at a level of $P < .05$.

Results

Disposition and demographics

Fifty-eight patients were identified as having received a transobturator suburethral sling by the author between July 2003 and June 2004. Two patients had not completed a preoperative IIIQ; 5 did not return the postoperative data set, and they were not responsive to telephone follow-up; 2 completed the postoperative data set incorrectly and were not reachable for instruction; 1 was not interested in participating; and 1 who failed to return the postoperative questionnaires was not contacted because her telephone had been disconnected. The 47 subjects who completed a full preoperative and postoperative data set comprised the final sample.

Patient characteristics

On initial presentation, 26 patients (55.3%) reported mixed urinary incontinence (MUI), 20 (42.6%) reported SUI alone, and 1 (2.1%) reported no leakage. Fourteen subjects (29.8%) had a history of at least 1 prior anti-incontinence procedure. All patients were confirmed to have urodynamic stress incontinence, with 9 (19.1%) identified as having ISD. Thirty-two subjects (68.1%) had concomitant surgical procedures at the time of sling placement, with a list of such procedures shown in Table II. Outcome data were collected and analyzed at an average follow-up of 8.5 ± 3.2 months (range 3 to 15 months).

Individual Incontinence Impact Questionnaire

The IIHQ scores for the entire sample improved significantly, as did scores within the subgroups of patients who had previous anti-incontinence surgery, patients with ISD, and patients who underwent concomitant surgery at the time of sling placement (Table III). A comparison of the mean change between preoperative and postoperative scores for each of the following subgroups showed no statistically significant differences: (1) previous anti-incontinence surgery (40.5%) versus primary anti-incontinence surgery (27.3%), $P = .15$; (2) patients with ISD (36.7%) versus patients without ISD (29.9%), $P = .48$; and (3) concomitant surgery (29.3%) versus sling only (35.2%), $P = .52$. 

### Table II Concomitant procedures

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal hysterectomy (with/without adnexae)</td>
<td>8</td>
<td>17.0</td>
</tr>
<tr>
<td>Anterior colporrhaphy</td>
<td>11</td>
<td>23.4</td>
</tr>
<tr>
<td>Paravaginal repair (abdominal)</td>
<td>8</td>
<td>17.0</td>
</tr>
<tr>
<td>Enterocoele repair (vaginal)</td>
<td>7</td>
<td>14.9</td>
</tr>
<tr>
<td>Enterocoele repair (abdominal)</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>Sacrospinous fixation</td>
<td>3</td>
<td>6.4</td>
</tr>
<tr>
<td>Posterior colporrhaphy</td>
<td>25</td>
<td>53.2</td>
</tr>
<tr>
<td>Rectal sphincter repair</td>
<td>5</td>
<td>10.6</td>
</tr>
<tr>
<td>Abdominal hysterectomy (supracervical)</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>Abdominal sacrocolpopexy</td>
<td>3</td>
<td>6.4</td>
</tr>
<tr>
<td>Rectopy (abdominal)</td>
<td>1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

### Table III Individual Incontinence Impact Questionnaire Scores

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Preop score (%)*</th>
<th>Postop score (%)*</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample (47)</td>
<td>43.0 ± 27.0</td>
<td>11.8 ± 16.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Previous anti-incontinence surgery (14)</td>
<td>56.6 ± 27.0</td>
<td>16.1 ± 22.8</td>
<td>.0003</td>
</tr>
<tr>
<td>Primary anti-incontinence surgery (33)</td>
<td>37.3 ± 25.3</td>
<td>10.0 ± 12.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Patients with ISD (9)</td>
<td>49.5 ± 21.4</td>
<td>12.8 ± 13.1</td>
<td>.0001</td>
</tr>
<tr>
<td>Patients without ISD (37)</td>
<td>41.5 ± 28.2</td>
<td>11.6 ± 17.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Concomitant surgery (32)</td>
<td>44.3 ± 27.6</td>
<td>15.0 ± 18.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sling only (15)</td>
<td>40.4 ± 26.5</td>
<td>5.2 ± 8.4</td>
<td>.0004</td>
</tr>
</tbody>
</table>

* Scores reported as mean ± SD.  
† A paired t test was used.
Patient Satisfaction Questionnaire

On review of PSQ responses (Table IV), 45 patients (95.7%) were “completely satisfied” or “somewhat satisfied,” and 42 subjects (89.4%) reported their leakage as “much better or better.” Forty subjects (89.4%) responded yes to having fewer accidents than before treatment, and 42 of 47 (89.4%) had no postoperative restrictions in activity. Thirty-four patients (72.3%) had either “no leakage” or leakage in the amount of “a drop or two” and were considered subjective cures.

Of the 13 subjects (27.7%) with persistent leakage, 11 (84.6%) were “completely satisfied” or “somewhat satisfied”; 8 (61.5%) considered their leakage to be “much better or better”; 9 (69.2%) had “fewer accidents”; 9 (69.2%) had “smaller” leakages than before surgery; all quantified their leakage as only “pad or clothing damp”; and 9 (69.2%) reported no restrictions in activity.

With regard to postoperative voiding function, 46 patients (97.9%) had slight or no difficulty emptying the bladder, with only 1 subject (2.1%) reporting moderate difficulty with evacuation.

Telephone query as to type of leakage

Of the 13 patients with persistent incontinence of more than “a drop or two” as per the PSQ, 3 had persistent urge urinary incontinence (UUI); 4 had de novo urge incontinence; 4 had persistent MUI; and 2 had persistent SUI as per patient characterization of leakage. Overall, 6 patients (12.8%) of the entire sample of 47 continued to leak with provocation, 7 (26.9%) of the 26 with preoperative MUI had persistent urge incontinence, and 4 (8.5%) of the sample of 47 exhibited de novo UUI.

Intraoperative complications

There were no intraoperative complications including recognized or unrecognized trauma to the urethra, bladder, or ureter. No hematoma formation or major vascular injury occurred.

Comment

The transobturator polypropylene midurethral sling was shown in this study to improve quality of life and provide high postoperative patient satisfaction. A significant reduction in the mean IIIQ score was seen in our sample following transobturator sling, with improvement also exhibited in patients independent of a history of previous anti-incontinence surgery, the preoperative diagnosis of ISD, or the performance of concomitant surgery at the time of sling procedure. As per the PSQ, 95.7% of subjects were completely satisfied or somewhat satisfied at a mean follow-up of 8.5 months, with only 2.1% of our sample reporting any postoperative voiding difficulty, rating such difficulty as moderate. No intraoperative complications occurred.

<table>
<thead>
<tr>
<th>Question</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How satisfied are you with your progress?</td>
<td></td>
</tr>
<tr>
<td>Completely satisfied</td>
<td>33 (70.2)</td>
</tr>
<tr>
<td>Somewhat satisfied</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>Not satisfied</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>2. Overall, do you feel that your leakage is:</td>
<td></td>
</tr>
<tr>
<td>Much better or better</td>
<td>42 (89.4)</td>
</tr>
<tr>
<td>About the same</td>
<td>4 (8.5)</td>
</tr>
<tr>
<td>Worse or much worse</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>3. Currently do you leak even a small amount of urine?</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18 (38.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (61.7)</td>
</tr>
<tr>
<td>4. Are you having fewer accidents than before treatment?</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>42 (89.4)</td>
</tr>
<tr>
<td>5. Amount of urine lost in leakage?</td>
<td></td>
</tr>
<tr>
<td>No leakage</td>
<td>18 (38.3)</td>
</tr>
<tr>
<td>A drop or two</td>
<td>16 (34.0)</td>
</tr>
<tr>
<td>Pad or clothing damp</td>
<td>13 (27.7)</td>
</tr>
<tr>
<td>Pad or clothing soaked</td>
<td>0</td>
</tr>
<tr>
<td>6. Are leakages larger, smaller, or about the same as before treatment?</td>
<td></td>
</tr>
<tr>
<td>No leakage</td>
<td>18 (38.3)</td>
</tr>
<tr>
<td>Larger</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Smaller</td>
<td>25 (53.2)</td>
</tr>
<tr>
<td>About the same</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>7. How much does the leakage of urine restrict your activities now?</td>
<td></td>
</tr>
<tr>
<td>No leakage</td>
<td>18 (38.3)</td>
</tr>
<tr>
<td>Not at all</td>
<td>24 (51.1)</td>
</tr>
<tr>
<td>Some of the time</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>All of the time</td>
<td>0</td>
</tr>
<tr>
<td>8. How disturbing is the leakage?</td>
<td></td>
</tr>
<tr>
<td>Not having leakage</td>
<td>18 (38.3)</td>
</tr>
<tr>
<td>Not at all disturbing</td>
<td>16 (34.0)</td>
</tr>
<tr>
<td>Somewhat disturbing</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>Extremely disturbing</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>9. Do you experience any vaginal pain, pressure, or protrusion?</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40 (85.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>10. Are you having any difficulty emptying your bladder?</td>
<td></td>
</tr>
<tr>
<td>Greatly</td>
<td>0</td>
</tr>
<tr>
<td>Moderately</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Slightly</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Not at all</td>
<td>36 (76.6)</td>
</tr>
<tr>
<td>11. Since your treatment with us, have you had a bladder or kidney infection?</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>36 (76.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>12. How has treatment affected your ability to have sexual relations?</td>
<td></td>
</tr>
<tr>
<td>More able</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>About the same</td>
<td>20 (42.6)</td>
</tr>
<tr>
<td>Less able</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>14 (29.8)</td>
</tr>
</tbody>
</table>
The primary weakness of this study was its relatively short mean follow-up of 8.5 months. Longer follow-up would either confirm the durability of our results or reveal less favorable outcomes if the sling were to fail over time.

The main strength of the study was that of the use of perioperative questionnaires to determine patient benefit. Retrospective chart reviews typically yield higher success rates as compared with questionnaire-based outcome analyses, presumed to be the result of physician bias toward reporting success or the tendency of the patient to portray her symptoms as improved in a face-to-face physician encounter. Sirls et al reported on a cohort of 102 women who completed an outcome analysis questionnaire following modified Pereyra bladder neck suspension and compared questionnaire-based symptom improvement with that gleaned from a retrospective review of charts of the same patients. Ninety-one subjects (89%) were considered cured or improved on the basis of retrospective chart review, whereas only 65 patients (64%) were cured or improved according to outcome analysis (mean follow-up of 25 months).

Outcome analysis in our study was provided by the PSQ, used previously by Burgio et al in the placebo-controlled evaluation of behavioral versus drug treatment for UUI. In its most current form, Richter et al used the PSQ in the postoperative evaluation of 102 women who underwent placement of a cadaveric fascia lata sling for ISD. At a follow-up of 12 months, 90.2% of patients who received a cadaveric fascia lata sling were either “completely satisfied” or “somewhat satisfied,” with durability of these results exhibited through 48 months.

Quality-of-life instruments are complementary to outcome analysis because they provide for a real-life assessment of the impact of symptoms on activities of daily living. Although validated specifically for the assessment of incontinence symptoms, the short forms of the Incontinence Impact Questionnaire-7 and the Urogenital Distress Inventory-6 were shown by Fitzgerald et al to change favorably in those who were subjectively continent after a Burch colposuspension or suburethral sling procedure (follow-up of 3 months).

Similarly, Vassallo et al reported significant improvements in the Incontinence Impact Questionnaire-7 and Urogenital Distress Inventory-6 questionnaire scores of 151 patients who underwent TVT placement (mean follow-up of 22.1 months). In our study, we used the IIIQ in a similar fashion, measuring improvement in quality-of-life parameters in patients who received transobturator sling placement. Of note was a correlation between the percentage of subjects showing an improvement in IIIQ scores (87.2%) and the percentage of patients reporting their leakage as “much better or better” (89.4%) on PSQ.

In summary, the transobturator midurethral polypropylene sling provides a significant improvement in quality of life and high patient satisfaction in the relative absence of perioperative morbidity, representing an excellent alternative to retropubic midurethral sling procedures.

References

Following midurethral versus bladder sling procedures

Sylvia M. Botros, MD, a,* Yoram Abramov, MD, a Roger P. Goldberg, MD, MPH, a Jennifer L. Beaumont, MS, b Sanjay Gandhi, MD, a Jay-James R. Miller, MD, a Peter K. Sand, MD a

Evanston Continence Center, Feinberg School of Medicine, Northwestern University, Chicago, IL a; Center on Outcomes, Research, and Education (CORE), Evanston Northwestern Healthcare, Evanston, IL b

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KEY WORDS
Bladder neck sling
Midurethral sling
Urge incontinence
Detrusor overactivity

Objective: The objective of the study was to compare detrusor overactivity and urge urinary incontinence rates after midurethral slings versus bladder neck slings.

Study design: Three hundred forty subjects underwent midurethral slings or bladder neck slings. Comparisons were made using Student’s *t* test and *χ*2 test. Multivariate analysis was performed to detect confounding factors.

Results: More patients in the midurethral sling group resolved detrusor overactivity than in the bladder neck sling group (38% versus 15%, *P* < .001). In addition, subjects in the midurethral sling group had significantly lower rates of de novo detrusor overactivity than subjects in the bladder neck sling group (29% versus 62%, *P* = .002). The only significant predictors of postoperative detrusor overactivity were preoperative detrusor overactivity (*P* < .001) and sling type (*P* < .001). After adjusting for preoperative detrusor overactivity, bladder neck slings significantly increased the risk for persistent detrusor overactivity (odds ratio 3.9).

Conclusion: Midurethral slings have increased rates of resolution of detrusor overactivity and lower rates of de novo detrusor overactivity than transvaginal bladder neck sling procedures. © 2005 Mosby, Inc. All rights reserved.

The midurethral tension-free slings are replacing retropubic urethropexies and bladder neck slings as the standard treatment of stress urinary incontinence. Their relative ease and minimally invasive nature combined with high success rates contribute to their popularity. One advantage of midurethral slings over bladder neck slings may be a lower rate of voiding dysfunction.

Concomitant detrusor overactivity (DO) and urge urinary incontinence (UUI) may occur in up to 50% of stress urinary incontinence cases and are often overlooked when evaluating surgical success. Urge urinary incontinence and DO can have a profound impact on quality of life. Detrusor overactivity and UUI after surgery are often grouped with paruresis as voiding dysfunction. It is not clear, however, that DO and UUI are directly related to obstructive slings in the same way obstructive voiding and retention are. Cardozo et al suggested that de novo DO was a result of nerve damage following bladder dissection and not necessarily a result of obstruction.
On the basis of the existing literature, it is not clear that bladder neck slings cause increased de novo DO and UUI over midurethral tension-free slings. However, it is difficult to draw firm conclusions about DO because of the paucity of data. The purpose of this study was to compare the rates of resolution and new-onset of UUI as well as DO following midurethral versus bladder neck procedures at a single referral center.

Material and methods

Three hundred forty patients were identified from a surgical database with accrual dates from December 1988 to September 2004. All subjects identified had stress or mixed urinary incontinence confirmed by urodynamic testing and underwent transvaginal midurethral slings (Tension free vaginal tape [TVT] [Ethicon, Inc., Somerville, NJ] or SPARC, [American Medical Systems, Minnetonka, MN] n = 145) or transvaginal bladder neck slings anchored to Cooper’s ligament (Capio CL slings, [Capio CL, Boston Scientific, Natick, MA] n = 195). Subjects received a routine office evaluation including a 24-hour voiding diary, detailed history, physical and pelvic exam, Q-tip test, urinalysis, postvoid residual volume assessment, and spontaneous uroflowmetry. Standardized multichannel urodynamic evaluation was performed on all but 7 patients preoperatively and all willing and available patients 14 weeks postoperatively.

All definitions conformed to the standards recommended by the International Continence Society except where specifically noted. Low-pressure urethra was defined as a maximum urethral closure pressure 20 cm or greater H2O on urethral closure pressure profilometry. Subjective UUI was defined as any leakage of urine immediately preceded or accompanied by urgency before reaching the toilet and graded on a Likert scale (0 = none, 1 = rare, 2 = some, 3 = quite a bit, and 4 = severe). This Likert scale, however, has not been validated.

