Prophylactic use of antibiotics for nonlaboring patients undergoing cesarean delivery with intact membranes: A meta-analysis

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OBJECTIVE: We performed a meta-analysis to examine the role of antibiotic prophylaxis in preventing postoperative infections among nonlaboring women undergoing cesarean delivery with intact membranes.

STUDY DESIGN: A computerized literature search was performed with MEDLINE. Studies were included if they contained data on patients undergoing cesarean delivery in the absence of labor and ruptured membranes. Only randomized trials with a placebo control group were included.

RESULTS: Seven studies were found. Use of antibiotics decreased the risk of all infectious outcomes reported. When the results of 4 studies were pooled, prophylactic antibiotic use was associated with a significant reduction in postoperative fever (relative risk, 0.25; 95% confidence interval, 0.14-0.44). A similar reduction was noted for endometritis in 4 studies (relative risk, 0.05; 95% confidence interval, 0.01-0.38). Two studies reported on wound infection and showed a trend toward a protective effect (relative risk, 0.59; 95% confidence interval, 0.24-1.45).

CONCLUSION: The prophylactic use of antibiotics reduces the risk of postoperative infectious complications after cesarean delivery even in the population at lowest risk. (Am J Obstet Gynecol 2001;184:656-61.)

Key words: Cesarean delivery complications, meta-analysis, prophylactic antibiotic use

Women undergoing cesarean delivery have a significant incidence of many infectious complications, including fever, wound infection, endometritis, bacteremia, urinary tract infection, and pelvic abscess. Although there are a number of well-defined risk factors for infectious complications after cesarean delivery, these complications still occur in patients without risk factors. For laboring patients prophylactic antibiotic use is recommended by The American College of Obstetricians and Gynecologists and by other consensus panels. In contrast, there is no consensus regarding the potential benefits of prophylactic antibiotic use for nonlaboring women undergoing cesarean delivery with intact membranes. Uniform recommendations do not exist for this situation, and The American College of Obstetricians and Gynecologists states, “Routine prophylaxis for elective cesarean delivery is controversial. Prophylaxis is not recommended routinely in low-risk patients.”

Data from the 1998 National Vital Statistics Report suggest that there is a huge pool of such cases. In 1998, >150,000 cesarean deliveries for malpresentation and >305,000 repeat cesarean deliveries were performed, most of which were probably elective cesarean deliveries in the absence of ruptured membranes or labor. Postoperative infections do occur among these patients, despite the well-established lower risk of infection than among laboring and high-risk patients. The large number of cesarean deliveries performed on low-risk women suggests that there is a large group of women with potentially preventable postoperative infectious complications. We performed a meta-analysis to study the role of antibiotic prophylaxis in cesarean delivery of nonlaboring patients with intact membranes.

Material and methods

A MEDLINE literature search was performed with the key words cesarean section and antibiotics to find randomized controlled trials. The search included articles published after 1966 that were included in the MEDLINE database as of February 1, 2000. In addition, the Cochrane Library database was searched, and the bibliography of each article and related review articles were reviewed to locate further studies. The search was restricted to published data in the English language.
A trial was included if the following criteria were met:
1. Patients were randomly assigned to the treatment groups.
2. There was a placebo control group.
3. Information on blinding was clearly stated.
4. The study included a distinct group of patients clearly identified as nonlaboring and with intact membranes.
5. The study included data on at least one of our outcomes of interest (fever, endometritis, or wound infection) for our subgroup of interest, and these outcomes were clearly defined and reported.

Two of the authors independently performed the literature search and extracted pertinent data from each study to a data sheet. The third author reviewed this process and resolved inconsistencies in the data collection.

Mantel-Haenszel $\chi^2$ tests for homogeneity of effect were performed with Excel (Microsoft Corporation, Redmond, Wash) spreadsheet. Heterogeneity was not statistically significant, thus justifying the use of the fixed-effect Mantel-Haenszel odds ratio and relative risk as the summary measures throughout our analysis. Studies with odds ratios equal to 0 were not included in the test of heterogeneity. In the endometritis analysis only 1 study reported a non-0 odds ratio, making a statistical test for heterogeneity unmeaningful. For this analysis the fixed effect model was used for consistency with the fever analysis. Summary Mantel-Haenszel odds ratios and relative risks were calculated with Epi Info 6.0 statistical software. Because of the difficulties in computing confidence limits for small studies with relative risks of 0, the figures show individual and summary odds ratios. Exact confidence intervals were reported for odds ratios whenever small cell counts (<5) were present. Sensitivity analysis was performed by excluding each individual study and recalculating the summary odds ratio. Summary group mean incidences of adverse outcomes were calculated by weighting the sample size. An $\alpha$ of .05 was chosen for statistical significance. Ninety-five percent confidence intervals are reported throughout.

