Prophylactic dosing adjustment in pregnancy based upon measurements of anti-factor Xa levels

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Abstract
Objective. To determine the necessity for monitoring of anti-factor Xa levels in pregnant women taking low molecular weight heparin (LMWH).
Study design. A review of a hematological database with chart review was undertaken to identify patients on LMWH. Levels were drawn monthly. They were considered suboptimal if prophylactic and therapeutic doses of LMWH had an anti-Xa value <0.2 U/mL and 0.6 U/mL, respectively. Variables of interest included age, parity, thrombophilias, and antiphospholipid antibody syndrome.
Results. Of 30 patients, three required therapeutic-dose LMWH and 27 were on prophylaxis. Sixty-six percent on a therapeutic dose required a dose change, whereas 11% on a prophylactic dose were changed (p = 0.013). None of the variables were predictive of a need for change. One thromboembolic event was noted while on prophylactic-dose LMWH.
Conclusions. No single variable is predictive of a need for dose change. Patients on a therapeutic dose were more likely to need change.

Keywords: Low molecular weight heparin, pregnancy, anticoagulation, thrombophilias

Introduction
Pregnant women require anticoagulation for a variety of reasons. Women who have had a previous thromboembolism, certain of the thrombophilias, atrial fibrillation, or a history of recurrent spontaneous abortions are all candidates for anticoagulation. Heparin has been used for anticoagulation in pregnancy, and the safety of this medication has been established [1,2].

Low molecular weight heparin (LMWH) is an effective alternative to traditional unfractionated heparin (UFH) in patients requiring chronic anticoagulation [2–4]. In many cases it is the preferred alternative because it has decreased heparin-associated side-effects including heparin-induced thrombocytopenia (HIT), hemorrhage, and osteopenia [3]. It also has a longer half-life allowing less frequent dosing intervals, and more predictable response. This makes it a desirable drug for pregnant patients. Anti-factor Xa activity can be used to monitor concentrations of the drug, but this is not commonly performed because of its predictable dose–response profile.

Pregnancy is associated with many alterations in maternal physiology. A study by Casele and co-workers suggests that there are significant differences in mean peak concentrations of anti-factor Xa activity when drawn in the first trimester, third trimester, and postpartum [5]. Pregnant patients requiring anticoagulation do not routinely have anti-factor Xa activity drawn. This study is a retrospective cohort review evaluating if monitoring of anti-factor Xa activity is necessary when using LMWH during pregnancy.
Methods

This study was undertaken after approval was obtained from Mount Sinai Medical Center's Institutional Review Board. A retrospective review of a hematological database was undertaken to identify pregnant women using LMWH. All patients who were either receiving subcutaneous injections of enoxaparin or dalteparin were included in this analysis. Patients were referred to the hematologist for either a known previous thromboembolic event, a history of a thrombophilia, a history of recurrent pregnancy loss defined as greater than or equal to 2 previous first trimester losses, or a second trimester loss of a morphologically normal fetus or stillbirth. A thrombophilia work-up was then performed on all patients including factor V Leiden, homocysteine level, prothrombin gene mutation, functional and antigen levels of proteins C, S, and antithrombin III, and lupus anticoagulant and anticardiolipin antibodies. Patients were excluded from review if they had a history of renal or liver disease, or preeclampsia in the current pregnancy. The prophylactic starting doses for all patients were enoxaparin 40 mg daily or dalteparin 5000 IU daily. All of the patients requiring therapeutic dosing were on enoxaparin, with 1 mg/kg as the starting dose.

Anti-factor Xa levels were drawn monthly or sooner if dose adjustment was necessary. These levels were all obtained four hours after a dose of medication. Levels were considered suboptimal if patients on prophylactic- and therapeutic-dose LMWH had an anti-Xa value less than 0.2 U/mL and 0.6 U/mL, respectively [1]. Variables of interest included age, parity, the presence or absence of one or more of the hereditary thrombophilias, and antiphospholipid antibody syndrome. Statistical analysis to compare the hereditary thrombophilias, and antiphospholipid parity, the presence or absence of one or more of the hereditary thrombophilias, and antiphospholipid antibody syndrome found that none of these variables were predictive for a need to change dosing. One patient experienced a deep vein thrombosis (DVT) while on prophylactic-dose LMWH and was increased to a therapeutic dose. No other thromboembolic events were noted.

We had information about body mass index (BMI) for 15 out of the 33 patients. The average BMI in the group that required a change in medication was similar to that in the group that did not require dose-adjustment, 28.0 ± 3.0 versus 25.8 ± 3.3, p = 0.103, but, because of the observational nature of this review, it is not powered to show a difference.