Multichannel urodynamic testing included urethrocystometry, urethral pressure profiles, and pressure flow studies. Postvoid residual volume was obtained after spontaneous voiding, and urethrocystometry was performed at a filling rate of 80 mL/min with the patient sitting in a birthing chair at a 45-degree angle. The bladder was filled to maximum cystometric capacity, defined as feeling discomfort, piloerection, or simply inability to stand further filling, while intravesical pressure was recorded. If no vesical contraction was noted, the test was repeated in the standing position with provocative maneuvers. Supported and unsupported urethral closure pressure profiles were performed with the patient sitting at a 45-degree angle at maximum cystometric capacity. Voiding pressure studies were performed with the patient in the seated position and the catheters in place. Abdominal, urethral, and bladder pressures were measured with 8F Mikrotip (Millar Instruments, Inc, Houston, TX) transducer catheters. Detrusor overactivity was defined as an involuntary detrusor contraction of any magnitude associated with urgency or leakage of urine on filling urethrocystometry.

The bladder neck slings were comprised of allograft material and were attached to Cooper’s ligament using a push-and-catch suturing device (Capio CL, Boston Scientific Corp, Natick, MA). The distance between Cooper’s ligament from 1 side to the other was measured, and the graft was cut to size for each patient. Care was taken not to place the sling on excess tension. The sling technique has been previously described. Subjects received a routine office evaluation including a 24-hour voiding diary, detailed history, physical and pelvic exam, Q-tip test, urinalysis, postvoid residual volume assessment, and spontaneous uroflowmetry. Standardized multichannel urodynamic evaluation was performed on all but 7 patients preoperatively and all willing and available patients 14 weeks postoperatively.

Table I Demographics, history, and preoperative characteristics

<table>
<thead>
<tr>
<th>Age (y), mean (SD)</th>
<th>Bladder neck slings</th>
<th>Midurethral slings</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>66.9 (12.9)</td>
<td>57.7 (12.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td>160 (83%)</td>
<td>71 (77%)</td>
<td>.212</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>26.6 (4.6)</td>
<td>27.9 (5.9)</td>
<td>.028</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>115 (58%)</td>
<td>43 (23%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Denominators for percentages are numbers of patients with nonmissing data for that variable. POP-Q, pelvic organ prolapse quantification; PVR, post void residual.

Table II Concomitant procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Capio CL (n = 195)</th>
<th>TVT/SPARC (n = 145)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>59 (30%)</td>
<td>51 (35%)</td>
<td>.338</td>
</tr>
<tr>
<td>Anterior repair</td>
<td>179 (92%)</td>
<td>97 (67%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Posterior repair</td>
<td>95 (49%)</td>
<td>61 (42%)</td>
<td>.224</td>
</tr>
<tr>
<td>SSVVS</td>
<td>63 (32%)</td>
<td>16 (11%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Items are in bold to highlight significant findings. SSVVS, Sacrospinous vaginal vault suspension.

6 Low-pressure urethra was defined as a maximum urethral closure pressure 20 cm or greater H2O on urethral closure pressure profilometry. Subjective UUI was defined as any leakage of urine immediately preceded or accompanied by urgency before reaching the toilet and graded on a Likert scale (0 = none, 1 = rare, 2 = some, 3 = quite a bit, and 4 = severe). This Likert scale, however, has not been validated.

7 Detrusor overactivity was defined as an involuntary detrusor contraction of any magnitude associated with urgency or leakage of urine on filling urethrocystometry.

8 The sling technique has been previously described.

9 Univariate comparisons between the 2 groups were made using 2-tailed Student’s t test or \( \chi^2 \) tests where appropriate. A P value less than .05 was considered statistically significant for all comparisons. Multiple
logistic regression analysis was performed to detect possible confounding factors. Data were analyzed with SAS (version 8.2, SAS Institute, Inc, Cary, NC). The study was approved by the Evanston Northwestern Institutional Review Board Committee for Human Subjects.

### Results

Table I lists the baseline characteristics of the 2 groups. Concomitant procedures for each group are listed in Table II. Preoperatively subjects who underwent bladder neck slings had higher rates of subjective urge urinary incontinence (85% versus 68%, \( P < .001 \)) and DO (76% versus 61%, \( P = .005 \)) as well as low pressure urethras (62% versus 11% \( P < .001 \)) than patients who underwent midurethral slings.

Of the women who had DO preoperatively, more patients in the midurethral sling group had resolution of DO at 3 months than in the bladder neck sling group (38% versus 15%, \( P < .001 \)) as well as better resolution of UUI symptoms (48% versus 32%, \( P = .025 \)). Table III lists the comparison of preoperative and postoperative DO and UUI between the 2 groups.

Table IV lists the results of the univariate analysis. The only independent predictors of postoperative DO were preoperative DO (\( P < .001 \)) and bladder neck sling procedure (\( P < .001 \)) in the multivariate analysis (Table V). After adjusting for preoperative DO, bladder neck slings significantly increased the risk for persistent DO (odds ratio 3.9) over midurethral slings. Rates of retention for the bladder neck slings versus midurethral slings, defined as a postvoid residual 100 cc or more, were 20% versus 19% (\( P = .851 \)) preoperatively and 27% versus 14% postoperatively (\( P = .024 \)). Four subjects in each group required urethrolysis (2% bladder neck versus 3% midurethral sling).

### Comment

These results suggest that midurethral slings offer higher rates of resolution of DO and UUI than bladder neck slings and are associated with lower rates of postoperative DO. Preoperative DO and sling type were the most significant risk factors for postoperative DO.

Persistent or de novo DO or UUI following sling surgeries poses a dilemma for both patients and surgeons treating stress urinary incontinence because of their potential adverse impact on the patients’ quality of life and satisfaction from the surgery. In men, urethral obstruction because of prostatic hypertrophy may cause DO, but the relationship of obstruction to DO is not as clear in women. One explanation for DO and UUI may
be disruption of the nerve supply because of extensive dissection.\textsuperscript{5} Regardless of the etiology, women with DO and UUI have worse quality-of-life scores than stress urinary incontinent patients on validated questionnaires.\textsuperscript{3,4} This becomes significant when a patient substitutes UUI for stress urinary incontinence because of treatment.

The effects of midurethral slings on UUI and DO are not well characterized. The tension-free nature of the tape in conjunction with minimal dissection should, in theory, decrease rates of de novo DO and UUI. Nonetheless, the published rates of de novo UUI for TVT are not substantially less than those reported for bladder neck slings. The published rates of de novo UUI with the TVT procedure range from 4.4\% to 9\%.\textsuperscript{9-12} Similarly, the majority of published rates of de novo UUI for bladder neck slings range from 6\% to 10\%,\textsuperscript{11,13-16} with the exception of 2 studies that found rates ranging from 43\% to 53\%.\textsuperscript{10,12}

Overall we found rates of de novo UUI consistent only with the last 2 studies mentioned for bladder neck slings\textsuperscript{17,18} and higher than the rest for midurethral slings. This may be due to our objective follow-up and our rigorous definition of UUI. Most studies in the literature are chart reviews, and Franco et al\textsuperscript{17} found that objective follow-up differed significantly from chart reviews in their population. They described a de novo UUI rate of 9\% with chart review that increased to 53\% with more objective follow-up.\textsuperscript{17} Amundsen et al\textsuperscript{18} quoted a de novo UUI rate of 15\%, but this was calculated for the entire cohort. When looking at patients who did not have UUI preoperatively in their study, 43\% developed UUI postoperatively. Our rates of UUI are consistent with these careful studies. We recognize the retrospective nature of our study, but we routinely assessed UUI at each visit with a Likert scale and defined UUI as any incontinence associated with urgency.

Our rates of DO are also higher than reported in the literature, but we feel this is due to our definition of maximum cystometric capacity. The International Continence Society defines maximum cystometric capacity as the volume at which the patient feels she can no longer delay micturition.\textsuperscript{15} We continue to fill beyond this point because we feel this is precisely the time that the patient would demonstrate DO or UUI if unable to reach a toilet. We believe our findings to be clinically significant because there is no difference in technique between the 2 groups. In addition, 75-85\% of patients with documented DO preoperatively had subjective symptoms of UUI. Differences in rates of DO may be exacerbated by differences in urodynamic methodology in interinstitutional comparisons. Another explanation for the increased rates of DO after the bladder neck slings may be an improvement in our ability to detect and measure involuntary detrusor contractions in subjects undergoing bladder neck slings with low pressure urethra preoperatively. When the sling increased its urethral closure pressure and intrinsic urethral resistance,\textsuperscript{19} we may have been able to postoperatively measure low-pressure DO that was not detectable before. Finally, tensioning may have been increased in patients with low-pressure urethra; however, low-pressure urethra was not a significant predictor of DO in the final analysis.

Few studies directly compare rates of resolution of UUI as well as de novo UUI for slings and TVTs, and the ones that do, do not indicate any significant differences with regards to UUI or DO.\textsuperscript{9-15} This is one of the larger cohorts in the literature looking at the rates of resolution of DO and UUI and 1 of few comparisons between midurethral tension-free slings and bladder neck slings performed in the same center. We recognize that the two populations differ significantly, and unfortunately, because of the retrospective nature of the study, we were not able to change these variables; however, we were able to adjust for them using logistic regression, and none of the possible confounding factors contributed to the significance of the outcomes. Additionally, we recognize the lack of validated quality-of-life questionnaires in the subjective evaluation of patients as a weakness of our study, but the assessment of quality of life was not the hypothesis of this analysis. The strength of our study is the combined subjective and objective comparison of 2 cohorts in the same center. The definitions of DO and UUI are uniform between the 2 groups, and any difference in outcome can not be attributed to differences in technique or definition.

Our study identifies a benefit of midurethral slings with regard to resolution of UUI and DO. We also identified a significant reduction in the occurrence of de novo DO, compared with bladder neck slings. However, we saw no difference in the development of the symptom of de novo UUI. This may be a result of a small sample size of patients without preoperative UUI; alternatively, the difference noted may not be clinically significant. Our study corroborates findings that indicate that rates of de novo UUI are similar between the 2 groups.\textsuperscript{9-15}

In conclusion, midurethral tension-free slings were found to confer significant benefit to women in decreasing the rates of de novo DO and resolutions of UUI when compared with bladder neck slings but were not different for the onset of de novo UUI symptoms. These findings may represent important factors to consider in evaluating surgical outcomes and counseling surgical patients.

References


Delivery mode is a major environmental determinant of stress urinary incontinence: Results of the Evanston-Northwestern Twin Sisters Study

Roger P. Goldberg, MD MPH,* Yoram Abramov, MD, Sylvia Botros, MD, Jay-James Miller, MD, Sanjay Gandhi, MD, Angel Nickolov, Wendy Sherman, Peter K. Sand, MD

Evanston Continence Center, Northwestern University Medical School, Evanston, IL

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KEY WORDS
Stress urinary incontinence
Childbirth
Epidemiology
Identical twins

Objective: We studied a large cohort of identical twin sisters, utilizing the unique properties of a twin research design to explore the relationship between obstetrical delivery mode and stress urinary incontinence.

Study design: An anonymous 67-item survey was completed by 271 identical twin pairs (n = 542) at the world’s largest annual gathering of twins. Logistic regression for repeated binary measures was used to evaluate risk factors and accounting for shared genetics within pairs.

Results: The twins had a mean age of 47.1 years (range 15 to 85 years), and stress urinary incontinence was reported by 51.8%. Stress urinary incontinence was associated with age (P = .001), parity (P = .001), obesity (P = .002), and birth mode, with vaginal delivery conferring a considerable increase in stress urinary incontinence risk relative to cesarean section (odds ratio 2.28, 95% confidence interval 1.14 to 4.55, P = .019).

Conclusion: Vaginal delivery mode represents a potent determinant of stress urinary incontinence, carrying more than twice the risk of cesarean section. This study of identical twins provides new insight into the epidemiology of female incontinence.

Stress urinary incontinence (SUI) is a widely prevalent disease entity in the female population, having an impact on 15-50% of postreproductive women before menopause. Its etiology is multifactorial, influenced by both environmental (nurture) and genetic (nature) risk factors. Pregnancy and childbirth are regarded as key environmental determinants, and more than 60% of incontinent women associate its onset with pregnancy, childbirth, or the postpartum. However, the impact of birth mode on incontinence, and the possible protective role of cesarean section, have remained subjects of intense debate. Several observational studies have identified higher rates of incontinence after vaginal delivery and lower, but not absent, risk after cesarean section.
The objective of the Evanston-Northwestern Twin Sister Study was to investigate key risk factors for incontinence, using an identical twin study design. Twin studies are unique in their ability to evaluate environmental risk factors and differentiate them from genetic determinants. Adult monozygotic twins share identical genetics but differ in their environmental exposures, thus providing built-in control over genetic variance and a natural research model for the assessment of environmental risk. When a disease trait such as SUI is discordant among identical twins, it provides a valuable research opportunity to investigate and understand an environmental exposure such as obstetrical delivery mode. We hypothesized that identical twins discordant for SUI would demonstrate significant differences in their modes of delivery.

Material and methods

A 67-item survey of incontinence and pelvic floor symptoms was administered at the Twins Days Festival, the world’s largest annual gathering of twins held in Twinsburg, Ohio. The survey was offered to all women visiting the research tent at the 2003 and 2004 festivals. Respondents were invited to participate in an anonymous survey and received $10 (U.S. dollars) for their participation. Participants were instructed to complete their survey without assistance and to avoid conferring with their twin sister.

The survey was a compilation of validated questionnaires (Pelvic Floor Distress Inventory and Incontinence Impact Questionnaire), a sociodemographic and medical questionnaire, and Likert symptom scales. “Any SUI” (“slight,” “moderate,” or “greatly”) was defined as an affirmative reply to the question, “Do you leak urine with coughing, straining, laughing, physical activity, or exercise?” Women responding “none” were categorized as “no SUI.” SUI symptoms were quantified by episodes per week (1 to 2, 3 to 5, 5 to 10, more than 10). “Bothersome SUI” was defined as any degree of SUI accompanied by an affirmative response to the question, “Do you consider this to be socially bothersome?” Demographic data included age, parity, body mass index (BMI), menopausal status, delivery mode, length of second stage of labor, forceps, episiotomy, and fetal weight. Cesarean sections were defined as being performed before labor began; in labor, before pushing; or after onset of pushing. Medical history included questions potentially relating to incontinence, including asthma, constipation, smoking, and pelvic surgery.

Medical, obstetrical, and demographic factors underwent bivariate and stepwise multivariate analyses performed with Excel for Windows (Microsoft, Redmond, WA) and SAS (SAS Institute, Inc, Cary, NC). To account for correlated data (ie, shared genetics) between twins, we implemented a logistic regression model for repeated binary measures. Three regression models were built to evaluate all putative risk factors while maintaining statistically valid reference groups. The first (model A) included all respondents to examine the general impact of parity with nulliparous women as a reference. Model B was limited to twin pairs with 2 parous sisters (regardless of their delivery modes), enabling valid comparison of vaginal versus cesarean birth. Model C was limited to pairs in which both sisters delivered vaginally, enabling comparison of episiotomy and forceps. Explanatory variables were chosen to enter multivariate models based on $P$ values less than .250 in bivariate logistic regressions in which the outcome variable was assigned 1 if SUI was present and 0 otherwise. The 3 initial models included all such explanatory variables as well as second- and third-order interactions. Nonsignificant variables were dropped using backward elimination. $P$ values .05 or less were considered significant.

Model A utilized 271 identical twins pairs ($n = 542$). There were 10 potential explanatory variables considered for the multivariate model, including number of pregnancies; total parity; smoking history; paternal and maternal BMI; age (defined categorically for all analyses: younger than 40 years, 40 to 49 years, 50 to 59 years, older than 60 years); menopause; duration of the second stage of labor; asthma; and hysterectomy. This model was used for analyzing general demographic and medical risk factors and parity but not birth mode because it included nulliparous respondents.

Model B was estimated with all factors listed for model A plus 2 additional obstetrical factors: delivery mode (cesarean section only versus 1 or more vaginal deliveries) and weight of largest baby (less than 4000 g versus 4000 g or more). This model was applied to a subsample of 173 twin pairs ($n = 346$) in which both sisters had given birth at least once. This parous-parous twin sister cohort was used specifically for comparing vaginal and cesarean birth modes, the main focus of this analysis.

Model C was estimated on a subsample of 137 identical twin pairs for which both sisters had 1 or more prior vaginal births ($n = 274$). This model was used for analyzing risk factors exclusive to vaginal birth, specifically episiotomy and forceps.

The study was approved by the Investigational Review Board of Evanston Northwestern Healthcare.