### Table I. Summary of studies included in meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study period</th>
<th>Location</th>
<th>Population</th>
<th>Relevant exclusions</th>
<th>Antibiotic regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al</td>
<td>Aug 1970–Jan 1971</td>
<td>The Johns Hopkins Hospital, Baltimore</td>
<td>Resident service; patients admitted night before surgery</td>
<td>Cephalothin 1.0 g intravenously on call to operating room, 2.0 g intraoperatively, then 1.0 g intravenously every 6 h for 48 h, then 0.5 g intramuscularly every 6 h for 72 h</td>
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<tr>
<td>Duff and Park</td>
<td>Oct 1976–Mar 1977</td>
<td>Walter Reed Army Medical Center, Washington, DC</td>
<td>Military; mixed white and nonwhite; private and clinic</td>
<td>Penicillin allergy</td>
<td>Ampicillin 1.0 g intravenously on call to operating room, then at 6 and 12 h after operation</td>
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<tr>
<td>Dillon et al</td>
<td>Sep 1979–Apr 1980</td>
<td>Children’s Hospital of Buffalo, Buffalo, NY</td>
<td>Evidence of active infection, penicillin or cephalosporin allergy, or recent antibiotic treatment</td>
<td>Cefoxitin 2.0 g intravenously after cord clamping, then 4 and 10 h after operation</td>
<td></td>
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<tr>
<td>Duff et al</td>
<td>Jan 1979–Jun 1980</td>
<td>Walter Reed Army Medical Center, Washington, DC</td>
<td>Patients in labor or with ruptured membranes</td>
<td>Ampicillin 1.0 g intravenously 30 minutes before surgery, repeated 4 and 8 h later</td>
<td></td>
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<tr>
<td>Apuzzio et al</td>
<td>1977-1981</td>
<td>University Hospital of the New Jersey Medical School, Newark, NJ</td>
<td>Adolescents (15-18 y); 90% black</td>
<td>Ticarcillin 6.0 g after cord clamping</td>
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<tr>
<td>Roex et al</td>
<td>Apr 1983–Oct 1984</td>
<td>Academisch Ziekenhuis der Vrije Universiteit, Amsterdam, The Netherlands</td>
<td>Antibiotic use with 7 d of admission; evidence of active infection at admission; allergy to penicillin or cephalosporin; impaired renal or liver function</td>
<td>Cefoxitin 2.0 g intravenously after cord clamping, then 1.0 g 6 and 12 h later</td>
<td></td>
</tr>
<tr>
<td>Mahomed</td>
<td>Nov 1986–Mar 1987</td>
<td>Harare Central Hospital, Harare, Zimbabwe</td>
<td>“All patients who had an elective lower segment caesarean section before the onset of labour or rupture of membranes were eligible”</td>
<td>Crystalline penicillin 2 mU and chloramphenicol 500 mg injected* on call to operating room</td>
<td></td>
</tr>
</tbody>
</table>

*Intravenous or intramuscular route not specified.
Results

A total of 632 articles were found in the initial literature search. All but 24 could be excluded by reviewing the abstract. Of the 24 reviewed further, 7 studies met criteria for inclusion in our meta-analysis. Among the 17 articles reviewed but excluded, the most common reasons for exclusion were no placebo used or no reported outcomes specific to our low-risk population (nonlaboring patients with intact membranes). Several of the excluded articles included “elective” groups that included patients in early labor or shortly after rupture of membranes. A single excluded article reported information on nonlaboring patients with intact membranes, but the data in the text conflicted with the data in the table. Because the conflict was substantial and could not be resolved, the article was excluded. Review of the Cochrane Library and individual bibliographies from the reviewed studies and published review articles did not detect any qualifying articles not already found.

Each of the 7 included studies used a different antibiotic regimen (Table I). Preoperative or intraoperative (at cord clamp) doses were given in all studies, and most studies repeated several doses after the operation. Two studies used a single preoperative dose alone. The studies were performed in a variety of institutions on three continents. The studies also used a variety of different outcome definitions (Table II). In many instances our group of interest was only a small subgroup of a much larger study, so several subgroups were quite small, ranging from 12 to 15 subjects up to the largest study, which had 232 subjects (Table III).

Four studies reported data on postoperative fever. All but 1 study showed a protective effect, and 2 studies showed individually statistically significant protective effects. In the absence of antibiotic use the baseline incidence of fever was 24% (95% confidence interval, 7%-40%). A Mantel-Haenszel summary relative risk was calculated with all 4 studies (relative risk, 0.25; 95% confidence interval, 0.14-0.44). Fig 1 displays the odds ratios and confidence intervals for each individual study, as well as the summary odds ratio. Exclusion of any single study changed the summary odds ratio only minimally. Even exclusion of the largest study changed the summary measures only slightly (odds ratio, 0.25; 95% confidence interval, 0.08-0.69) and did not change statistical significance. The Mantel-Haenszel test for homogeneity of effects showed no evidence of heterogeneity (P = .50) among the studies.