Results

Thirty-three patients were identified from the hematological database. Of these 33 patients, 22 were referred for recurrent pregnancy loss. A thrombophilia work-up was undertaken, and a thrombophilic condition was identified in 21 patients. All were started on anticoagulation. The remaining 11 patients were either referred with a diagnosis of a thrombophilia or for a history of a previous deep venous thrombus or thromboembolic event. Two of the patients were excluded from the review because LMWH was discontinued after bleeding, and a third patient was excluded after suffering a third, first trimester spontaneous abortion. Of the 30 patients included in the review, three required therapeutic LMWH and 27 required a prophylactic dose. Twenty-seven patients were on enoxaparin, and three were on dalteparin. All the patients who required therapeutic dosing were on enoxaparin.

Table I summarizes the various thrombophilias of this study population. One patient was placed on anticoagulation for a history of recurrent first trimester pregnancy loss, although she tested negative for the thrombophilias. Sixty-six percent (2/3) of patients on a therapeutic dose required a dose change, versus 11% (3/27) of patients on a prophylactic dose (p = 0.013). The mean decreases in levels noted throughout the pregnancy for the patients receiving a prophylactic dose who did and did not need to be changed were −0.060 U/mL and −0.003 U/mL, respectively (p = 0.006). A binary logistic regression evaluating advanced maternal age (AMA), parity, the presence or absence of one or more of the hereditary thrombophilias, and antiphospholipid antibody syndrome found that none of these variables were predictive for a need to change dosing. One patient experienced a deep vein thrombosis (DVT) while on prophylactic-dose LMWH and was increased to a therapeutic dose. No other thromboembolic events were noted.

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Comment

The typical dose–response seen with low molecular weight heparin makes it a desirable drug for anticoagulation. Intuitively, in certain physiological states with altered hemodynamic status like trauma or pregnancy, this typical response may be different [6–8]. There is also the belief that obesity causes a change in the response to LMWH related to decreased absorption in adipose tissue [6].

Table I. Patient characteristics (n = 30).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td>22–41</td>
</tr>
<tr>
<td>Multiparous</td>
<td>11</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>19</td>
</tr>
<tr>
<td>MTHFR C677T mutation</td>
<td>9</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td>4</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>9</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>2</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>17</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>1</td>
</tr>
<tr>
<td>No thrombophilia</td>
<td>1</td>
</tr>
</tbody>
</table>
Pregnancy is a state of hemodynamic change. Total blood volume is increased by 40–45%, with a 30–50% increase in cardiac output [9]. The glomerular filtration rate (GFR) is increased up to 50% above the pre-pregnancy state. This will affect LMWH distribution, since this type of drug is renally cleared.

The Sixth American College of Chest Physician’s Consensus Conference on Antithrombotic Therapy evaluated, among other issues, the use of antithrombotic agents during pregnancy [1]. They agreed that the optimal dosing for prophylaxis is not known, however, the target range for anti-factor Xa levels in this group is 0.2 to 0.6 U/mL [1].

This study directly evaluates the issue of LMWH dose–response in pregnancy. The cohort of patients was being anticoagulated for a variety of reasons. Anti-factor Xa levels decreased on average by 0.003 U/mL in those patients who did not need to be changed, and by 0.060 U/mL in those who needed a change. This change was calculated over the duration of the pregnancy, with most patients being followed from the first trimester. It is conceivable to use the larger of the two numbers to calculate the anticipated decrease in anti-factor Xa levels during the pregnancy, however this value was only calculated from a group of 30 women.

There are several limitations to this descriptive study. First, the sample size is small. Only 30 patients on low molecular weight heparin who had antifactor Xa levels drawn were identified in the database, and of these, only three were on the therapeutic regimen. We cannot, therefore, draw any conclusions from the therapeutic group. However, because we know that a patient’s weight changes in pregnancy, the dose of LMWH should also change. Next, although most patients were on enoxaparin, there were a few patients in the study on dalteparin. And finally, because of the retrospective nature of this review, we were not able to verify patient compliance with their regimens. Therefore, these results are not meant to be conclusive. The one patient in the study cohort who developed a DVT while on prophylactic enoxaparin did not have a level measured prior to the DVT. She had been on the drug for three weeks when the DVT was diagnosed. She was then increased to 80 mg of enoxaparin twice a day based on her weight, and remained event free and therapeutic for the remainder of the pregnancy.

Our results suggest that in managing pregnant patients on LMWH, measuring anti-factor Xa levels should be considered, especially in patients requiring therapeutic dosing. This result, however, is limited by the small number of patients in either group. No specific type of thrombophilia was indicative of a need for dose change, suggesting that it cannot be predicted. Although the patients requiring prophylactic dosing needed a change less often than the therapeutic group, there were still 11% in that group that needed a dose change based on suboptimal levels. Finally, it is important to note that aside from the one patient who suffered a DVT before a level could be measured, there were no other adverse thromboembolic events in any of the other patients, regardless of their anti-factor Xa levels. Our study question of whether anti-factor Xa levels in pregnancy are necessary should be better addressed by a larger prospective clinical trial.

Acknowledgements

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References