Results

The survey was completed by 271 identical twin sister pairs ($n = 542$). One hundred forty-six women were nulliparous, 85 had 1 previous birth, and 310 had 2 or more births. Demographic and medical characteristics are summarized in Table I.
SUI was reported by 51.8% of the overall cohort; among symptomatic women, 75% reported 1 to 2 weekly episodes, 13% reported 3 to 5, 8% reported 5 to 10, and 4% reported more than 10 weekly episodes. Among premenopausal women, 43% reported SUI versus 63% of postmenopausal women (P < .001). The mean age (SD) of incontinent women was 51.0 years (12.7) versus 45.0 years (14.7) for women without SUI (P < .001). Mean BMI (SD) was 27.5 (6.3) for women with SUI, greater than 25.4 (5.7) for continent women. (P < .001). Thirty-seven percent of women with SUI characterized it as socially bothersome, translating into a 15.5% rate of bothersome SUI within the overall sample.

With respect to obstetrical delivery mode, 87.1% of parous women reported 1 or more vaginal deliveries, and 12.9% had delivered by cesarean section only. Rates of SUI were 67.1% and 47.7%, respectively, compared with 24% of nulliparas (P < .001). Sixty-three percent of subjects with 1 prior vaginal birth reported SUI versus 69.4% of women with 2 or more vaginal deliveries. Other descriptors included previous episiotomy (54.4%), cesarean section after labor pushing (4%), cesarean section before pushing (10%), and elective (before labor) cesarean section (7%).

Regression model A focused on general demographic and medical factors and the effect of parity. This model confirmed significant associations between SUI and age (odds ratio [OR] 2.3 for age 40 to 49 years; OR 2.50 for age 50 to 59 years, OR 2.8 for age older than 60 years, P = .008), menopause (OR 1.49, P = .05), and increasing parity, with a dose effect observed relative to nulliparous respondents (OR 2.27 for 1 birth, 4.33 for 2 or more births, P = .001). Obesity, defined as BMI greater than 30, conferred a significantly higher risk of SUI (OR 3.39, P < .001), but overweight (BMI 25 to 29.9) had no association (OR 1.35, P = .216). Thus, parity and obesity emerged as major environmental risk factors for SUI.

The major study findings derive from regression model B, consisting of 173 parous-parous twin pairs (n = 346), evaluating the impact of obstetrical delivery mode. Vaginal birth mode was strongly predictive of SUI, associated with more than doubling of the risk after cesarean section (OR 2.28, 95% confidence interval [CI] 1.14 to 4.55, P = .019); stated differently, cesarean section conferred a more than 2-fold reduction (OR 0.44, 95% CI 0.22 to 0.87, P = .019). Obesity (BMI 30 or greater) remained a risk factor for SUI, even after controlling for birth mode (OR 3.14, 95% CI 1.51 to 6.56, P = .002). Interestingly, parity was no longer predictive of SUI in this model, its effect washed out by the impact of delivery mode and BMI. Weight of the largest newborn was not associated with SUI risk. Significant environmental predictors of SUI according to the final model are summarized in Table II.

Regression model C included 137 twin pairs (n = 274) in which both sisters had at least 1 previous vaginal birth and evaluated risk factors specific to the vaginal birth mode (ie, operative delivery and episiotomy). Neither forceps (OR 1.41, P = .25) nor episiotomy (OR 0.97, P = .92) was predictive of SUI when compared with nonoperative vaginal birth.

“Bothersome SUI” was influenced by 3 variables: parity, age, and BMI. The rate was 5.6% among nulliparous women, increasing to 9.5% after 1 birth and 21.8% after 2 or more deliveries (P < .001). Obesity carried twice the risk (22.3%) of normal weight (11.5%, P = .004). Increasing age was associated with increasing risk (9.6% under age 40 years, 15.8% age 40 to 49 years, 18.1% age 50 to 59 years, and 20.7% for age 60 years or more). Bothersome SUI appeared to be more common among women with previous vaginal birth than after cesarean section (21.1 versus 10.5%, OR 2.28, P = .44); however, the sample size was not adequate to test this association with a multivariate model. No associations were identified between bothersome SUI and other

### Table I  Demographics and medical conditions in the twin sister cohort (n = 542)

<table>
<thead>
<tr>
<th>Variable</th>
<th>SUI (n), %</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>47.1 (15-85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median parity</td>
<td>2 (0-7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>46.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>16.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>26.4 (6.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>90.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>6.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian American</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>13.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic cough</td>
<td>2.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>3.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUI surgery</td>
<td>3.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>20.2%</td>
<td></td>
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</tr>
</tbody>
</table>

### Table II  Environmental predictors of SUI in 173 parous-parous identical twin pairs (n = 346)

<table>
<thead>
<tr>
<th>Mode of delivery</th>
<th>SUI (n), %</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>67.1 (298)</td>
<td>2.28</td>
<td>1.14-4.55</td>
<td>.019</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>47.7 (44)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30 (obese)</td>
<td>3.14</td>
<td>1.50-6.56</td>
<td>.002</td>
</tr>
<tr>
<td>25 to 29.9 (overweight)</td>
<td>1.44</td>
<td>0.84-2.47</td>
<td>.189</td>
</tr>
<tr>
<td>20 to 24.9 (normal weight)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sample size does not total 346 because of missing data (n = 5).
obstetrical factors, including forceps (OR 0.92, \( P = .80 \)), episiotomy (OR 1.18, \( P = .64 \)), and macrosomia (OR 1.05, \( P = .87 \)).

Comment

Urinary incontinence is associated with a substantial public health burden, and for many women, pregnancy and childbirth represent important predisposing events. However, comparing the effects of vaginal and cesarean delivery on incontinence risk has posed a formidable methodological challenge. A wide array of potential confounding factors needs to be considered, including differences in genetic constitution. Genetic predisposition may underlie the observation that 2 women with closely similar obstetrical experiences can manifest completely different degrees of incontinence and pelvic dysfunction; altered metabolism of collagen, elastin, and alpha-1 antitrypsin have all been hypothesized as constitutional elements that may influence risk.

The fact that some women are genetically destined for SUI, regardless of childbirth, has been borne out clinically by several investigators including Francis, finding up to half of incontinent primigravida women noted some leakage before their first pregnancy, and also Buchsbaum et al., who identified SUI in 30% of nulliparous menopausal nuns. SUI is indeed a product of not only obstetrical history and environment but also genetic predisposition. Within study samples consisting of unrelated subjects, innumerable genetic differences between subjects may influence the risk of SUI and can never be fully adjusted for.

A prospective randomized clinical trial comparing vaginal with cesarean birth would represent an ideal method for sorting genetic variance among subjects and isolating the effect of birth mode on incontinence. One randomized clinical trial comparing vaginal versus cesarean delivery for breech presentation did, in fact, reveal a lower rate of incontinence after cesarean section. However, no randomized trials have compared vaginal and cesarean birth for normal, vertex deliveries.

Identical twin studies are regarded as an optimal natural experimental design in which environmental traits can be assessed with unparalleled biological control over genetic factors. Between genetically identical twins, differences in observed traits are likely to have resulted from environmental factors. When identical twin pairs are discordant for the primary outcome of interest, this provides a powerful opportunity to evaluate environmental determinants.

Our aim in studying this large cohort of identical twin sisters was to gain new insight into a controversial women’s health topic: the influence of delivery mode on incontinence. SUI was reported by 51.8% of subjects overall, and women delivering vaginally demonstrated a significantly higher likelihood of SUI than their biological counterparts who delivered by cesarean section (OR 2.28, 95% CI 1.14 to 4.55, \( P = .019 \)). Interestingly, the impact of birth mode was strong enough to nullify the effect of parity in the multivariate analysis, thus suggesting that with respect to SUI risk, a woman’s choice of delivery mode may be more important than the number of children she chooses to have.

Placing this study into the context of existing literature, one may conclude that delivery mode is indeed a major determinant of SUI risk among younger postreproductive women but that with advancing age and beyond menopause, differences in SUI rates are determined less and less by obstetrical factors because obstetrical effects are washed out by the equalizers of age, hypoestrogenism, declining urethral function, and genetic predisposition.

Although this study provides new insight into the relationship between vaginal birth and SUI, these findings should not be misconstrued as justification for elective cesarean section. Even if elective cesarean section would decrease the risk of SUI for some women, it is essential to factor the significant morbidity and costs that would accompany this narrow gain. Moreover, pregnancy for some women is enough to cause pelvic dysfunction, with delivery route playing only a minor role. We believe that women’s health care providers should promote a balanced debate, based on the best existing scientific evidence.

Limitations of this study include potential recall bias, particularly with respect to obstetrical details (ie, fetal weight, length of labor). However, this is unlikely to have influenced the major variables of interest (ie, delivery mode and the presence of SUI). Moreover, we were unable to fully investigate cesarean subtypes because few women delivered solely by elective cesarean section before the onset of labor. Previous studies have indeed suggested that timing of cesarean sections may largely determine their degree of protection. Therefore, the protection offered by planned cesarean section could potentially be greater than the aggregate effect (combining elective and after-labor cesarean sections) we observed.

By applying an identical twin research design to female incontinence, this study provides control over elements of genetic variance (nature) that typically confound the analysis of environmental factors (nurture) within samples of unrelated individuals. This comparison of biologically identical twins confirms that delivery mode plays a major role in the etiology of postreproductive SUI, with more than doubling of risk after vaginal birth, compared with cesarean section.

The overall risks and benefits of vaginal versus cesarean delivery should be a subject of continued debate, involving a broad array of physical and psychological factors lying well beyond the scope of this analysis. We suggest that pelvic health be routinely discussed between clinicians and expectant mothers, regardless of whether...
her delivery mode is vaginal or abdominal, including a stronger focus on the primary prevention of pelvic floor dysfunction during pregnancy, childbirth, and beyond.

References

Diabetes and urinary incontinence in 50- to 90-year-old women: A cross-sectional population-based study

Cynthia M. Lewis, MD, a,* Ronald Schrader, PhD, b Angela Many, MD, a Mary Mackay, MS, b Rebecca G. Rogers, MDa

Department of Obstetrics and Gynecology, University of New Mexico Health Sciences Center,a and Department of Mathematics and Statistic, Clinical Research Center, School of Medicine, University of New Mexico, b Albuquerque, NM

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KEY WORDS
Insulin-requiring diabetes
Urinary incontinence
Risk factors

Objective: The purpose of this study was to examine the association between urinary incontinence and diabetes in a large community-based population of women.

Study design: The Health and Retirement Study is a large multistage area probability sample of households in the United States. Data were collected from 10,678 women aged 50 to 90 years. Dependent variables were no, mild, and severe incontinence. Independent variables consisted of demographic and health data. Diabetes was dichotomized into insulin-requiring (IRDM) and non–insulin-requiring disease (NIRDM). Survey-based ordered logistic regression was used to simultaneously analyze associations between incontinence groups.

Results: Urinary incontinence was reported by 22% (2319/10,678) of women. IRDM was associated with urinary incontinence (odds ratio [OR] 1.63; 95% CI 1.28-2.09), but NIRDM was not (OR 1.20; 95% CI 1.00-1.45).

Conclusion: IRDM is independently associated with urinary incontinence in women ages 50 to 90 years, independent of patient body mass index, comorbidities, or age.

Diabetes is epidemic in the United States, affecting both adults and children.1 In 2001, the prevalence of diabetes in adults ages 50 to 70 years was 11.2% to 15.5%, and the disease is more prevalent in women.2 Diabetes is closely associated with obesity and cardiovascular risk factors.3 The cost of this disease is estimated at 98.2 billion dollars in direct and indirect costs annually.4

Urinary incontinence is also common, affecting 10% to 40% of postmenopausal women5 and costing the economy $16.3 billion annually.6 Women with incontinence account for 76% of this direct cost. Urinary incontinence is associated with increased risk for skin disorders, falls, and urinary tract infections. Onset of incontinence in the elderly contributes to admissions to nursing homes.6 Incontinence also impacts a woman’s quality of life, including relationships and sexual function.7

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Lower urinary tract dysfunction in patients with diabetes is well documented. Impaired detrusor contractility with urinary retention is known to be associated with diabetes. The correlation of urinary incontinence and diabetes is less well studied. Some reports state that there is no correlation for females, while others report up to a 40% to 70% increased prevalence of incontinence in women with diabetes. The aim of this study is to determine the prevalence of urinary incontinence in women with diabetes compared with women without diabetes in a large community-based population. We will also examine whether the severity of diabetes correlates with the severity of incontinence.

Materials and methods

The Health and Retirement Study (HRS) is a population-based, longitudinal study of older Americans funded by the National Institute on Aging. The study was developed and conducted by the University of Michigan’s Institute for Social Research to provide data on persons from preretirement into retirement, including information on health, insurance, finances, family support systems, labor status, and retirement planning. Since 1992, the data have been collected by interviews with respondents in 2-year intervals called waves. The database is distributed to the public via a secure web site requiring online registration. Because confidentiality requirements were met, University of New Mexico Human Research and Review Committee approval was waived.

The HRS uses a national multistage area probability sample of households in the United States. Two-fold oversampling of Hispanic and black women relative to white women and Florida residents, because of the high density of older populations, was performed. The oversampling of Hispanic and black populations was critical to the success of the study because retirement decisions, family structure, health conditions, and economic resources are thought to be different for the Hispanic and black populations than for the white population. Oversampling provides a large enough sample to permit independent analysis of these populations. To compensate for the unequal probabilities of selection for these populations, respondent sampling weights were used.

This study uses responses collected in 2000 (wave 5) and includes community-dwelling women aged 50 to 90 years. Surveys were conducted by trained interviewers who contacted participants by telephone or in face-to-face interviews. All data are self-reported. Survey questions pertaining to subject characteristics, including demographics and health, were used for data analysis.

Women were asked, “...during the last 12 months, have you lost any amount of urine beyond your control?” Then they were asked, “On about how many days in the last month have you lost any urine?” Women who answered “zero days” were classified as continent. This definition of continent was selected in an effort to eliminate the effect of transient causes of urinary incontinence, such as urinary tract infection, on the data analysis. If women were unable to report how many days they had lost urine in the last month, they were prompted with additional questions: “Was that more than 5 days?” and if they answered yes to this question, “More than 15 days?” Incontinence was classified as mild if women reported loss of urine on 15 or fewer days, and severe if they reported greater than 15 days of incontinence a month based on a previous study using the HRS database. If they could not quantify the number of days of urine loss, they were excluded from further analysis. The type of incontinence was not identified.

The questions about diabetes included were: 1) “Has your doctor ever told you that you have diabetes or high blood sugar?”; 2) “Are you now taking medication that you swallow?”; 3) “Are you now using insulin shots or a pump?”; 4) “Has your diabetes caused you to have trouble with your kidneys or protein in your urine.” The survey did not distinguish between type 1 and type 2 diabetes; therefore, diabetes was dichotomized into non-insulin-requiring (NIRDM) and insulin-requiring diabetes (IRDM). IRDM and renal pathology connote more severe or long-standing disease; those with renal pathology were considered IRDM. Covariates were identified from the literature and included age, parity, race/ethnicity, body mass index (BMI), difficulty in performing 1 or more activities of daily living (ADLs), and medical conditions. Age was analyzed in 5-year intervals. Parity was categorized as no children, 1 or 2 children, or more than 2 children. BMI was calculated as kg/m². Medical conditions assessed in this study included heart disease, hypertension, stroke, lung disease, cancer, and arthritis. The questions regarding ADLs addressed the subject’s basic functioning status, inquiring about difficulty with dressing, walking, bathing, eating, getting in or out of bed, and using the toilet.

Survey-based ordered logistic regression was used to simultaneously analyze independent associations between no, mild, and severe incontinence using STATA (STATA Corporation, College Station, TX). This form of regression calculates one odds ratio for comparisons between all 3 incontinence groups for each independent variable, allowing analysis of ordinal dependent variables. Pearson chi-square was used to determine independence between bivariate relationships and multiple comparisons of means was performed by analysis of variance (ANOVA) using SAS (SAS, Cary, NC). The nonproportional sampling of the HRS is accounted for by using sampling weights provided. Significance was defined as $P < .05$. Records with missing values for any of the variables used in the model were deleted.
Results

Selection criteria were met by 10,678 women aged 50 to 90 years. Data on continence were not available from 1.7% of the subjects, and they were not included in the analysis. Two thousand and nineteen (21.7%) women reported urinary incontinence. Of these, 1321 (57%) had mild and 998 (43%) had severe incontinence. Demographic and health data are listed in Table I. Non-Hispanic whites comprised the majority of the population and were used as the reference group for ethnicity.