Similar calculations were done for endometritis, in which pooling of all 4 studies that reported endometritis as an outcome yielded a summary relative risk of 0.05 (95% confidence interval, 0.01-0.38). The pooled risk of endometritis in the placebo group was 11% (95% confidence interval, 0%-24%). Fig 2 displays the summary odds ratio data. Sensitivity analysis yielded only minimal change with the exclusion of any single study. Exclusion of the largest study changed the largest change, but this change was only slight and did not change statistical significance (odds ratio, 0.06; 95% confidence interval, 0.00-0.44).

Two studies presented data on wound infection. One had no wound infections in either group. Mahomed presented data on wound infection broken into three categories according to severity. Pooling the data from the two most severe categories (wounds with oozing or pus) yielded a nonsignificant trend toward protection (6.1% vs 10.3%; relative risk, 0.59; 95% confidence interval, 0.24-1.45). Two other articles remarked that there were no wound infections in the treatment groups, but these articles did not give individual data for the placebo groups in our subgroups of interest.
Three studies presented data on infection by pooling several types of infection. Allen et al. presented data on morbidity that combined fever with “other clinical signs of obvious infection” and noted a nonsignificant decrease in risk (0% vs 43%; relative risk, 0.00; odds ratio, 0.00; 95% confidence interval, 0.00-3.18). Dillon et al. combined endometritis and wound infection and also noted a nonsignificant decrease (0% vs 25%; relative risk, 0.00; odds ratio, 0.00; 95% confidence interval, 0.00-1.58). Mahomed presented all morbid events (fever, wound infection, and endometritis) and noted a significant decrease (16% vs 37%; relative risk, 0.39; odds ratio, 0.28; 95% confidence interval, 0.14-0.54).

A number of other individual outcomes were presented in several studies. Duff et al. presented data on need for initiation of antibiotics after the operation and noted a trend toward decreased need after prophylaxis (2.4% vs 15%; relative risk, 0.16; 95% confidence interval, 0.02-1.26). Mahomed presented data on patients with postoperative stays >8 days and noted a significant decrease with prophylaxis (2.6% vs 9.4%; relative risk, 0.28; 95% confidence interval, 0.08-0.97). Duff et al. reported a nonsignificant difference in length of stay (4.3 vs 4.6 days).

Several outcomes did not occur in either group in a number of studies. Four studies specified that no life-threatening infections occurred. Three studies specified that no cases of septic pelvic thrombophlebitis occurred. Four studies specified that no pelvic abscesses occurred. Two studies specified that no episodes of septic shock occurred. One study specified that no urinary tract infections occurred. Dillon et al. specified that no patients were readmitted. Duff and Park and Roex et al. specified that there were no adverse effects noted from the study drugs. Three reports specified that no patients underwent reoperation. Several other studies did report rare occurrences.
of these outcomes but did not specify whether they were in our groups of interest.

**Comment**

The prophylactic use of antibiotics in many obstetric-gynecologic procedures, particularly nonelective cesarean delivery, is well established in clinical practice. The most recent ACOG Technical Bulletin on the subject specifically states that “short-course antibiotic prophylaxis in women undergoing nonelective cesarean delivery reduces both endometritis and wound infections” and further endorses antibiotic prophylaxis for cesarean delivery in laboring patients as “cost-effective.”

The American College of Obstetricians and Gynecologists states that routine prophylaxis is controversial for elective cesarean delivery. However, these low-risk deliveries remain an important problem. The placebo groups in the studies we reviewed had high baseline incidences of fever (28%) and endometritis (11%), which suggests that even these supposedly low-risk cesarean deliveries carry an appreciable risk. Although statistics for this group are not strictly collected, 1998 National Vital Statistics Report data suggest that there may be as many as 500,000 such cases each year, so that even with a lowered baseline risk there is still a huge number of potentially preventable infections.

