Enoxaparin treatment in women with mechanical heart valves during pregnancy

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OBJECTIVE: This prospective audit reports pregnancy outcomes, anticoagulation complications, and anti-Xa levels in women with mechanical heart valves who were treated with therapeutic enoxaparin plus aspirin during pregnancy.

STUDY DESIGN: Between 1997 and 1999, 11 women with mechanical heart valves were treated with enoxaparin, 1 mg/kg twice daily, and aspirin, 100 to 150 mg daily during 14 pregnancies. Predose and 4-hour postdose anti-Xa levels were monitored monthly.

RESULTS: There were 9 live births, 3 miscarriages, and 2 terminations. In 48 months of enoxaparin treatment, one woman who had a documented valve thrombosis when she presented at 8 weeks’ gestation also had a valve thrombosis at 20 weeks’ gestation. There were no enoxaparin-related hemorrhagic complications. Mean (SD) anti-Xa levels were 0.46 (0.12) U/mL predose and 0.89 (0.22) U/mL 4 hours postdose.

CONCLUSION: Successful pregnancy outcome may be achieved with therapeutic subcutaneous enoxaparin, but its efficacy at preventing valve thrombosis remains uncertain. Further data are required before use of enoxaparin during pregnancy in women with mechanical heart valves can be recommended. (Am J Obstet Gynecol 2001;185: 633-7.)

Key words: Mechanical heart valves, anticoagulation, pregnancy, low-molecular-weight heparin

In women with mechanical heart valves, lifelong anticoagulation is essential to minimize the risk of valve thrombosis and thromboembolic complications. During pregnancy, anticoagulation therapy in these women poses a dilemma as optimal treatment for the mother is in conflict with optimal treatment for the fetus.

Warfarin is the treatment of choice to reduce maternal risks of thromboembolic complications in women with mechanical valves. Women who take warfarin throughout pregnancy have an estimated 3.7% risk of thromboembolic complications, with a 1.8% risk of maternal death, reducing to 0.5% in prospective studies.1,4 Warfarin crosses the placenta and is associated with adverse fetal effects, including a late fetal loss rate of 12%.14 Congenital anomalies occur in 6.4% of live births in which the fetus was exposed to warfarin through pregnancy, with rates of 10% to 12% reported in prospective studies where warfarin therapy continues beyond 6 weeks’ gestation.3 In a recent study, these fetal effects were related to the warfarin dose and were not seen in women needing up to 5 mg/day, but almost half of the 58 pregnancies required a higher dose of warfarin and among this half, fetal loss occurred in 76%.3

Concerns about fetal exposure to warfarin have led some doctors to recommend the use of heparin during pregnancy in women with mechanical heart valves, particularly in the first trimester.5 Compared with warfarin, unfractionated heparin has been associated with a greater risk of thromboembolic events in women with mechanical heart valves during pregnancy, but it is difficult to determine the exact risk as the heparin dose and level of anticoagulation is often unclear or inadequate.1,4

The increased risk of valve thrombosis associated with unfractionated heparin treatment may, in part, be due to difficulty in achieving therapeutic anticoagulation throughout the day.5 Low-molecular-weight heparins (LMWHs) have improved bioavailability and a longer half-life, resulting in more consistent anticoagulation over a 24-hour period,7 and they do not cross the placenta,8 so they may be a suitable treatment option for pregnant women with mechanical valves.

However, there is very little information regarding the efficacy and safety of using LMWHs in pregnant women with mechanical heart valves. To date, there are 2 case reports of women taking therapeutic nadroparin throughout pregnancy9 and another 2 cases of LMWH treatment of uncertain duration during pregnancy, both with no thromboembolic complications. There is also a series in
which 10 pregnant women with mechanical valves were treated with prophylactic doses of nadroparin in the first trimester, and valve thrombosis occurred in 2 pregnancies, highlighting the need to prescribe therapeutic anticoagulation in these women.

In this prospective audit, we report our experience with the use of therapeutic enoxaparin in women with mechanical valves, their pregnancy outcomes, thromboembolic and hemorrhagic complications, and anti-Xa levels throughout the pregnancies.

Materials and methods

Between January 1997 and December 1999, a record was maintained of all pregnant women with mechanical heart valves who were treated with therapeutic enoxaparin under the care of a multidisciplinary maternal-fetal medicine team at a single tertiary level obstetric hospital. Women who presented at any gestation and chose to be treated with enoxaparin were included in this audit. They were also treated with aspirin, 100 to 150 mg/d during pregnancy.