Comparisons were made between women without diabetes, with NIRDM, and with IRDM (Table II). Women without diabetes were younger than those with non–insulin-requiring diabetes \((P < .001)\). BMI varied between the groups with a 1 unit increase progressing from no diabetes to IRDM. Women with diabetes reported a greater prevalence of incontinence than those without diabetes, and women with IRDM reported the highest prevalence of incontinence, followed by those with non–insulin-requiring diabetes and women without diabetes \((P < 0.001)\). Parity was also different between these groups, with mean parity ranging from 3.1 to 3.9.

Parity was not a risk factor for urinary incontinence in this sample population. The continence status of nulliparous women or women delivering 1, 2, 3, 4, or 5 or more children was not different \((P = .059)\). Parity was then reanalyzed by grouping women as nulliparous women, a parity of 1 or 2, or more than 2 children. Comparing these 3 groups confirmed no differences in the prevalence of incontinence \((P = \text{NS})\). Parity was therefore eliminated from multivariate analysis.

Limitations in any ADL were a strong predictor of incontinence \((OR 2.48; 95\% \text{ CI} 2.15-2.85)\). ADLs were dichotomized into none versus 1 or more for logistic regression. Limitations in performing ADLs significantly masked the effects of age and stroke on incontinence and, therefore, ADLs were removed from the final analysis.

Diabetes was associated with an increased risk of urinary incontinence. IRDM increased the odds of having urinary incontinence by 63\%, and NIRDM was weakly associated with incontinence \((OR 1.20; 95\% \text{ CI} 1.00-1.45)\). Age conferred a small but significant increased risk for incontinence for each 5-year interval \((OR 1.01; 95\% \text{ CI} 1.003-1.02)\). Each unit increase in BMI resulted in a 19\% increased odds for incontinence. Non-Hispanic white ethnicity, cancer, lung disease, hypertension, heart disease, stroke, and arthritis were also predictors of incontinence \((\text{Table III})\). Each ethnicity analyzed had a significantly lower risk of incontinence than the non-Hispanic whites. This difference was greatest in the blacks \((OR 0.46; 95\% \text{ CI} .38-.56)\).

Comment

In this large cross-sectional study of community-dwelling women in the United States aged 50 to 90 years we found IRDM to be a risk factor for both mild and severe urinary incontinence independent of other

---

**Table I** Demographic and health data*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population ((n = 10,678))</th>
<th>Continent ((n = 8359))</th>
<th>Mild incontinence ((n = 1321))</th>
<th>Severe incontinence ((n = 998))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(^1)</td>
<td>67.1 (9.9)</td>
<td>67.7 (10.1)</td>
<td>72.2 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>73.8</td>
<td>73.7</td>
<td>82.7</td>
<td>83.1</td>
</tr>
<tr>
<td>Black</td>
<td>14.9</td>
<td>16.1</td>
<td>11.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.7</td>
<td>6.3</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Other</td>
<td>3.6</td>
<td>3.9</td>
<td>2.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>7.0</td>
<td>6.4</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>1-2 children</td>
<td>35.5</td>
<td>35.0</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>&gt;2 children</td>
<td>57.5</td>
<td>58.6</td>
<td>57.4</td>
<td></td>
</tr>
<tr>
<td>BMI(^1)</td>
<td>26.9 ± 5.8</td>
<td>27.1 ± 5.9</td>
<td>27.0 ± 6.4</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIRDM</td>
<td>9.2</td>
<td>8.6</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>IRDM</td>
<td>4.7</td>
<td>4.9</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>48.9</td>
<td>54.1</td>
<td>62.7</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>17.3</td>
<td>21.6</td>
<td>35.8</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>5.4</td>
<td>8.2</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>7.9</td>
<td>11.2</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>11.5</td>
<td>13.9</td>
<td>20.7</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>58.8</td>
<td>70.2</td>
<td>80.7</td>
<td></td>
</tr>
</tbody>
</table>

* Percentage of population by continence group.

\(^1\) Mean (SD).

---
risk factors found in this population. Other significant risk factors included non-Hispanic white race, older age, increasing BMI, and all medical comorbidities analyzed except NIRDM.

Insulin-requiring diabetes conferred a 63% increased odds of urinary incontinence when compared with continent women and those with mild incontinence. This agrees with other studies that found urge incontinence increased among women with diabetes.\textsuperscript{5,15,16} Unfortunately, we were unable to distinguish the type of incontinence women in our study population reported. Type 2 diabetes comprises approximately 80% of all cases of diabetes, and insulin requirements indicate severe or longstanding disease. These patients would be at greater risk for neurologic and/or vascular pathology. This may explain why only the women with IRDM have such a great risk of incontinence.

Increasing BMI\textsuperscript{17} and lung disease\textsuperscript{18} are conditions known to increase abdominal pressure and are associated with stress incontinence. Increasing age was associated with urinary incontinence and may be the result of medical comorbidities related to aging, changes in muscle mass or strength, neurologic, or vascular changes. Arthritis was strongly associated with incontinence. This may be secondary to limited mobility\textsuperscript{15} or an autoimmune interaction involving the lower urinary tract, creating urge-type symptoms. Cardiovascular disease, including hypertension, heart disease, and stroke, increased the odds of incontinence 19% to 50%. It is difficult to cull out the impact of the vascular component on incontinence versus the association with other comorbidities, such as diabetes.

White women were at the greatest risk for urinary incontinence when compared with black, Hispanic, or “other” ethnicities. Our data support previous studies showing black women have a lower prevalence of incontinence than white women.\textsuperscript{12,14,15} This is somewhat paradoxical because blacks also have a higher prevalence of obesity and diabetes. Protective factors may include differences in black female pelvic morphology,\textsuperscript{19} and functional and morphologic differences in the urethral sphincteric and support system of black women.\textsuperscript{20} There may also be differences in the reporting of bothersomeness between ethnicities and this may result in skewed results.

We found women with limitations in performing 1 or more ADLs at a 2.5-fold increased risk for urinary incontinence. Clinically, it makes sense that women experiencing problems with mobility may experience difficulty with toileting. However, including ADLs in the analysis overwhelmed the effects of age and stroke as risk factors for incontinence, both of which have been associated with urinary incontinence.\textsuperscript{16} Several reports have confirmed the association between health status and performance of ADLs in older populations.\textsuperscript{21} In essence, the presence of limitations in ADLs may be largely dependent on the presence of comorbidities. Because of this relationship, ADLs were removed from the final analysis.

A significant strength of the study is that it is a large population-based study of older community-dwelling individuals. To date, this is the largest study reporting the association between diabetes, increasing weight, and urinary incontinence. Oversampling of minority populations provides more power to the health and social differences between ethnic groups. These factors strengthen the external validity of the study.

The 22% prevalence of incontinence in our study is comparable to that found by others.\textsuperscript{14,15} The sampling size and strategy of this study may explain why the prevalence is less than other studies of older community-dwelling women.\textsuperscript{5} Self-reported data are a limitation of this study; however, studies have determined that self-reported data have acceptable validity to determine differences between groups.\textsuperscript{22} The structure of the questionnaire did not allow us to distinguish the type of urinary incontinence,

### Table II Comparison of women without and with diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>No diabetes</th>
<th>NIRDM</th>
<th>IRDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*\textsuperscript{1}</td>
<td>67.10 ± 10.1</td>
<td>68.33 ± 9.3</td>
<td>67.44 ± 9.3</td>
</tr>
<tr>
<td>Parity*\textsuperscript{1}</td>
<td>3.21 ± 2.2</td>
<td>3.54 ± 2.5</td>
<td>3.9 ± 2.7</td>
</tr>
<tr>
<td>BMI*\textsuperscript{1, v}</td>
<td>26.72 ± 5.8</td>
<td>27.74 ± 5.9</td>
<td>28.75 ± 6.7</td>
</tr>
<tr>
<td>Urinary incontinence\textsuperscript{1}</td>
<td>23.52%</td>
<td>28.37%</td>
<td>33.39%</td>
</tr>
</tbody>
</table>

\* Data expressed as mean and SD. \textsuperscript{1} Age different for only women with no diabetes and women with non–insulin-requiring diabetes. \textsuperscript{v} OR for each unit increase in BMI. All comparisons \( P < .001\). Percentages were compared using the chi-square test. Multiple comparisons of means were performed using ANOVA.

### Table III Risk of urinary incontinence

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>1.01 (1.00-1.02)</td>
<td>.004</td>
</tr>
<tr>
<td>BMI\textsuperscript{1}</td>
<td>1.02 (1.01-1.03)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hispanic\textsuperscript{1}</td>
<td>0.692 (0.52-0.92)</td>
<td>.012</td>
</tr>
<tr>
<td>Black\textsuperscript{1}</td>
<td>0.46 (0.38-0.56)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Other\textsuperscript{1}</td>
<td>0.64 (0.44-0.95)</td>
<td>.026</td>
</tr>
<tr>
<td>NIRDM</td>
<td>1.20 (1.00-1.45)</td>
<td>.052</td>
</tr>
<tr>
<td>IRDM</td>
<td>1.63 (1.28-2.09)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.23 (1.05-1.44)</td>
<td>.009</td>
</tr>
<tr>
<td>Lung disease</td>
<td>1.61 (1.36-1.92)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.19 (1.06-1.34)</td>
<td>.003</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1.40 (1.22-1.60)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.50 (1.22-1.85)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.86 (1.65-2.11)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

\* Age analyzed in 5-year intervals. \textsuperscript{1} OR for each unit increase in BMI. Reference group is non-Hispanic white women.
which may have allowed a more specific analysis regarding risk factors for urinary incontinence. The route of delivery was not defined and this may have had an impact on the outcome of parity as a risk factor for urinary incontinence.

Urinary incontinence is prevalent in menopausal noninstitutionalized women.\textsuperscript{12,13} Diabetes is increasing in the United States\textsuperscript{2} and, with other comorbidities, is an independent risk factor for urinary incontinence. Healthcare providers should recognize this and endeavor to improve screening for urinary incontinence and promote patient education in an effort to decrease the morbidity suffered by patients and improve quality of life.

References

Objective: The purpose of this study was to describe levator ani (LA) anatomy in postterm nulliparas using 3-dimensional (3-D) magnetic resonance (MR).

Study design: Nulliparas (n = 84) with uncomplicated, postterm pregnancies underwent an MR (4 mm slices, 0 gap) of the uterus and pelvis. LA volume and morphometry were assessed using 3-D post-processing software.

Results: LA insertion into the symphysis was visible in 93%, and the iliococcygeus muscle assumed a convex shape (arch) in the 92% of the 84 women. The LA shape was characterized as “U” in 53% and “V” in 47%. Mean LA volume was 13.5 (3.7) cm³. There was a positive association between LA volume and higher fetal station (P = .02) and increasing BMI (P < .001). However, no relationship between LA volume and station was found after adjusting for BMI.

Conclusion: BMI was correlated with LA volume in postterm nulliparas. LA insertion into the symphysis and the iliococcygeus arch were well-preserved overall and morphometry was variable.

Although pelvic organ prolapse has been associated with parity in many epidemiologic studies, it is unknown whether pregnancy, parturition, or a combination of these factors contributes to this association.1-3 There are surprisingly few studies on the effects of pregnancy upon the pelvic floor. Pregnant women have been found to have increased stages of prolapse compared with age-matched nonpregnant controls.4 In addition, women have been found to have increasing prolapse as pregnancy progresses; however, the effect of the gravid uterus upon the pelvic floor remains largely unexplored.5 Magnetic resonance imaging (MRI) has been used to identify anatomic defects in women with pelvic floor dysfunction.6-9 Levator ani dysmorphology identified by MRI has been associated with urinary incontinence as well as pelvic organ prolapse.7-11 The majority of these studies have been performed in older, parous women with recognizable pelvic floor defects on clinical exam. Relatively few studies have used MRI to describe pelvic floor anatomy in nulliparous women of childbearing age, and none have evaluated the pelvic floor in pregnancy.12-16

Muriel K. Boreham, MD,a Michael V. Zaretsky, MD,a Marlene M. Corton, MD,a James M. Alexander, MD,a Donald D. McIntire, PhD,a Diane M. Twickler, MDa,b

Department of Obstetrics and Gynecology,a Department of Radiology,b University of Texas Southwestern Medical Center, Dallas, TX

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Therefore, the aim of this study was to describe levator ani morphology in nulliparous women at term using MRI. Furthermore, we utilized 3-dimensional (3-D) reconstruction reformatting techniques to assess the feasibility of estimating levator ani volume, as well as determining its relationship to the fetus.

**Material and methods**

At Parkland Memorial Hospital (Dallas, TX), women whose pregnancies reach 41 completed weeks are referred to a postdates obstetrics clinic. Information about each patient’s pregnancy, labor course, and neonatal outcomes is prospectively collected and entered into a computerized database. From July 7, 2003 through April 19, 2004, nulliparous women scheduled for induction were asked to participate in a University of Texas Southwestern Medical Center Institutional Review Board–approved study of MRI of the maternal pelvis and fetus. The current project was a part of this ongoing study and evaluated levator ani morphometry in these women.

Nulliparous women were seen in clinic, evaluated, and approached about participation in the study. Those women with an immediate indication for delivery, previous cesareans, hypertension, insulin-dependent diabetes, known fetal anomalies, and stillbirths were not considered candidates. In addition, women weighing more than 360 pounds were excluded from the study because of the weight limit of the MRI table.

After informed consent was obtained, the patients were escorted to the imaging suite, where they underwent an MRI protocol consisting of 2 single shot fast spin echo (SSFSE) T2 weighted scans (TE = 60, 44 cm field of vision, 512 × 256 matrix). A 1.5 Tesla GE Signa magnet was employed (General Electric Medical Systems, Milwaukee, WI). Based on chemical shift artifact and acquisition, our hypothetical resolution was between 0.86 and 1.7 mm.

A torso coil was used on all but 3 patients, whose large size necessitated the use of the body coil. The MR sequence for this study was a 4 mm, 0 gap acquisition aligned axial to the maternal pelvis at an angle parallel to the obstetric conjugate. This 90-second sequence averaged 40 to 50 images, which included the entire fetal head and the maternal pelvis.

From this 90-second acquisition, 1 investigator (M.B.) performed all biometric and volumetric analyses. Utilizing a 3-D reconstruction workstation (GE Advantage Windows 4.1, General Electric Medical Systems), optimal orientations were selected to obtain 2-dimenisonal and volume measurements. LA volume and arch were evaluated from coronal images. LA insertion into the pubic symphysis and levator hiatus shape were evaluated using images reformed at a 90-degree angle to the skin of the back at the L5-S1 disk space of the spine. This technology enables the user to produce the appropriate orthogonal planes necessary for those measurements from a single acquisition.

To quantify the subjective decision regarding the shape of the levator hiatus (“U” vs “V”), the distance between the lateral borders of the levator ani muscle is demonstrated. First, a reference line (dotted line) was drawn through the center of the pubic symphysis. The measurement of the distance between the lateral borders of the elevators was then taken at a right angle to the reference line (solid line). The insertion of the levator ani muscle into the pubis symphysis is shown in (B). In (C), the left levator ani is not identified. “V”-shaped (B) and “U”-shaped (D) genital hiatuses are shown.
The levator ani volume was estimated on consecutive coronal images. Once the urethra was identified, the levator ani muscle was outlined using region of interest software in each consecutive slice until the levator ani was no longer distinguishable from the rectum. On average, 6 to 7 slices were included in the calculation for each subject. In order to avoid arbitrary decisions regarding the borders of the LA when contiguous with structures of similar T2-weighted intensity, if the margin of the levator ani was not clear, it was not measured. For example, when the LA appeared to be contiguous with the rectum, no portion of the levator was measured. Therefore, volume estimates most likely represent an underestimation of the levator ani volume. Computer reformatted volumes of the levator ani were obtained from consecutive 4 mm, 0 gap slices. Actual volume estimates were obtained from the sum of measurements from 6 to 9 slices per individual.

The levator ani volume was estimated on consecutive coronal images. Once the urethra was identified, the levator ani muscle was outlined using region of interest software in each consecutive slice until the levator ani was no longer distinguishable from the rectum. On average, 6 to 7 slices were included in the calculation for each subject. In order to avoid arbitrary decisions regarding the borders of the LA when contiguous with structures of similar T2-weighted intensity, if the margin of the levator ani was not clear, it was not measured. For example, when the LA appeared to be contiguous with the rectum, no portion of the levator was measured. Therefore, volume estimates most likely represent an underestimation of the levator ani volume. Computer reformatted volumes of the levator ani were obtained from the sum of these outlined regions of interest. Station was also evaluated in this acquisition (M.Z.). BMI was calculated from weight and height information obtained the day of the MR examination, and fetal weight at birth was recorded.