Smaill and Hofmeyr17 systematically reviewed the role of antibiotic prophylaxis in cesarean delivery for the Cochrane Database of Systematic Reviews. They provided a superb review of the extensive data for nonelective cesarean delivery and touched on the role of antibiotic prophylaxis for elective cesarean delivery. However, there were a number of limitations to their analysis. Their definition of elective cesarean delivery excluded patients in labor but included patients with ruptured membranes, making for a group at somewhat higher risk. They also included studies that used antibiotic irrigation, which is not the way in which antibiotic prophylaxis currently is usually administered. They also included studies without a placebo arm (with a no-treatment arm instead). These studies, which would have been impossible to blind, have the potential for bias. Further, by limiting their review to studies already in the Cochrane Controlled Trials Register, they did not include a number of articles with useful information. Small and Hofmeyr noted statistically significant decreases in fever (odds ratio, 0.32; 95% confidence interval, 0.22-0.48) and endometritis (odds ratio, 0.24; 95% confidence interval, 0.11-0.49) and a trend toward protection against wound infection (odds ratio, 0.71; 95% confidence interval, 0.39-1.30).

Our goal in this meta-analysis was to specifically address the efficacy of prophylactic use of systemic antibiotics in truly elective cesarean delivery as derived from published randomized placebo controlled trials. We used strict inclusion criteria and an expanded search to rigorously address this question. We did not seek out unpublished data, which does raise the issue of publication bias. We believe that publication bias is unlikely, however, because much of our data came from subgroups in larger studies, and the results of these small subgroups usually were not essential to the decision to submit or publish the manuscript.

Because a large body of literature supports the prophylactic use of antibiotics in abdominal hysterectomy, we postulated that there would be a similar benefit for elective cesarean delivery, which is also a clean-contaminated procedure with infection risk from the same urogenital flora. The chief difference between these two elective procedures is that the cuff is not directly entered in elective cesarean delivery; despite this, there clearly is risk of the same vaginal flora reaching the peritoneal cavity through the slightly dilated pregnant cervix and the uterine incision. Our meta-analysis demonstrated a clear beneficial effect of antibiotic prophylaxis for nonlaboring women with intact membranes. The outcomes of fever and endometritis were significantly reduced, and there was a trend toward reduction of wound infection. The magnitudes of our summary relative risks (0.05 and 0.24, respectively) suggest large reductions in these outcomes.

Furthermore, these effects were statistically significant regardless of patient population or choice of antibiotics. The magnitudes of the effects in individual studies varied little despite large differences in study populations, which suggests a consistent, convincing reduction in morbidity with the prophylactic use of antibiotics. We performed an extensive sensitivity analysis in which exclusion of any single study did not alter either the summary odds ratio or its statistical significance. Therefore our meta-analysis clearly supports the prophylactic use of antibiotics for elective cesarean delivery. Postoperative infectious complications were reduced by prophylaxis even among nonlaboring women undergoing cesarean delivery with intact membranes.

One potential criticism of our analysis is that many of the antibiotic regimens used in these studies were older drugs not commonly currently used in the United States. Another criticism might entail differences in frequency of dosing (single preoperative dose versus repeated postoperative dosing). In fact, however, our analysis showed that the protective effect was achieved regardless of the choice of antibiotic or the dosing schedule. These findings are consistent with prophylactic antibiotic use in other areas of obstetric and gynecologic surgery. In the extensive body of literature on prophylactic antibiotic use for decreasing postoperative infection among laboring patients undergoing cesarean delivery, vaginal hysterectomy, or abdominal hysterectomy, a huge number of different antibiotics have been studied. As reviewed by Henssell, regardless of which antibiotic was used, a protective effect was nearly always demonstrated. This seems to suggest that any antibiotic is effective in clean-contaminated cases, and choice should therefore be based on such other factors as cost.
Our study did not address several potential concerns regarding the prophylactic use of antibiotics, in particular, its cost-effectiveness and the potential for emergence of resistant organisms. Both are complicated questions beyond the scope of our meta-analysis. Also, although the included studies showed a protective effect across an extremely wide variety of institutions and locations, most were at teaching hospitals or involved clinic populations. None of the studies had a truly extremely low-risk upper–socioeconomic status population exclusively operated on by persons other than trainees. Some recommendations regarding prophylactic antibiotic use are based on factors other than these issues, however, particularly the incidence of the complication in question. Hunt et al.\(^{18}\) recommended the use of antibiotic prophylaxis if the rate of operative site infection exceeds 5%. We noted an 11% baseline incidence of endometritis and a 28% incidence of fever. The endometritis risk clearly merits attempts at prevention. Fever is frequently disregarded as an outcome by authors, because a large proportion are from benign, noninfectious causes. We agree that fever is not as significant as endometritis or wound infection; we do believe that it is a valid secondary outcome, however, because the presence of postoperative fever is disturbing to the patient, and its evaluation does consume resources. On the basis of our meta-analysis, we suggest considering the prophylactic use of antibiotics for all elective cesarean deliveries, and we recommend prophylaxis in populations in which the combined incidence of endometritis and wound infection among women not in labor undergoing cesarean delivery with intact membranes is ≥5%.

REFERENCES