All women were seen within 48 hours of referral to the hospital, and those who presented in the first trimester had the following treatment regimens discussed:

1. Enoxaparin, 1 mg/kg twice daily, from 5 weeks’ gestation until 13 weeks’ gestation, returning to warfarin until 34 to 36 weeks and then switching back to enoxaparin until delivery
2. Enoxaparin, 1 mg/kg twice daily, from 5 weeks’ gestation through pregnancy until delivery
3. Warfarin through pregnancy, switching to therapeutic enoxaparin from 34 to 36 weeks until delivery

Women were advised of the maternal and fetal risks with all therapeutic options. In particular, they were informed of the fetal risks associated with warfarin (congenital anomalies and a late fetal loss rate) and the maternal risks associated with unfractionated heparin treatment (including thrombocytopenia, osteoporosis, bone fractures, and thromboembolism with possibility of maternal death). It was explained that enoxaparin, which does not cross the placenta, might provide more consistent anticoagulation throughout the day than unfractionated heparin, but it was not known whether enoxaparin would lower the risk of thromboembolic events in pregnancy. With their doctors, the women decided on their own anticoagulation regimen, and at 12 weeks’ gestation, switching back to warfarin was discussed again.

At 38 weeks’ gestation, women were scheduled for induction of labor and were changed from enoxaparin to therapeutic intravenous heparin 24 hours before induction. The heparin infusion was stopped when labor was established. Between 2 and 6 hours postpartum, women were restarted on low dose intravenous heparin (500 U/h); between 12 and 36 hours postpartum, the dosage was increased to therapeutic anticoagulation with intravenous heparin or subcutaneous enoxaparin, 1 mg/kg twice daily. After cesarean section, therapeutic anticoagulation was achieved more cautiously and administered beyond 24 hours post delivery. Warfarin was commenced day 1 or 2 postpartum, and therapeutic heparin or enoxaparin was continued until an international normalized ratio (INR) >2.0 was maintained. The INR target was 3.0 to 4.0 in women with Starr-Edwards valves (Starr-Edwards, Irvine, Calif) and 2.5 to 3.5 in women with Medtronic Hall (Medtronic, Minneapolis, Minn) and St Jude valves (St Jude, Minneapolis, Minn).

Baseline maternal characteristics, past medical and obstetric history, details of pregnancy outcome, and thromboembolic and hemorrhagic complications were recorded.

Definitions

Miscarriage refers to all spontaneous fetal losses before 20 weeks’ gestation. Termination includes all medically induced fetal losses before 20 weeks’ gestation. Thromboembolic complications refer to valve thrombosis or embolism manifest by new, permanent, or transient neurologic deficit (excluding hemorrhage) or peripheral arterial embolism. Hemorrhagic complications refer to any anticoagulant-related hemorrhage that required transfusion, surgery, or hospitalization.

Monitoring

During treatment with enoxaparin, anti-Xa levels and platelets were monitored monthly in 12 pregnancies and once each trimester in 2 pregnancies. Anti-Xa levels were initially checked 3 to 5 days after starting treatment or after a dosage change. Predose and 4-hour postdose, anti-Xa levels were measured with the aim of maintaining therapeutic anti-Xa levels throughout a 24-hour period. The therapeutic anti-Xa range in our laboratory was 0.3 to 0.7 U/mL. Our approach was to reduce the enoxaparin dose by 10 mg twice daily if an anti-Xa level was >1.2 U/mL. Enoxaparin dosage changes were under the discretion of the physician caring for the woman.

Statistics

Data are presented as mean and standard deviation (SD) or median and range.

Results

Eleven women with a mean (SD) age of 30 (5.9) years underwent 14 pregnancies while taking enoxaparin. Eight women were of Pacific Island or Maori ethnicity, 2 were white, and 1 was Asian. The underlying medical conditions leading to valve replacement were rheumatic heart disease (n = 9), bicuspid aortic valve (n = 1), and aortic root dilatation with dissection secondary to Marfans (n = 1). Valve types and site are outlined in Table I. Before valve replacement, these women had 9 pregnancies with 7 live births and 2 terminations. After valve replacement...
and before pregnancies using enoxaparin, there were 13 further pregnancies. There were 4 live births, 4 terminations, and 5 miscarriages, including 2 mid-trimester losses associated with warfarin use. There was one previous thromboembolic complication associated with unfractionated heparin treatment during pregnancy.