Parametric variables were examined for statistical normality in their distributions by use of the Shapiro-Wilk statistic. Measurements were compared across groups using the Student $t$ test, Pearson chi-square tests,
and analysis of variance with Student–Newman-Keuls for multiple comparisons. Analysis of covariance was used to determine independent variables and linear regression was performed for multivariate analysis.

For reliability determinations, the evaluations were independently and blindly repeated upon randomly selected samples for intrarater reliability (10%, M.B.) and interrater reliability (20%, M.C.). For the classification variable of levator hiatus shape, the Kappa statistic is reported with 95% CIs. A plot of the difference between the 2 observed values of a subject and the mean of those values was created (Bland-Altman figures) for parametric values.17 Statistics were performed using SAS version 9.1 (SAS Institute, Cary, NC).

**Results**

A total of 120 patients were consented for the study. Of these, 13 women did not complete the MRI (1 claustrophobia, 1 spontaneous rupture of membranes before procedure, and 11 did not present for the MRI). Of 107 subjects, 78.5% (n = 84) had MR studies which could be utilized for pelvic floor analysis. Analysis of data was confined to these 84 women. The mean age of the cohort was 22 ± 5 years, range 15 to 42. The racial distribution of the cohort was 84.5% (n = 71) Hispanic, 11.9% (n = 10) African American, 2.4% (n = 2) white, and 1.2% (n = 1) other. The mean BMI was 31 ± 5, range 21 to 49.

The mean postprocessing time per patient was approximately 10 minutes. The insertion of the levator into the pubic symphysis was identifiable in 94% (n = 79) of women (Figure 1). Inability to visualize the insertion into the pubic symphysis was bilateral in all instances. The levator ani shape was characterized as a U in 53.0% and a V in 47.0% of women. In an attempt to quantify the difference between the U and the V configurations, the distance between the lateral borders of the levator ani muscles was determined. Although the distance between the lateral borders of the muscles determined to have a U-shaped appearance significantly wider (47.4 ± 7.6 mm) than the V-shaped appearance (42.4 ± 5.0 mm, P < .001), this was not a bimodal distribution. An example of a U- and V-shaped appearance of the levator hiatus, as well as the measurement technique, is shown in Figure 1. The iliococcygeus assumed a convex shape (arch was present) on the right in 89% (n = 75) and on the left in 92% (n = 77) of women (Figure 2A-C). Six women (8%) had a discontinuous levator ani.

The mean estimated levator ani volume was 13.6 ± 3.8 cm³ (range 3.3 to 22.7). An example of a region of interest encompassing the levator ani is shown in Figure 3. Levator ani volume was significantly increased as a function of increasing BMI, P < .001. There was also a negative association between levator ani volume and fetal station, P = .008, r = −0.3 (Table I). However, BMI is a confounder and the association between levator ani volume and station is not present (P = .09) when BMI is taken into account using regression analysis. Birth weight was not associated with levator ani volume. Station, BMI, birth weight, and levator ani volume were not associated with the shape of the levator hiatus (P = .87, .67, .25, and .99, respectively).

Intrarater reliability measurements showed good agreement except in determination of the levator hiatus shape (κ 0.26, 0.14-0.65). This is not surprising because the U and V shapes appear to be a continuum rather than bimodally distributed. There was moderate interrater reliability for levator hiatus shape, κ 0.769 (0.354-1.0). Bias estimation and evaluation of intra- and interrater reliability for measurements of the levator ani volume and levator hiatus width are shown in Table II. In addition, Bland-Altman figures were created for LA volume and levator hiatus width. Greater than 95% of the values fell within 2 SDs; thus, reproducibility was shown.16

<table>
<thead>
<tr>
<th>Table II</th>
<th>Bias estimation and evaluation of intra- and interrater reliability for measurements of the levator ani volume and the lateral to lateral LA (LTL-LA) width</th>
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</thead>
<tbody>
<tr>
<td>Measure</td>
<td>Mean difference in measurements (original–next) and 95% CI</td>
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<tr>
<td>LA volume (cm³)</td>
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<tr>
<td>Right LTL-LA width (mm)</td>
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<td>Total LTL-LA width (mm)</td>
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**Comment**

We have described levator ani muscle morphometry in nulliparous women at term using MRI with 3-D reformatting. The technique by which the acquisitions were obtained allowed a 3-D reconstruction with an average post processing time of 10 minutes. Levator ani morphology, volume, and the insertion into the pubic symphysis were clearly identified. There was significant variation of levator ani morphology; however, overt signs of injury were remarkably infrequent. Indeed, we found anatomy similar to that which has been reported in nulliparous women.16

Our finding of the absence of an identifiable insertion of the levator ani into the pubic symphysis in 6% of our
population could be taken to suggest that pregnancy in and of itself may lead to pelvic floor damage. However, in a study of 80 nulliparous women, disruptions of the levator ani insertion were not seen. Therefore, one must take the potential limitations of our scanning protocol into consideration. The rapid imaging time of a SSFSE allows one to image a moving fetus well; however, the images can be prone to blurring. As discussed in Materials and methods, our hypothetical resolution is between 0.86 and 1.7 mm. Therefore, if the levator insertion was not seen, it was either absent or the muscle was <2 mm thick and beyond conspicuity.

Another difference between our study and those in nulligravid women is the finding of lower estimates of levator ani volume. Levator ani volume estimates have been reported in nulligravid to vary between 32.2 and 46.6 cm³. In the current investigation, our average volume estimate of 13.6 cm³ may indicate the levator ani muscle in term pregnancies is very thin and portions may be beyond conspicuity in our protocol.

In addition, different acquisition techniques may explain this difference. The SSFSE employed in the current study allowed an acquisition time of 90 seconds; however, it may not be the optimal technique for pelvic floor muscle evaluation in pregnancy. For example, LA volume was likely underestimated in the current study because the puborectalis was not measured if it could not be distinguished from the rectum and external anal sphincter. Our 4 mm, 0 gap slice thickness is an advantage and offers the potential of improved measurements. Other studies have used acquisitions with a larger number of averages, which may improve resolution of the levator ani. However, the cost of improved resolution is longer acquisition time and potential motion artifact. Finally, our cohort was mainly women of Hispanic ethnicity, whereas most other studies have a different racial distribution.

The effects of fetal and maternal parameters upon levator ani volume were analyzed. Interestingly, fetal weight was not associated with LA volume. Although a lower fetal station was associated with decreasing levator volume, this relationship disappeared after adjusting for maternal BMI. Indeed, increasing BMI was associated with increased levator ani volume, independent of other analyzed variables. Other studies have not had sufficient variation of BMI or numbers of participants to evaluate the effect of BMI upon estimated LA volume. The correlation between BMI and LA volume merits further study.

Hoyte et al have shown significant differences in levator volume, integrity, and shape between controls and women with prolapse or urinary incontinence. The shape of the iliococcygeus has been reported to be either a “U” or a “V” shape. In the current study, the morphometry of the levator ani complex had significant variability with slightly more than half of the women, demonstrating a V-shaped appearance and the remainder a U-shaped appearance. The poor interrater reliability emphasizes subjectivity of this determination in the current study. More importantly, the measurements taken between the lateral edges of the levator ani at the level of the levator hiatus suggest these arbitrary categories are actually a continuum based on the lack of a truly bimodal distribution. Muscle thickness and variable fat deposition between the medial border of the muscle and the lateral border of the vaginal wall are factors that may account for the variability noted in this study. In addition, the supine position may affect pelvic musculature morphometry. We did not demonstrate an effect of levator ani volume, maternal BMI, or birth weight on levator ani morphology.

Flattened iliococcygeus muscles were seen in 11% of women. This finding has been described in patients with idiopathic combined fecal and urinary incontinence. Our study was limited by the lack of information on symptomatology and knowledge about pelvic floor defects on clinical exam. That said, this finding may be a normal variant because Singh et al described a flattening of the iliococcygeus in the posterior portion of the muscle in asymptomatic, nonpregnant nulliparas. Our finding may simply be further evidence of significant heterogeneity in the appearance of the levator and, thus, reflect normal biologic variability.

Findings from this study show the pelvic floor is easily analyzed using MRI and postprocessing technique. Variation in morphology of the levator ani is common, and injury is uncommon in otherwise asymptomatic nulliparous women at term. In fact, the anatomy of the pelvic floor in postterm women is similar to that reported in the nulligravid. The main difference between our findings and those reported in nulligravidas is that of a lower levator ani volume. Whether this is because of imaging or measuring technique or, conversely, is an effect of pregnancy will require longitudinal study. Much more information is needed to further evaluate the effects of pregnancy upon the levator ani muscle, including longitudinal data, determination of optimal MR imaging techniques, and evaluation of findings as they relate to clinical symptoms and outcomes.

References


Objective: The objective of the study was to characterize the vascular anatomy over the superior pubic rami.

Study design: Detailed dissections of the retropubic space were performed in 15 fresh female cadavers. Vessels crossing the superior pubic rami were inspected for width, course, communications, and relationship to the midline of the pubic symphysis and the obturator canal.

Results: Vessels 1 mm or greater in width connecting the obturator vessels and inferior epigastric or external iliac vessels were noted in 10 of 15 (66.7%) cadavers: 9 (60%) had veins, 5 (33.3%) had arteries, and 4 (26.7%) had both. In all specimens, the vessels crossed over the superior pubic rami lateral to or at the level of the obturator canal, which was on average 5.4 cm from the midline of the pubic symphysis.

Conclusion: Communicating vessels crossing the superior pubic rami were present in the majority of specimens. Understanding this anatomy should aid the surgeon in avoiding vascular complications.

The term corona mortis, or crown of death, describes vascular connections between the external iliac system and the obturator vessels in the retropubic space (space of Retzius). Lymphatics and preperitoneal fatty tissue often obscure the anatomy of the superior pubic rami, preventing direct visualization of the vessels found in this region. Laceration of the corona mortis can result in catastrophic bleeding because these vessels connect high-volume systems and may retract into the obturator canal. Vessels that cross the superior pubic rami are variously referred to as accessory, anomalous, communicating, or variant vessels or pubic branches of the obturator or inferior epigastric vessels. However, not all these vessels connect the internal iliac (obturator) to the external iliac systems, and thus not all constitute a corona mortis vessel.

According to classic anatomy texts, accessory obturator arteries are found in at least 1 of 5 individuals. However, several anatomic studies have shown that venous connections crossing the superior pubic rami are found in much higher numbers. These vessels may be injured during retropubic space procedures such as the Burch urethropexy, paravaginal defect repairs, and...
midurethral or pubovaginal slings. Therefore, it is important to understand the anatomy of the space of Retzius, with its vascular variability and potential hazards. We conducted an anatomic dissection study of fresh adult female cadavers to further characterize the variation of vessels that pass over the superior pubic ramus and to describe the relationship of these vessels to known anatomic landmarks.

**Materials and methods**

Detailed dissections of the retropubic space were performed in 15 fresh adult female cadavers. The cadavers were obtained from the Willed Body Program at the University of Texas Southwestern Medical Center at Dallas. This study was considered exempt by the University of Texas Southwestern Medical Center Institutional Review Board in accordance with the Code of Federal Regulations, Title 45. Height, weight, and age of the body donor at the time of death were recorded when available.

Following entry into the abdominal cavity, the space of Retzius was carefully developed by bluntly dissecting the fat and loose areolar tissue from the pelvic side wall medially toward the bladder. Care was taken not to disrupt the vessels that coursed over the superior pubic rami. Detailed dissections of the external iliac and inferior epigastric vessels, the obturator neurovascular bundle, and all vessels crossing over the superior pubic rami between the pubic symphysis and the external iliac vessels were performed. The distance between the medial aspect of the obturator canal and midline of pubic symphysis and between the superior margin of the obturator canal and the upper border of the iliopectineal line were obtained in both sides of all 15 cadavers (Figure 1).

**Results**

Limited demographic data were available on 12 of the 15 cadavers. Mean age at time of death of the body donor at the time of death were recorded when available.

Measurements were taken twice and recorded using calipers and a plastic measuring ruler with the pelvis in supine position.

All vessels 1 mm or greater in width that crossed over the superior pubic rami were carefully dissected to determine whether they were of arterial or venous origin and to identify their source or termination. Connections of these vessels with the obturator vessels and/or their course into the obturator canal were noted.
donors was 77 years (range 46 to 95), and mean height was 64 inches (range 59 to 68). All but 1 of the cadavers was Caucasian; the remaining cadaver was of Hispanic ethnicity. Vaginal parity was unavailable.

**Relationship of the obturator canal to bony landmarks**

The mean distance from the midline of the pubic symphysis to the medial border of the obturator canal was 5.4 cm on the right (range 4.6 to 6.0) and 5.4 cm on the left (range 4.5 to 6.1). The mean distance from the upper portion of the iliopectineal line to the superior border of the obturator canal was 1.7 cm bilaterally (range 1.5 to 2.6) (Table I).

**Main obturator vessels**

Obturator vessels arising from or draining into the internal iliac vessels were noted in all but 1 pelvic half. In the exception, an obturator artery originated from the inferior epigastric and crossed over the superior pubic ramus to enter the obturator canal. In all cases, the obturator nerve entered the obturator canal superior to the vessels (Figure 2).

**Vascular connections between the external and internal iliac systems**

The most common vascular connections between the external and internal iliac systems were noted between the inferior epigastrics and the main obturator vessels (Figure 3). Overall, 9 of 15 (60%) pelvises had venous anastomoses and 5 of 15 (33%) had arterial anastomoses of 1 mm or greater in width. Bilateral venous anastomoses were seen in 5 cadavers (33%), and 2 (13%) had arterial anastomoses on both sides. A communicating vein coursed directly between the external iliac and the obturator veins in 3 cadaver sides (Table II).

**Location of the vascular connections between the external and internal iliac systems**

All vessels (1 mm or greater) connecting the external and internal iliac systems that coursed over the superior pubic rami were found to be lateral to the medial aspect of the obturator canal (Figure 3). On the right side of 1 cadaver, 3 1-mm veins crossed over the iliopectineal line medial to the level of the obturator canal. However, these vessels coursed between the obturator internus muscle and the inferior epigastric vein, and no connection with the obturator vein or obturator canal was identified.

<table>
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<th>Cadaver</th>
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<td>4, 3</td>
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EI, External iliac; IE, inferior epigastric; —, no vessel. Cadavers 2, 6, 11, and 13 had no identifiable communicating vessels.
Comment

In this study of fresh female cadaveric pelvises, vascular connections between the external and internal iliac systems were common. These were mainly venous and found between the inferior epigastric and obturator vessels. Therefore, we agree with other investigators that these vessels represent a variant of normal anatomy and should be referred to as variant or accessory and not as anomalous obturator vessels. All communicating vessels were identified lateral to the medial border of the obturator canal, which was always at least 4.5 cm lateral to the midline of the pubic symphysis.

Although the anatomy of the vascular variations over the superior pubic ramus is of common interest to orthopedic, general, and gynecologic surgeons, there is little information about these vessels in the gynecologic literature. The majority of anatomic studies of these anastomoses has focused on orthopedic or general surgery procedures and has used embalmed, male cadavers. Similar to the current study, previous investigations found venous connections between the external and internal iliac systems in 52% to 82% and arterial connections in 19% to 34% of pelvic sides.

The distances between the pubic symphysis and the vessels coursing over the superior pubic ramus found in our study are also consistent with previous reports. Tornetta et al. found a mean distance from the symphysis to the vessels of 6.2 ± 1.2 cm. Okcu et al. reported an average distance of 6.4 cm from the pubic symphysis for arterial anastomoses and 5.6 cm for venous anastomoses. In contrast to cadaveric studies, Karakurt et al. found angiographic evidence of an accessory obturator artery in 10 of 39 women and calculated that the average distance between the pubic symphysis and the accessory obturator artery was 3.62 cm. It is unclear whether this shorter distance is due to the effects of living tissue or to measurement technique.

Although there are papers describing the vascular anatomy of the retropubic space in relation to gynecologic surgery, few of these mention the communicating vessels that cross over the superior pubic rami. Shobeiri et al. found the tension-free vaginal tape to be located lateral to the obturator canal, exposing the ilipectineal line and placing retractors in the retropubic space should be safe if done medial to this anatomic landmark. Although branches of the inferior epigastric or obturator vessels were occasionally found crossing the superior pubic ramus medial to the obturator canal, these vessels were noncommunicating and were not greater than 1 mm in width. Although these medial vessels are more likely to be injured during retropubic surgery, it is our contention that significant hemorrhage is most likely to occur from injury to the vessels communicating between the high volume systems of the external (inferior epigastric) and internal (obturator) iliac vessels. If accessory obturator injury and hemorrhage occur in an abdominal procedure, the vessels can be clipped or ligated. If this fails, packing to tamponade the bleeding is appropriate. Vascular surgery consultation may be required. Successful hemostasis of an injured corona mortis vessel has been described using coil embolization. An important principle is to avoid injury to the obturator nerve while attempting to control the bleeding. Understanding the anatomic location of these accessory or variant obturator vessels and the location of the obturator canal should aid the gynecologic surgeon in avoiding serious vascular injuries.

References

Traumatic absence of the proximal urethra

Marcella L. Roenneburg, MD, a, * Clifford R. Wheeless, Jr, MD b

Mercy Medical Center a; The Johns Hopkins University School of Medicine, Department of Gynecology and Obstetrics, b Baltimore, MD

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KEY WORDS

Fistula
Urethrovaginal fistula
Traumatic absence of the proximal urethra
Obstetrical trauma

Objective: Traumatic absence of the proximal urethra is an obstetrical vesicovaginal fistula resulting from obstructed labors in Niger, Africa. Repair by direct reanastomosis was evaluated.

Study design: A prospective case series of 25 women with traumatic absence of the proximal urethra underwent a direct layered reanastomosis of the distal urethra to the urethrovesical junction. Results are based on 21 patients (84%) examined at follow-up.

Results: Seventeen patients (81%) had complete healing of their fistulas. After direct reanastomosis alone, 48% (10 of 21) were dry. An additional 7 patients (33%) suffered from urinary incontinence despite closure of their fistulas. Four patients (19%) had a persistent fistula.

Conclusion: Direct layered reanastomosis is an acceptable primary repair procedure for traumatic absence of the proximal urethra.

Vesicovaginal fistulas caused by obstetrical trauma remain common in the nonindustrial developing world. The United Nations Population Fund estimates that there are more than 2 million women currently living with fistulas in the sub-Sahara belt of Africa and that another 50,000 to 100,000 join their ranks each year. 1 Niger, Africa, is one of the poorest countries in the world with one of the highest birth rates estimated at 53 per 1000 people. 2 It also has one of the highest maternal mortality rates with a lifetime risk of 1 in 9. 3

Genitourinary fistulas are estimated to occur in 3 to 4 women per 1000 deliveries. 4 Vesicovaginal fistulas from obstructed labors are the result of the fetal head obstructed in the birth canal compressing the maternal bladder and urethra against the pelvic bones for a prolonged period of time. This prolonged compression leads to widespread ischemic injury with subsequent tissue necrosis and fistula formation. 5 Wall et al 5 described this as a broad field injury to the pelvis that then leaves the woman with a combination of injuries, both vascular and neurologic. This concept of a broad field injury aptly describes the obstetrical fistulas seen in Africa. The fistulas are of variable size, are surrounded by tissue with ischemic damage, have extensive scarring, and often have residual neurologic dysfunction. We report on our experience with the traumatic absence of the proximal urethra (TAPU) occurring within this context of a broad field injury that we encountered while managing patients with fistulas in Niger, Africa.

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Conducted at The National Hospital and Lamorde Hospital, Niamey, Niger, Africa.

* Reprint requests: Marcella L. Roenneburg, MD, Mercy Medical Center, The Weinberg Center for Women’s Health and Medicine at Mercy, 227 St. Paul Place, Sixth Floor, Baltimore, MD 21202.

E-mail: mroenneburg@mdmercy.com

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Material and methods

A prospective case series was undertaken to assess the success rate of direct reanastomosis of the remaining distal urethra to the urethrovesical junction as the primary technique for repair. All patients were examined and operated on during medical missions sponsored by The International Organization for Women and Development, Inc, a nonprofit organization. Preoperative evaluations, surgical repairs, and follow-up examinations were all performed by various American physicians volunteering at the National Hospital and at Lamorde Hospital in Niamey, the capital city of Niger. The institutional review board provided a waiver letter with regard to this research in Africa.

Between January 2004 and September 2004, a total of 30 women with TAPU-type injuries were identified in the 180 women with fistula examined. In this series TAPU represents 17% of all obstetrical fistulas. Two patients did not return for surgery and therefore were excluded from the study. Three other patients had such severe injuries, of which the TAPU was only 1 component, that a urinary diversion by hemi-Kock pouch urostomy to the rectosigmoid colon was indicated. These 3 patients were also excluded from the study. This left 25 women remaining in the study population.

Ages of the patients ranged from 14 to 40 years. All fistulas were due to obstetrical trauma and obstructed labor. Spontaneous or forceps delivery occurred in 21 of the 25 patients (84%), and 4 patients (16%) were delivered by cesarean section. Delivery resulted in a stillborn child for 17 of the 25 women (68%). In 6 patients (24%), the status of the infant was unclear from the records. Only 2 women (8%) were noted to have delivered a live child. There were 15 primigravidas (60%) in the study, and only 1 of these women (7%) had a living child.

The size of the fistulas varied from 1.5 cm to 6 cm, with the majority being 1.5 to 3 cm in length. Complete TAPUs, with a complete circumferential destruction of the proximal urethra, were described in 14 of 25 of the injuries (56%). These patients typically presented with a blind urethra on catheterization. The urethrovesical junction was replaced by a scarred communication between the bladder and the vagina through which urine was draining (Figure 1). The size of the fistulous tract determined the proximity of the ureteral orifices to the scarred edges. The remaining 11 of 25 patients (44%) had a partial TAPU with loss of the inferior and lateral portions of the proximal urethra (Figure 2). The urethra of these patients was easily catheterized. The absent portion of the proximal urethra allowed the inferior aspect of the catheter entering the bladder to be seen in the vagina. All patients were totally incontinent of urine from their TAPU. One woman had partial urinary retention because of an obstruction at the urethrovesical junction but continuous urinary incontinence from 2 other small vesicovaginal fistulas.

In all patients, surgical correction was performed in the lithotomy position under spinal anesthesia. All patients received preoperative antibiotics. There were 17 patients (68%) in the study population who had no
previous fistula surgeries and 8 women (32%) who had undergone 1 to 3 previous vaginal attempts at repairing their fistula.

At the time of surgery, all patients were re-examined under anesthesia and the extent of the fistula or fistulas were confirmed. In the patient with a complete TAPU, a sound or probe was placed in the distal urethra to help identify the scarred end of the urethra. An additional Foley catheter was placed directly into the bladder and helped identify the scarred edges of the fistulous opening. The edges of the fistula(s) were identified, incised, and widely mobilized. This often required releasing the densely scarred tissue with heavy cartilage scissors. The mobilization of the vagina from the bladder was extended as far as possible to the pubic bones. The blind distal segment of the urethra was identified by the location of the previously placed probe and opened allowing access to the obliterated lumen. The urethra was then widely mobilized. Depending on scarring, this was accomplished by a retrograde dissection on either side of the newly opened urethral lumen. However, this mobilization may be difficult where scarring is severe. It is then easier to proceed with an antegrade dissection. This is best accomplished by an inverted V-shaped incision above the urethral meatus. Dissection is pursued in a cephalad direction between the symphysis and the anterior urethra. This dissection is continued until the newly created opening in the distal urethra is reached. Over a Foley catheter, the urethral wall is reanastomosed with interrupted absorbable 2-0 or 3-0 sutures of braided polyglactin acid in four quadrants. A second layer reapproximates the previously mobilized fibromuscular tissues of the bladder and the urethra. A vaginal mucosal layer of absorbable suture completes the repair.

In patients with partial TAPU, the dissection of the urethra is better carried out laterally to reapproximate the dissected tissues without undue tension. When an additional bulbocavernous flap for adequate blood supply was deemed necessary, at the discretion of the operating surgeon, it was developed and placed before vaginal closure. A bulbocavernous flap was used on 7 of 25 patients (28%). A 16 or 18 french Foley catheter with gravity drainage was left in place for 2 weeks postoperatively.

Results

Follow-up is now available on 21 patients and ranged from 1 to 14 months. Results are unknown in 4 patients (19%) who have been lost to follow-up. Attempts are currently being made to locate these women with the help of the Peace Corps. Successful closure of the fistula was documented in 81% of patients (17 of 21), and 19% (4 of 21) were diagnosed with persistent fistula. Repair was successful by our primary procedure in 12 of the 21 patients (57%). Using only the layered direct reanastomosis of the distal urethra to the urethrovesical junction, 10 of 21 patients (48%) are dry. Half of these patients were complete TAPUs and the other half had partial TAPUs. Bulbocavernous flaps were selected for use on the more severely scarred and complex fistulas. Therefore, vascular flaps did not improve the success rates or continence rates in our series.

More than 1 surgery was needed to accomplish healing of the fistula in 5 of 17 patients (29%) whose fistulas were healed. Four patients required 2 surgeries to repair their TAPU injuries measuring from 1.5 to 3 cm. One patient had a large 6-cm complex fistula, which ultimately required 4 separate surgical procedures. The 4 patients with persistent fistulas will be scheduled for additional repair procedures in the near future.

An additional 2 patients are dry after undergoing a subsequent sling procedure. Suburethral sling procedures have been scheduled for 4 other patients at our next mission for treatment of their stress incontinence. Therefore 35% of our patients (6/17) suffered stress urinary incontinence or mixed urinary incontinence after their successful fistula surgery.

One partial TAPU has detrusor overactivity by simple cystometrogram and was started on anticholinergics. Two patients suffered urinary frequency and urinary retention from a urethral stenosis. Both of these patients were treated with urethral dilatation and their symptoms improved.

If we count all 4 patients lost to follow-up as wet in addition to the 4 failed repairs and count the 5 patients whose fistulas have healed but are currently wet from incontinence, our failure rate is 52%. Our dry rate, therefore, remains significant at 48%.

Comment

The TAPU is a commonly seen fistula in Niger, Africa. Obstructed labors in this country often result in the necrosis of the proximal urethra. Depending on the degree of trauma and necrosis, a variety of lesions are recognized. Some are complete with a blind distal urethra noted on examination and the open urethrovesical junction seen at the top of the vaginal vault. Others are partial with loss of the posterior and lateral portions of the urethra with only the roof of the urethra remaining. Some TAPUs also extend into the urethrovesical junction and trigone. Others have been noted to slough the urethra completely.

The extensive scarring periurethrally after a labor with outlet obstruction often makes repair procedures more difficult. The best approach to the repair of these types of fistulas has not been established. However, the
technique of wide mobilization of vaginal flaps was advocated by Elkins et al. Their failure rate with modified Latzko techniques in Africa was 75%, compared with a failure rate of 25% by utilizing wide mobilization of vaginal flaps for closure of fistulas.

Successful closure of their fistulas has been achieved in 17 patients (81%), with 5 patients requiring more than 1 surgery. Successful closure of the fistulas was achieved in 57% of our patients with our primary surgery. It is not possible to determine from this study whether TAPU-type urethral injuries are more difficult to achieve successful closure than other vesicovaginal fistulas. Elkins et al reported his primary success rate with urethral fistulas to be 83% to 90%. Repairs of obstetrical vesicovaginal fistulas of all types, regardless of the number of procedures, have been reported to have a 70% to 95% success rate. Therefore, our success rates for TAPU injuries seems to be similar to all obstetrical vesicovaginal fistulas. In a review of the literature, Elkins noted that primary failure of fistula repairs is more common with larger fistulas, especially when they involve the urethra. This was true for our patient with a large 6-cm fistula, who required 4 surgeries.

Because 48% of the patients seen on follow-up were dry from direct reanastomosis of the distal urethra to the remaining urethrovaginal junction with or without the use of vascular flaps, this is an acceptable primary procedure for repairs of TAPUs. The fact that half of these patients were complete TAPUs and half had partial destruction suggests that this distinction is not important in prognosis.

A number of patients with successful fistula repair will require a second surgery for placement of a suburethral sling for urinary incontinence from an intrinsic sphincter deficiency or mixed incontinence. Placement of a sling is not automatically indicated in the treatment of TAPU. In our series 35% of patients required a suburethral sling. It is thus reasonable to view this repair as a possible 2-stage procedure, with 35% of the patients requiring the second-stage sling procedure.

Elkins et al candidly pointed out that successful closure of a fistula does not necessarily equate to complete recovery of genitourinary function. These patients indeed usually exhibit a number of urinary dysfunctions as a result of their trauma. Murray et al reported from The Fistula Hospital in Addis Ababa a success rate of more than 90%. In this series, 55% of patients complained of urinary incontinence after successful fistula closure. Urodynamic studies documented that 57% had stress urinary incontinence, 7% detrusor overactivity, and 37% had mixed incontinence. Hilton reported the largest functional abnormalities were noted with urethral and bladder neck fistulas. Elkins et al reported on 20 patients with vesicovaginal fistulas involving the urethra, with failure of closure noted in 2 patients and 2 patients with urethral stenosis who required further treatment.

Mensah et al performed neurologic examinations of the perineum and lower limbs, and they performed electromyography of the lower limbs and the urethral sphincter on 20 women with obstetrical vesicovaginal fistulas and 10 normal women as controls. Women with vesicovaginal fistulas had a 68% rate of clinical neuropathy detected with electromyography. None of the women in the control group had a neuropathy. The risk of treatment failure increased proportionally to the severity of denervation. This study found that 73% of fistulas with severe denervation remained “unsusurable” or required multiple operations with persistent vesicosphincteric dysfunction.

Given all this information, it is not surprising that approximately 43% of our patients have urinary dysfunction after fistula repairs. The traumatic absence of the proximal urethra remains a challenging medical, surgical, and social problem. Our results are encouraging because 48% of the patients report being dry with a direct layered reanastomosis of the urethra after proper mobilization. Further urodynamic and neurologic studies are needed to better define prognostic factors and the best surgical approach.

References

Local anesthesia with sedation for transvaginal correction of advanced genital prolapse

Gunhilde M. Buchsbaum, MD,* Erin E. Duecy, MD

Department of Obstetrics and Gynecology, University of Rochester Medical Center, Rochester, NY

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Objective: The purpose of this study was to evaluate local anesthesia with sedation for vaginal surgery for advanced genital prolapse.

Study design: Five sacrospinous ligament suspensions and 12 vaginal paravaginal defect repairs performed under local anesthesia in 2004 were identified. Medical records and patient satisfaction questionnaire were reviewed. Patient demographics, degree of prolapse, duration of surgery, hospital stay, and responses to an anesthesia satisfaction questionnaires were recorded.

Results: All repairs incorporated placement of dermal allograft. Concomitant procedures included: 6 tension-free vaginal tape (TVTs), 12 posterior and 4 enterocele repairs. Mean patient age was 66.1 years. All patients had prolapse of apex or anterior wall ≥ grade 3. Mean OR time was 132 minutes. Average hospital stay was 1.2 days. No patient was converted to general anesthesia. All 17 patients were “very satisfied” with their surgical experience.

Conclusion: Local anesthesia with sedation can be successfully employed for most vaginal reconstructive surgeries with advanced genital prolapse. Patients report a high level of satisfaction.

In the coming years, gynecologic surgeons will be performing an increasing number of procedures on women over the age of 65. In 2002, over 200,000 gynecologic surgeries were performed on women over 65 in the United States. Population projections anticipate a doubling of the geriatric population over the next 30 years, so it is likely this number will substantially increase. Many of these surgeries will be vaginal reconstructive procedures for pelvic organ prolapse and urinary incontinence. Because these procedures are usually elective and are performed to improve quality of life, it is important to find ways to decrease the risks of surgery and allow more geriatric patients to benefit from reconstructive surgery.