At presentation, none of the women chose to be treated with warfarin throughout pregnancy, 2 chose to use enoxaparin with warfarin in the second trimester, and all other continuing pregnancies were treated with enoxaparin until delivery. Enoxaparin was commenced by 6 weeks’ gestation in 7 pregnancies, between 7 and 12 weeks’ gestation in 2 pregnancies, and during the second or early third trimester in 5 pregnancies. The median (range) days of treatment with enoxaparin in each pregnancy was 82 (7-236) days, with the total duration of enoxaparin treatment being 1443 days (48 months).

There was one valve thrombosis during enoxaparin therapy. This woman had a St Jude mitral valve and was in sinus rhythm. She had stopped warfarin 3 months before conception and presented at 8 weeks’ gestation, on no anticoagulation treatment, with transient ischemic attacks. Transesophageal echocardiography demonstrated normal valve leaflet motion but there was a mobile echo consistent with thrombus on the atrial side. She was treated with therapeutic enoxaparin, 0.93 mg/kg twice daily, with apparent resolution of the valve thrombus on transesophageal echocardiography 17 days later. Her anti-Xa levels were 0.22 U/mL pre-dose and 0.68 U/mL 4 hours postdose. She re-presented at 20 weeks’ gestation after further transient ischemic attacks. At that time her 4 hour postdose anti-Xa level was 0.62 U/mL. Her enoxaparin dose was increased to 1.05 mg/kg twice daily. A repeat transesophageal echocardiogram was suspicious of valve thrombosis with a spontaneous echo in the left atrium, increased echogenicity of the valve, and incomplete opening of the anteromedial hemidisc. Fluoroscopy confirmed an immobile hemidisc. She was changed to intravenous heparin until undergoing a Medtronic Mosaic (Medtronic) stented porcine valve replacement at 22 weeks’ gestation. Valve thrombus was confirmed at surgery with the anteromedial hemidisc fixed because of thrombus on the ventricular side and in the hinge mechanism. After surgery, this woman continued on therapeutic enoxaparin until 29 weeks’ gestation, when she continued taking only aspirin for the rest of her pregnancy. At 32 weeks’ gestation, preeclampsia developed and, at 35 weeks, she delivered by emergency caesarean section after a placental abruption.

Of the 14 pregnancies, there were 9 live births, 3 miscarriages, and 2 medical terminations. Among the 9 live births, 8 were induced vaginal deliveries at a mean (SD) of 38 (1.1) weeks and 1 caesarean section as described. All babies were healthy with a mean (SD) birth weight of 2906 (414) g. One baby was growth-restricted.

The 9 live births occurred in 7 pregnancies in which women had stopped taking warfarin either before conception (n = 2) or by 6 weeks’ gestation (n = 5), and 2 women who commenced enoxaparin after mechanical valves were inserted during the second trimester. Among the 7 pregnancies, 5 women commenced enoxaparin at 5 to 8 weeks’ gestation and continued it throughout pregnancy except for the woman who had the valve thrombosis. The sixth woman, with a Starr-Edwards mitral valve, had stopped warfarin before conception and was well at presentation at 17 weeks’ gestation. She took warfarin, 5 mg daily, from 17 to 29 weeks, changed to enoxaparin from 29 weeks because of concerns about preterm labor, but delivered at term. The seventh woman, with a St Jude aortic valve, had been treated from 5 weeks’ gestation with a subtherapeutic dose of unfractionated heparin (10,000 u/d) and had an embolic cerebrovascular accident at 25 weeks’ gestation. She was transferred to our care and was treated with enoxaparin for the duration of her pregnancy, with good recovery from her cerebrovascular accident.

Three fetal losses occurred during the first trimester in women being treated with enoxaparin: 2 miscarriages and 1 termination because of medical risks associated with pregnancy. The other 2 fetal losses were in the second trimester. One was a termination at 18 weeks’ gestation for fetal hydrocephalus in a woman who, at 14 weeks’ gestation, returned to warfarin, 5 to 6 mg daily, after switching to enoxaparin at 6 weeks. The other termination followed ovarian surgery at 15 weeks’ gestation in a woman who had been on warfarin, 10 mg daily, until 10 weeks, then switched to enoxaparin. Thirty-six hours before surgery, she stopped enoxaparin and was on intravenous heparin when she miscarried 4 days after surgery.

There were no hemorrhagic complications attributable to enoxaparin, but there were 2 associated with other anticoagulation treatments. The woman on intravenous heparin after ovarian surgery required transfusion and return to theatre. Another woman, on warfarin treatment alone, required a postpartum hysterectomy after presenting with vaginal bleeding 7 days postpartum. At presentation her INR was 1.8. There were no enoxaparin-induced thrombocytopenias or osteoporotic fractures.