In 1994, Ferry and Rankin reported the first large series of gynecologic procedures performed in an outpatient setting under local anesthesia. They were able to demonstrate that local anesthesia was accepted by women for procedures such as cervical cone biopsy, termination of pregnancy, hysteroscopy, and vulvar surgeries. Many such procedures are now commonly performed under local anesthesia. In 1995, Miklos et al published the first series of vaginal reconstructive surgeries performed under local anesthesia with sedation. Twenty elderly
women (mean age 80 years), who were considered poor candidates for general anesthesia, underwent a variety of procedures, including anterior and posterior repair, enterocele repair, and colpocleisis. They demonstrated the feasibility and success of such reconstructive procedures in women who might otherwise be denied surgical intervention. Two subsequent studies described the combination of vaginal reconstructive surgery and tension-free vaginal tape (TVT) under local anesthesia. In 2001, Jomaa performed 32 TVT procedures combined with anterior and/or posterior repair under local anesthesia with sedation. In 2003, Moore and Miklos successfully combined colpocleisis and TVT under local anesthesia and sedation in 30 consecutive patients. In a recently published study, Axelson and Bek performed 80 anterior repairs under local anesthesia with sedation, with a high rate of patient satisfaction. We have previously reported on 87 consecutive vaginal reconstructive procedures, including anterior and posterior colpopathies, enterocele repairs, and colpocleisis, performed under local anesthesia with sedation, with and without concomitant continence repair. While these reports are promising, they have been limited to relatively minor reconstructive procedures. Correction of apical prolapse with vaginal suspension procedures and complex vaginal reconstruction with dermal allograft reinforcement has not yet been reported. Our objective is to report our experience with local anesthesia with sedation for patients undergoing complex vaginal reconstructive procedures, including either sacrospinous ligament suspension or paravaginal defect repair.

Material and methods

The Internal Review Board of the University of Rochester granted exempt status for this study. All cases of complex vaginal reconstructive surgeries performed by the principal author (G.M.B.) at the University of Rochester Medical Center between January 2004 and September 2004 were reviewed. Complex vaginal reconstructive surgery was defined as any procedure including either vaginal sacrospinous ligament suspension or vaginal paravaginal defect repair. Excluded were anterior and posterior repairs, enterocele repair, colpocleisis, perineoplasty, and placement of suburethral slings because performance of these procedures under local anesthesia has previously been reported. Also excluded was vaginal hysterectomy because this was not attempted under local anesthesia at the time of this study.

For all cases reviewed, each woman had preoperative assessment including comprehensive medical history, 48-hour voiding diary, physical examination, and multichannel urodynamics. At the time of the preoperative visit, each woman was counseled regarding options for anesthesia: general anesthesia, regional anesthesia, and local anesthesia with sedation. Local anesthesia was the surgeon’s preference and potential benefits were discussed, including decreased postoperative nausea, less sore throat, and more rapid recovery. The principal author (G.M.B.), assisted by the fellow in urogynecology or the senior resident on the urogynecology service, performed all procedures. All surgeries were performed with patients in dorsal lithotomy position with Allen stirrups for support of the lower extremities. All patients received prophylactic antibiotics and wore sequential compression devices on their lower legs. Sedation was established by the anesthesia team before injection of local anesthetic by the surgeon. Sedation was, most commonly, a short-acting opioid in combination with midazolam and/or propofol; the agents used were chosen and titrated for patient comfort by the anesthesia team. The amount of sedation required depended on the patient's body mass index (BMI), desired level of awareness, and the duration of surgery. All patients breathed on their own. Local anesthesia was a mixture of 2% nesacaine and 0.5% bupivacaine with or without epinephrine in a 1:1 ratio. Epinephrine was added for cases expected to exceed 1-hour operative time. The maximum dose of local anesthetic was calculated based on the limiting dose for bupivacaine of 2 mg per kg of body weight. The maximum dose for each patient was determined at the onset of surgery. Local anesthetic was injected subcutaneously at the surgical site. If multiple procedures were performed during 1 case, each surgical site was injected just before incision at that site. Pudendal blocks, using 5 mL of local anesthetic on either side, were administered for sacrospinous ligament suspensions. We used a Capio (Boston Scientific, Boston, MA) suture placement and retrieval device for placement of the sutures into the sacrospinous ligament and arcus tendineus fascia pelvis.

Information was recorded from the medical record of each patient, including age, medical and surgical history, preoperative diagnosis, procedures performed, estimated blood loss, type and amount of local anesthetic and used, sedative agents used, surgical time, postoperative disposition and recovery, and length of hospital stay. Information on satisfaction with local anesthesia with sedation was also recorded from a postoperative questionnaire routinely administered to the principal author’s surgical patients prior to discharge from the hospital. The questionnaire included questions on overall satisfaction, pain, nausea, and ability to eat and ambulate after surgery, drowsiness, and comparison to previous anesthesia experiences (Table).

Results

A total of 20 complex vaginal reconstructive surgeries were performed between January 2004 and September
2004. Of these patients, only 3 did not have their surgeries performed under local anesthesia with sedation. Two patients had general anesthesia for concomitant abdominal surgeries (1 mini-laparotomy for bilateral salpingo-oophorectomy and 1 laparoscopic abdominal hernia repair). One patient opted for spinal anesthesia. The primary procedures performed under local anesthesia with sedation were 5 sacrospinous ligament suspensions and 12 paravaginal defect repairs. Every procedure included use of dermal allograft reinforcement. In addition, there were multiple concomitant procedures including: 4 enterocele repairs, 12 posterior repairs, 9 anterior repairs, 9 perineoplasties, 6 suburethral slings, and 1 perirectal injection. All primary procedures were performed for prolapse of grade 3 or greater; 1 patient had complete vaginal eversion.

The mean (± SD) age of patients was 66.1 (± 9.4) years, with a range from 50 to 79 years. Mean BMI was 27.8 (± 3.6) and ranged from 23.3 to 39.4. Eleven (65%) of the women had previously undergone hysterectomy; 4 (24%) had also undergone reconstructive surgery consisting of anterior and posterior repair. Review of the patients’ past medical histories revealed a variety of medical problems, including 7 (41%) with hypertension, 1 with history of myocardial infarction (5.9%), 4 (24%) with gastroesophageal reflux disease, 1 (5.9%) with insulin-dependent diabetes, 1 (5.9%) with asthma, and 13 (76%) with osteoarthritis.

The mean surgical time was 131.6 (± 36.8) minutes, with a range of 112 to 238 minutes. Mean estimated blood loss was 149.8 (± 117.9) mL, with a range of 10 to 500 mL. An average of 31.7 (± 10.8) mL of local anesthetic was used for each case. After surgery, 6 of the 17 women (35.3%) were admitted directly to the floor, bypassing the postanesthesia care unit. Mean length of stay was 1.2 (±.6) days, with a range of 1 to 3 days. Fourteen women (82.4%) were discharged to home within 24 hours of surgery. The only postoperative complication was severe nausea in response to narcotics, which was treated with antiemetics and the patient was discharged on postoperative day 2.

All the women (100%) described themselves as very satisfied (the highest rating on the questionnaire) with local anesthesia with sedation during their surgery. Only 1 (5.9%) patient reported experiencing any pain during the procedure. Two (11.8%) patients experienced nausea and 2 (11.8%) experienced drowsiness in the immediate postoperative period. Fifteen (88.2%) women were able to eat immediately after surgery, and 16 (94.1%) were able to ambulate immediately without assistance. All women had experienced some form of anesthesia in the past; 15 (88.2%) had previously had general anesthesia. All the women (100%) felt the local anesthesia with anesthesia was preferable to their previously experienced anesthesia, and all would recommend this form of anesthesia to a friend.

### Table: Patient satisfaction questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
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<tbody>
<tr>
<td>Overall, how satisfied were you with the anesthesia?</td>
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<tr>
<td><strong>Very satisfied</strong></td>
<td></td>
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<tr>
<td><strong>Somewhat satisfied</strong></td>
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<tr>
<td><strong>Somewhat dissatisfied</strong></td>
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<tr>
<td><strong>Very dissatisfied</strong></td>
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<tr>
<td><strong>Don't know</strong></td>
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<tr>
<td>Did you feel any pain during surgery?</td>
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<td><strong>Yes</strong></td>
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<tr>
<td><strong>No</strong></td>
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<tr>
<td>Did you feel nauseous after surgery?</td>
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<tr>
<td><strong>Yes</strong></td>
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<tr>
<td><strong>No</strong></td>
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<tr>
<td>Could you eat right away after surgery?</td>
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<td><strong>Yes</strong></td>
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<tr>
<td><strong>No</strong></td>
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<tr>
<td>Could you ambulate right away after surgery?</td>
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<td><strong>Yes</strong></td>
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<tr>
<td><strong>No</strong></td>
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<tr>
<td>Did you feel drowsy after surgery?</td>
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<td><strong>Yes</strong></td>
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<td><strong>No</strong></td>
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<tr>
<td>Have you ever had any other types of anesthesia?</td>
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<td><strong>Yes</strong></td>
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<td><strong>No</strong></td>
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<td>If yes, which one? General Spinal Epidural</td>
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<tr>
<td>How did local anesthesia compare with this/these other types of anesthesia?</td>
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<tr>
<td><strong>Better</strong></td>
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<td><strong>Worse</strong></td>
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<td><strong>The same</strong></td>
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<tr>
<td>Please explain:</td>
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<tr>
<td>Would you recommend surgery under local anesthesia to a friend?</td>
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<tr>
<td><strong>Yes</strong></td>
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<tr>
<td><strong>No</strong></td>
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<tr>
<td><strong>Maybe</strong></td>
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</tbody>
</table>

### Comment

The use of local anesthesia with sedation for vaginal reconstructive surgery allows procedures to be performed that can dramatically improve a patient’s quality of life, while avoiding the systemic effects of general anesthesia. Previously published case series clearly demonstrate the feasibility and success of this type of anesthesia for minor reconstructive procedures. Although the use of local anesthesia clearly benefits those of our patients who are elderly and at higher risk from general anesthesia, it should not be considered as an anesthetic option for the elderly only. It is also a viable anesthetic alternative for younger women who desire surgical intervention for symptomatic pelvic organ prolapse and urinary incontinence.

In this case series, we successfully performed 17 complex vaginal reconstructive surgeries under local anesthesia with sedation. Only 1 patient declined the use of local anesthesia with sedation and opted for regional anesthesia. No cases had to be converted to general anesthesia and there were no surgical complications. Most patients were able to ambulate and tolerated a regular diet immediately after surgery. The majority of patients were discharged home within 24 hours of surgery. All the patients were very satisfied with the experience and would recommend this type of anesthesia. Because we did not use a control group of patients undergoing similar procedures under general or regional anesthesia, we cannot make any assumptions on how
these outcomes compare with those of other modes of anesthesia. This series clearly demonstrates that the use of local anesthesia can safely be extended to almost all vaginal procedures. Patient satisfaction has been uniformly high.

References


Diagnosis of pulmonary embolism: A cost-effectiveness analysis

To the Editors: We are writing regarding the recent article by Doyle et al.1

Pulmonary embolism is a significant cause of morbidity and death during pregnancy and the postpartum period. Anticoagulation is the mainstay of therapy for deep venous thrombosis and pulmonary embolism.2

We agree with the authors that spiral computed tomography (CT) offers the most cost-effective method for diagnosing this potentially fatal condition and is the current investigation of choice in patients who are suspected of having pulmonary embolism. However, we would like to point out our concern regarding fetal radiation exposure with the use of CT during pregnancy.

We feel that an integrated, noninvasive, radiation-free diagnostic algorithm (combining clinical assessment/scoring system, D-dimer, and compression/color Doppler ultrasound) should be used initially and should be followed, if required, by spiral CT.

The authors themselves have pointed out that 40% of documented pulmonary embolisms have a positive compression ultrasound result.

In these subset of patients, anticoagulation therapy should be started immediately, without waiting for a subsequent detection of pulmonary embolism by other modalities, because the treatment options remain more or less the same. In patients with negative ultrasound results and a high clinical probability, spiral CT should still be done for pulmonary embolism. However, in patients with positive compression/color Doppler results, after immediate medical treatment (anticoagulants), one should perhaps do a magnetic resonance (MR) angiography, rather than CT angiography, in these pregnant patients who are suspected of having pulmonary embolism.

We also agree with the authors regarding the practical usefulness of MR angiography in these patients. Its main persisting diagnostic limitation includes poor sensitivity for subsegmental thrombi and poor interobserver agreement.3 It still has some obvious advantages; it does not involve ionizing radiations and is safe in patients with poor renal function. This is another aspect of MR angiography that we wish to highlight; for those patients with renal failure or those patients who are allergic to contrast for whom CT angiography/contrast-enhanced CT scan cannot be done, MR should be the next imaging modality that should be used in these patients. Recent studies have shown that it has a high sensitivity and specificity. Recent advances in MR technology have now enabled faster data acquisition so that pulmonary vasculature can be visualized in much less time without the need for contrast or breath holding.4

Kushaljit Sodhi, MD*
Department of Radiodiagnosis
PGIMER, Chandigarh-160012
E-mail: sodhiks@rediffmail.com

Shanujeet Kaur, MD
Department of Obstetrics & Gynaecology
Government Medical College & Hospital
Chandigarh, India

References

Reply

To the Editors: We thank Drs Sodhi and Kaur for their interest in our study. We agree that the spiral computed tomography (CT) is the most cost-effective method for diagnosing pulmonary embolism in pregnancy. Moreover, it appears that spiral CT is the most consistently accurate method of diagnosing pulmonary embolism, which remains one of the most common causes of maternal death in the United States.

We disagree with some aspects of the proposal for an integrated noninvasive diagnostic algorithm. Clinical assessment and scoring systems have been notoriously poor in making the accurate diagnosis of pulmonary embolism in pregnancy. Although there are theoretic concerns of fetal radiation exposure from spiral CT, the calculated fetal dose has been estimated to be 131 mGy, which is less than exposure with a ventilation/perfusion scan (370 mGy) and much less than the dose that a fetus receives from background radiation during the 9 months of pregnancy (1150-2550 mGy). By comparison, an exposure of at least 100,000 mGy is necessary before a pregnancy termination is considered. Furthermore, as noted in our article, compression/color Doppler ultrasound has a very low sensitivity for pulmonary embolism in pregnancy.

Finally, although the D-dimer test shows promise and is employed commonly in nonpregnant women, there remain concerns about the accuracy of this test in the pregnant woman. Therefore, until these issues can be resolved or until some new modality is developed that is highly sensitive and highly specific in pregnancy, spiral CT remains the clinical diagnostic test of choice and the most cost-effective option for suspected pulmonary embolism in pregnancy.

Nora M. Doyle, MD, MPH*
Michael Gardner, MD, MPH
Department of Obstetrics and Gynecology
Division of Maternal Fetal Medicine
University of Texas Health Sciences Center
6431 Fannin St
MSB 3.430
Houston, TX 77030
*E-mail: Nora.M.Doyle@uth.tmc.edu

References


Preterm predictors: Constipation, childbirth, and cervical surgery?

To the Editors: The inverse relationship between prepregnancy, maternal body mass index (BMI) and the rate of spontaneous preterm birth (SPB) in the Preterm Prediction Study is striking, particularly the confirmation of the high rate of SPB (16.6%) in women with BMI of <19 kg/m².

Suboptimal diet may be associated with sustained constipation and is remarkably common in developed societies. Denervation-reinnervation has been observed at all levels of the lower genital tract, including the uterus, cervix, vagina, and vulva in association with persistent constipation and difficult vaginal deliveries. Loop excision of the cervix may also cause denervation, a similar propensity to genital infection, and, increased rates of preterm premature rupture of membranes and SPB. Injury to the uterovaginal nerve plexi through sustained constipation, common surgical procedures, and previous intrapartum events may create the conditions for genital infection with increased and recurring rates of preterm premature rupture of membranes and SPB.

Known primary predictors of preterm labor offer a portrait of a single, black, teenaged mother of reduced socioeconomic status and low BMI who smokes, has regular stressful life events, and has recurrent preterm
deliveries. Simple dietary measures, moderate intrapartum treatment, and fewer surgical procedures may conserve her innervation, protect her from genital tract infection, and recurrent preterm pregnancy loss?

Martin Quinn, MB ChB, MD, MRCOG*
Department of Obstetrics & Gynaecology
Hope Hospital
Stott Lane
Salford, M6 8HD, UK
*E-mail: quinnobgyn@aol.com

References

Reply

To the Editors: We thank Dr Quinn for the comments on our observation regarding an inverse relationship between prepregnancy maternal BMI and the rate of spontaneous preterm birth. Dr Quinn hypothesizes that denervation-reinnervation of the lower genital tract as the result of constipation may be a cause for the increased rate of spontaneous preterm birth in women who are underweight because of suboptimal diet. He also believes that injury to the uterovaginal nerve plexi through sustained constipation, common surgical procedures, and previous intrapartum events may create the conditions for genital infection with increased, and recurring, rates of preterm premature rupture of membranes and spontaneous preterm birth.

In our report, there was a continuous inverse correlation between increasing BMI and the incidence of spontaneous preterm birth. These findings sustained after correction for other variables associated with spontaneous preterm birth that included parity, maternal age, education, black race, history of spontaneous preterm birth, and bacterial vaginosis.1 According to Dr Quinn’s theory, the association between obesity and the reduced rate of spontaneous preterm birth can be attributed to a better quality of food that is consumed by obese women that causes a lower rate of constipation. Unfortunately, this may not be the case. Pecora et al.,2 in 1897 subjects, found that the prevalence of constipation was 8.3% in obese patients compared with 1.5% in normal weight control subjects. Fast food consumption also has strong positive associations with weight gain and insulin resistance, which suggests that fast food increases the risk of obesity and type 2 diabetes mellitus.3 Thus, obesity is associated with low fiber-low quality food and constipation, which appears to contradict Dr Quinn’s hypothesis. Furthermore, because our results were adjusted for bacterial vaginosis, and obese women appear to have an increased tendency for infections, there is no evidence that, in our cohort, genital infection is the cause for the higher rate of spontaneous preterm birth in the underweight women. However, further study is needed to determine whether simple dietary measures and fewer surgical procedures can reduce the risk for spontaneous preterm birth in the underweight women. However, in developed countries, the use of multivitamins and dietary supplements have not had a major impact on reducing preterm birth.4

Israel Hendler, MD*
Cora A. McPherson, PhD
Robert L. Goldenberg, MD
National Institute of Child Health and Human Development
Maternal-Fetal Medicine Units Network
National Institutes of Health
Bethesda, MD
*E-mail: ihandler@med.wayne.edu

References
Variable effect of prothrombotic factors on fetomaternat circulation

To the Editors: We read the article of Salomon et al1 with interest.

While congratulating the authors on their work, we would like to highlight 2 points that might have escaped their attention. Their population was highly selected in respect of reproductive history and was heterogeneous with regard to types of thrombophilia.

They entered only healthy nulliparous women at 14 to 16 weeks of gestation with no ultrasonic evidence of fetal anomaly.1 Selecting women with these criteria means the exclusion of women with a history of miscarriage, infertility, or thrombotic events. Evidence shows that these are the women in whom vascular abnormalities of the placental bed can and should be looked for.

Common prothrombotic factors of an “unselected” population include a wide variety of inherited and acquired abnormalities. Genetic defects that were studied by the authors included factor V Leiden (FVL), prothrombin variant-G20210A (FIIvar), and methylene-tetrahydrofolate-reductase 677T-polymorphism (MTHFR 677T). In the authors’ study population, 36 women (5.7%) carried FVL either alone or in combination with other abnormalities (24 G12 cases). According to large meta-analyses, only FVL of the studied abnormalities is related to poor obstetric outcome. Deficiencies of natural anticoagulants (protein S, protein C, and antithrombin-III) occur with >10% frequency each among pregnancies of women with inherited thrombophilia.2 The authors may argue that none of these prothrombotic abnormalities occurred in their population. Nonetheless, looking for them was not mentioned in the methods that they used.

No subgroup analysis was performed to compare uteroplacental blood flow of FVL carriers with that of pregnant women without prothrombotic factors. The increased proportion of pathologic Doppler measurements among carriers of factor V Leiden, however, was reported by Lindquist and Gudmundson.3

In Hungary, the most common form of inherited thrombophilia is FVL carriership that occurs with 9.3% frequency.4 We analyzed all 339 pregnancies of 160 FVL carrier women.5 Irrespective of the pregnancy order, approximately one sixth of the pregnancies ended in miscarriage. Pregnancies of women with combined thrombophilia had an 8.1-times higher odds of miscarriage (P = .0045) than those with heterozygosity for FVL alone. Interestingly, the same women with combined prothrombotic defect had 3.6-times higher odds (P = .0471) of preeclampsia and 14.1-times higher odds (P = .0381) placental abruption.

Therefore, we believe, the conclusion that prothrombotic factors in nulliparous women do not compromise fetomaternat circulation, at least among factor V Leiden carriers, should be taken with caution.

Robert Póka, MD, PhD*
S. Vad, MD
I. Balogh, PhD
É. Ajzner, MD, PhD
Department of Obstetrics and Gynecology
University Medical School of Debrecen
PO Box 37
4012 Debrecen, Hungary
*E-mail: pokar@jaguar.dote.hu

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Reply

To the Editors: We thank Dr. Póka et al for their letter. Our study was designed to address the question whether thrombophilias per se cause adverse outcomes of pregnancy and whether they compromise blood flow in the uteroplacental fetal unit.

Answers to these questions could not have been attained by the inclusion of patients with potential confounding factors, such as previous thrombotic events or other previous adverse outcomes of pregnancy. Obviously, our data, which were based on a prospective cohort study, contrast previous case control association studies that unfortunately have been translated into the hasty use of anticoagulant therapy.

Non-thrombophilic factors, thrombophilic factors, and both thrombophilic and non-thrombophilic factors hypothetically may be the causes of adverse outcomes of pregnancy. Our data weaken the argument that thrombophilic factors per se play a role but do not rule out the possibility that they enhance, to an unknown extent, the effect of non-thrombophilic factors.

Proteins C and S were not measured because the expected number of affected subjects was approximately 1 to 2/644 and ! 1 in 644. Analysis of blood flow measurements in patients with the various thrombophilias would not yield definitive conclusions because of the relatively small number of patients.

Ophira Salomon
Reuven Achiron
David Steinberg
Uri Seligsohn*
The Amalia Biron Research Institute of Thrombosis and Hemostasis
Sheba Medical Center
Tel-Hashomer 52621, Israel
*E-mail: seligson@sheba.health.gov.il

Urinary angiogenic factors in preeclampsia

To the Editors: We read with interest the article by Buhimschi et al1 in which the authors describe the measurement of urinary soluble fms-like tyrosine kinase 1 (sFlt-1) and other angiogenic factors in women with preeclampsia. To measure sFlt-1 in maternal urine seems to be a simple and noninvasive method for the detection of manifest preeclampsia or even for an early screening. However, to our knowledge, urinary sFlt-1 was thought to be detectable only in pathologic states because the protein with a size of approximately 100 kd is too large to be secreted in urine from a healthy kidney. Only in the situation of renal damage is sFlt-1 reported to be measurable in the urine. Therefore, urinary placental growth factor, a smaller molecule that mirrors sFlt-1 changes is the preferred urinary marker to assess an imbalance between angiogenic and antiangiogenic factors.2 Thus, we found it interesting that Buhimschi et al1 report significant urinary sFlt1 values in healthy nonpregnant and healthy pregnant patients. We wonder how the authors comment on this discrepancy.

We have shown that the excess of sFlt-1 is not totally specific for preeclampsia because it is also observable in patients with intrauterine growth retardation and normotension.3 Thus, the finding of increased urinary sFlt-1 could be a diagnostic tool for different pregnancy disorders. Further studies have to show whether the documented sFlt-1 elevation in urine precedes the clinically evident disease as described for serum sFlt-1.4 If so, the measurement of urinary sFlt-1 could be alone or in combination with uterine Doppler evaluation as an early test for pregnancy complications such as preeclampsia or intrauterine growth retardation. Because our group has shown that women who are in the second trimester with abnormal uterine perfusion and subsequent
pregnancy complications have elevated serum sFlt-1 values, the measurement of urinary instead of serum sFlt-1 could be an even easier method for risk stratification.

Holger Stepan, MD*
Renaldo Faber, MD
Department of Obstetrics and Gynecology
University of Leipzig
Philipp-Rosenthalstr 55
Leipzig 04103, Germany
*E-mail: holger.stepan@medizin.uni-leipzig.de

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Reply

To the Editors: We report immunoreactive levels of soluble fms-like tyrosine kinase 1 (sFlt-1) in our control groups. For the nonpregnant and pregnant healthy control subjects, the sFlt-1 median levels corrected for urinary creatinine concentrations were 10.5 pg per mg creatinine (range, 0.4-48.1 pg/mgc) and 15.6 pg/mgc (range, 0.1-65.8 pg/mgc), respectively. Our results suggest normal pregnancy is not characterized by significant changes in the urinary outpouring of sFlt-1 because the difference between the 2 groups is statistically not significant. Considering that the minimal detectable levels in the sFlt-1 enzyme-linked immunosorbent assay are less than 5 pg/mL, our data reflect minimal concentrations of this antiangiogenic factor in the urine for both pregnant and nonpregnant control subjects. In contrast, women with severe preeclampsia had urinary concentrations of sFlt-1 that were almost 10 times higher compared with the control groups (145.5 pg/mgc; range, 6.4-990.7 pg/mgc). The hypothesis that a damaged glomerular barrier is the sole explanation for the urinary presence of sFlt-1 appears to be somehow simplistic because sFlt-1 is expressed constitutively in the adult kidney. Therefore, minimal detectable levels for sFlt-1 in nonpregnant and pregnant healthy control subjects should not come as a surprise. Nevertheless, the data concerning the fractional excretion of sFlt-1 suggest that the dramatic increase in sFlt-1 urinary concentration that is characteristic of severe preeclampsia could be the result of 2 separate phenomena that occur in parallel and may have additive effects: “endogenous” renal production and glomerular “leakage.” We appreciate the previous pilot work of Drs Stepan and Faber and thank them for their interest in our studies.

Catalin S. Buhimschi, MD*
Department of Obstetrics, Gynecology and Reproductive Science
Yale University
Yale New Haven Hospital
20 York St, FMB 339
New Haven, CT 06520
*E-mail: catalin.buhimschi@yale.edu

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Corrections


Jan Dickinson, MD, is part of the University of Western Australia, Perta, Western Australia.

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The article, “Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: Findings from the initial screen of a randomized trial,” by Buys et al published in November 2005 (volume 193, p. 1630-9) is missing material in the Figure. Below is the completed figure.
Target Population: Men and women ages 55-74 with no personal history of prostate, lung, colorectal or ovarian cancer

154,942 Randomized

76,705 Male

78,237 Female

39,122 Control Group

39,115 Intervention

5,386 Did not receive either screen

4,913 Prior oophorectomy *

28,803 Received initial CA125
28,519 Received initial TVU
28,816 Received at least one test
28,506 Received both tests

Figure  Flow of participants into the PLCO Trial. *Ineligible for screening.
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Analysis of knowledge and attitudes of adult groups before and after attending an educational presentation regarding adolescent sexual activity (Sulak et al). 2005;193:1945-54

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Delay of preterm birth in sheep by THG113.31, a prostaglandin F2α receptor antagonist (Hirst et al). 2005;193:256-66

Progesterone for prevention of recurrent preterm birth: impact of gestational age at previous delivery (Spong et al). 2005;193:1127-31

Prophylactic cerclage in the management of triplet pregnancies (Rebarber et al). 2005;193:1193-6

Short cervical length after history-indicated cerclage: is a reinforcing cerclage beneficial? (Baxter et al). 2005;193:1204-7

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Are alterations in plasma protease concentrations during labor associated with poor obstetric outcomes? (Knight et al). 2005;193:283-8


Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial (Khoury et al). 2005;193:1292-301 (Editors’ choice)

Evidence-based surgery for cesarean delivery (Berghella et al). 2005;193:1607-17 (Review article)

Fetal response to maternal methadone administration (Jansson et al). 2005;193:611-7 (Editors’ choice)

High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes (McCarthy et al). 2005;193:612-7 (Editors’ choice)

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The interrelationship between ethnicity and obesity on obstetric outcomes (Ramos and Caughey). 2005;193:1089-93


Is fetal gender associated with adverse perinatal outcome in intrauterine growth restriction (IUGR)? (Quinones et al). 2005;193:1233-7

Is zygosity or chorionicity the main determinant of fetal outcome in twin pregnancies? (Carroll et al). 2005;193:757-61

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Perinatal outcomes in women with preterm rupture of membranes between 24 and 32 weeks of gestation and a history of vaginal bleeding (Hnat et al). 2005;193:164-8

Periviable birth at 20 to 26 weeks of gestation: proximate causes, previous obstetric history and recurrence risk (Mercer et al). 2005;193:1175-80


Projected benefits of universal or scheduled antepartum corticosteroids to prevent neonatal morbidity: a decision analysis (Boggess et al). 2005;193:1415-23

Prophylactic cerclage in the management of triplet pregnancies (Rebarber et al). 2005;193:1193-6

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First trimester uterine artery Doppler abnormalities predict subsequent intrauterine growth restriction (Dugoff et al). 2005;193:1208-12


Maternal plasma concentrations of IGF-1, IGFBP-1, and C-peptide in early pregnancy and subsequent risk of gestational diabetes mellitus (Qu et al). 2005;193:1691-7

Maternal serum soluble fms-like tyrosine kinase 1 concentrations are not increased in early pregnancy and decrease more slowly postpartum in women who develop preeclampsia (Powers et al). 2005;193:185-91


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Twin-to-twin transfusion syndrome at 11 weeks of gestation (Sueters et al). 2005;193:887-8


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Dioxin-like activity and maternal thyroid hormone levels in second trimester maternal serum (Foster et al). 2005;193:1900-7

An elevated maternal plasma, but not amniotic fluid, soluble fms-like tyrosine kinase-1 (sFlt-1) at the time of mid-trimester genetic amniocentesis is a risk factor for preeclampsia (Park et al). 2005;193:984-9

High-dose vaginal misoprostol versus concentrated oxytocin plus low-dose vaginal misoprostol for mid-trimester labor induction: a randomized trial (Nuthalapaty et al). 2005;193:1065-70

The identification of risk of spontaneous fetal loss through second-trimester maternal serum screening (Huang et al). 2005;193:395-403

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- Characteristics associated with suboptimal viral suppression at delivery in human immunodeficiency virus-1–infected pregnant women (Louis et al.). 2005;193:1266-9

Premenstrual syndrome


- Isolated fetal pyelectasis and chromosomal abnormalities (Coco and Jeanty). 2005;193:732-8


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- Early fetal echocardiography—a reliable prenatal diagnosis tool (McAuliffe et al.). 2005;193:1253-9


- Evidence-based obstetric ethics and informed decision-making by pregnant women about invasive diagnosis after first-trimester assessment of risk for trisomy 21 (Nicolaides et al.). 2005;193:322-6 (Editors’ choice)


- The identification of risk of spontaneous fetal loss through second-trimester maternal serum screening (Huang et al.). 2005;193:1208-12

- The impact of gestational age on the sonographic detection of aneuploidy (Picklesimer et al.). 2005;193:1243-7


- Noninvasive prenatal RHD genotyping by real-time polymerase chain reaction using plasma from D-negative pregnant women (Zhou et al.). 2005;193:1966-71

- Patient preference regarding first-trimester aneuploidy risk assessment (Sharma et al.). 2005;193:1429-36

- Pre-emptive placement of a presealant for amniotic access (Cortes et al.). 2005;193:1197-203

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- Deep hypotension and associated electrocardiographic changes during prolonged cord occlusion in the near term fetal sheep (Wibbens et al.). 2005;193:803-10

- A prospective, randomized comparison of vaginal misoprostol versus intra-amniotic prostaglandins for mid trimester termination of pregnancy (Su et al.). 2005;193:1410-4

- The mean weekly increment of amniotic fluid TDx-FLM II ratio is constant during the latter part of pregnancy (Bildirici et al.). 2005;193:1685-90

- Obstetric outcomes after surgical abortion at ≥20 weeks’ gestation (Chasen et al.). 2005;193:1161-4

- Perinatal outcomes in women with preterm rupture of membranes between 24 and 32 weeks of gestation and a history of vaginal bleeding (Hnat et al.). 2005;193:164-8

- Suspension and treatment of the macrosomous fetus: a review (Chauhan et al.). 2005;193:332-46 (Review article)

- Targeting the respiratory muscles of fetal sheep for prenatal gene therapy for Duchenne muscular dystrophy (Weisz et al.). 2005;193:1105-9


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- Plasma CRH measurement at 16 to 20 weeks’ gestation does not predict preterm delivery in women at high-risk for preterm delivery (Sibai et al.). 2005;193:1181-6


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Progesterone modulation of inflammatory cytokine production in a fetoplacental artery explant model (Shields et al). 2005;193:1144-8

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Discriminatory proteomic biomarker analysis identifies free hemoglobin in the cerebrospinal fluid of women with severe preeclampsia (Norwitz et al). 2005;193:957-64

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