<table>
<thead>
<tr>
<th>Valve type/site</th>
<th>No. of women</th>
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<tbody>
<tr>
<td>Starr-Edwards</td>
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<tr>
<td>Mitral</td>
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<tr>
<td>Aortic</td>
<td>1</td>
</tr>
<tr>
<td>Mitral and aortic</td>
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</tr>
<tr>
<td>Aortic</td>
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</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2</td>
</tr>
<tr>
<td>Previous thromboembolism</td>
<td>3</td>
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Table I: Maternal characteristics
Enoxaparin levels. Anti-Xa levels throughout pregnancy and enoxaparin dose per kilogram twice daily are shown on Figure 1. The mean (SD) enoxaparin dose was 0.99 (0.1) mg/kg twice daily. Overall mean (SD) predose anti-Xa levels were 0.46 (0.12) U/mL and 4 hours postdose were 0.89 (0.22) U/mL.

Women were started on enoxaparin 1 mg/kg twice daily according to their weight at presentation (rounding to nearest 10 mg dose) and generally left on that dose for the rest of the pregnancy. On 5 occasions, in 4 pregnancies, the enoxaparin dose was reduced by 10 mg twice daily when the predose anti-Xa level was mean (SD) 1.14 (0.2) U/mL. The highest anti-Xa level was 1.34 U/mL.

There were four predose anti-Xa levels <0.3 U/mL, mean (SD) 0.26 (0.03) U/mL. In one woman the enoxaparin dose was increased by 10 mg twice daily with subsequent therapeutic anti-Xa levels. In the other 3 there was no adjustment of enoxaparin dose. One woman miscarried and another delivered a few days later. The third woman, who had the valve thrombosis, had a predose anti-Xa level of 0.22 U/mL and continued the same dose of enoxaparin, as described.

Comment

This consecutive case series reports the use of therapeutic enoxaparin (1 mg/kg twice daily) with 100 to 150 mg aspirin in women with mechanical heart valves during 14 pregnancies. There was one nonfatal valve thrombosis in 48 months of enoxaparin treatment. This woman had a valve thrombosis at presentation before commencing enoxaparin. Although the thrombus was not seen 2 weeks after initiating enoxaparin treatment, it is not known whether a residual nidus predisposed to further thrombus formation at 20 weeks.

With our series, there are now 18 pregnancies reported in women with mechanical valves who have received therapeutic LMWH treatment.6,9 The total duration of exposure to therapeutic LMWH in these women is more than 66 months with a single valve thrombosis. This compares to a report of one thromboembolic event in 20 months of treatment with therapeutic unfractionated heparin in pregnant women with mechanical valves and one thromboembolic complication in 294 months of exposure to warfarin.2

The importance of achieving a therapeutic anticoagulation effect throughout the day in women with mechanical valves during pregnancy has been previously highlighted,1, 5, 6 but the clinical significance of anti-Xa levels as a measure of this is unknown. The predose anti-Xa levels of nearly all women in our study were within the usual therapeutic range (0.3-0.7 U/mL) and the postdose levels were often above the range, with the highest level being 1.34 U/mL. There were no hemorrhagic complications associated with this level of anticoagulation. It is an interesting observation that the woman who thrombosed her valve had the lowest predose anti-Xa level (0.22 U/mL) in the group, and her dose of enoxaparin was not increased. In women with mechanical valves, maintaining a therapeutic anti-Xa level throughout a 24-hour period may be important. Further studies, with sufficient power, are required to correlate enoxaparin dose and anti-Xa levels with clinical outcomes.

Our audit also highlights women’s concerns about pregnancy risks with warfarin. Some of the women had previous fetal losses while taking warfarin. Two women stopped taking warfarin before conception, and 2 others had stopped as soon as they knew they were pregnant but did not seek immediate medical advice about anticoagulation. Noncompliance with anticoagulation poses a major risk to these women.11 Only 2 women elected to take warfarin in the second trimester: one had a successful pregnancy outcome, and fetal hydrocephalus developed in the other, presumed secondary to intracerebral bleeding, and her pregnancy was terminated. One woman took enoxaparin through 2 pregnancies even though she had a transient ischemic attack while taking unfractionated heparin in an earlier pregnancy. Despite providing detailed information to the women with clear statements that warfarin was superior at protecting their valves, most women chose increased risks to their own health rather than take a medication associated with adverse fetal effects.

In conclusion, successful pregnancy outcome may be achieved with therapeutic subcutaneous enoxaparin, but its efficacy at preventing valve thrombosis remains uncertain. Further studies are required before enoxaparin treatment in women with mechanical valves can be recommended.
We thank Mrs R. Taylor who assisted with data collation.

REFERENCES