Acute Complications of Unfractionated Heparin Thromboprophylaxis After Cesarean Delivery

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OBJECTIVE: To explore the relative safety of heparin thromboprophylaxis by comparing complication rates of 2 retrospective cohort groups.

STUDY DESIGN: After a change in departmental protocol to include 3 doses of unfractionated heparin for all patients undergoing cesarean deliveries, complication rates of cesarean deliveries before (n = 501) and after (n = 500) the policy change were compared.

RESULTS: Outcomes for postoperative hematocrit, estimated blood loss, platelet counts, and wound complications were not different between the 2 groups.

CONCLUSION: This regimen of heparin does not increase adverse acute postoperative outcomes, but more research is required to determine if it is efficacious in reducing rates of venous thromboembolism. (J Reprod Med 2014;59:3–6)

Keywords: cesarean section, maternal mortality, postoperative complications, thromboembolism.

Venous thromboembolism (VTE) is a major cause of maternal mortality and morbidity in the developed world.1,2 The incidence of VTE associated with pregnancy has been demonstrated to be 1–2 per 1,000 deliveries, and it has been shown to increase with advancing maternal age.3–6 The risk of VTE is approximately 10 times higher in pregnant women when compared to controls in the same age group, and the risk of VTE in puerperium is almost 25 times higher, with the risk per day higher after delivery than at any other point in the pregnancy.7–9 The risk of death from VTE during pregnancy is 12 times higher than that in nonpregnant women.10 These dramatic increases in risk are most likely attributable to the natural alteration of clotting factor profiles in pregnancy, leading to a hypercoagulable state and impaired thrombolysis, while progestins encourage a crescendo of changes within the vasculature, promoting venous stasis which peaks at term.2,11

Between 1991 and 1997 VTE accounted for 1% of all maternal deaths in the United States, although this number may be falsly low due to underreporting and attribution to other conditions.2,12 Ve-
nous thrombus can also damage valves in veins, leading to a disabling postthrombotic syndrome in >20% of patients, with patients experiencing a constellation of chronic pain, swelling, hyperpigmentation, dermatitis, ulcers, venous gangrene, and lipodermatosclerosis.13,14

Although postpartum thromboprophylaxis is well established in the United Kingdom, it has not been routinely employed in the United States. The current guideline from the Royal College of Physicians recommends the near universal administration of “combined VTE prophylaxis with mechanical methods and low molecular weight heparin (or unfractionated heparin for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are undergoing surgery, including caesarean section.”15 These steps are recommended by the American Congress of Obstetricians and Gynecologists (ACOG) only in patients “with additional risk factors.”16 The inconsistencies in the use of thromboprophylaxis are due to a paucity of data as to its benefits and associated complications.

**Materials and Methods**

In October 2006 a departmental protocol of routine heparin prophylaxis after cesarean section was initiated due to a sharp rise in the number of at-risk patients (e.g., obese). All patients undergoing primary cesarean section received 5,000 units of unfractionated heparin subcutaneously every 8 hours until they were fully ambulatory. The VTE prophylaxis was begun within 6 hours of delivery. In 2008 patients who underwent cesarean section prior to and after the implementation of this protocol for heparin thromboprophylaxis were compared as retrospective cohort groups with the goal of identifying any indication of possible adverse impact attributable to thromboprophylaxis. Relevant demographic and outcome variables were identified through the use of a literature review.

A power analysis was conducted, and it was determined that using an alpha of 0.05 and a very large sample size would ensure a power >0.80. A total of 1,001 charts were reviewed, 500 in the prophylaxis group and 501 controls, and data were collected and entered by one reviewer. Fisher’s exact tests were completed on all demographic and salient outcome data in order to compare experimental and control groups. Statistical analysis was performed using the OpenOffice 2.3 Calc spreadsheet application and R version 2.6.0.

**Results**

The most common indication for cesarean section was arrest of dilation (approximately 30% of each group). The groups did not differ by indication for cesarean delivery. There were no significant differences between the group demographics.

Outcomes for postoperative hematocrit, estimated blood loss, platelet count, maximum temperature postpartum, and days at discharge did not disfavor the heparin group. There were 3 wound complications in the heparin group that involved either postoperative incisional bleeding (1 case) or wound seroma (2 cases). Analyses of these results yielded no statistically significant differences between the two groups (Table I).

**Discussion**

Heparin prophylaxis following primary cesarean section does not increase the risk of postpartum hemorrhage, significant anemia, wound complications, or the need for antibiotics. These findings are a boon in the quest to reduce a leading cause of maternal morbidity and mortality. Its importance is likely to increase in coming years as rates of cesarean sections and maternal risk factors—such as BMI > 30 and maternal age > 35—continue to rise at an explosive rate.17

There is a well-defined obesity epidemic in this country and in the world.18 Birth rates for women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heparin (± SD)</th>
<th>No heparin (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (yrs)</td>
<td>30.6 ± 5.8</td>
<td>30.5 ± 5.4</td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>38.45 ± 2.25</td>
<td>38.45 ± 2.61</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>3,214 ± 706</td>
<td>3,165 ± 778</td>
</tr>
<tr>
<td>Regional anesthesia (%)</td>
<td>94.4</td>
<td>92.4</td>
</tr>
<tr>
<td>Operative time (mins.)</td>
<td>53.7 ± 17.55</td>
<td>44.6 ± 18.7</td>
</tr>
<tr>
<td>Preoperative HCT (grams)</td>
<td>35.9 ± 3.34</td>
<td>36.32 ± 3.71</td>
</tr>
<tr>
<td>Postoperative HCT (grams)</td>
<td>30.6 ± 3.83</td>
<td>30.8 ± 3.99</td>
</tr>
<tr>
<td>Preoperative platelet count (in k)</td>
<td>252 ± 69</td>
<td>247 ± 65</td>
</tr>
<tr>
<td>Postoperative platelet count (in k)</td>
<td>220.08 ± 60.5</td>
<td>212.64 ± 56.77</td>
</tr>
<tr>
<td>EBL (cc)</td>
<td>760 ± 218.9</td>
<td>719 ± 209.7</td>
</tr>
<tr>
<td>Tmax pp</td>
<td>99.3 ± 0.91</td>
<td>99.8 ± 0.75</td>
</tr>
<tr>
<td>Postpartum antibiotics (%)</td>
<td>46.60</td>
<td>63.47</td>
</tr>
<tr>
<td>Days to discharge (pp)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>DVT</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Indicates statistically significant results where p ≤ 0.05. (There were no statistically significant differences between the two groups.)

HCT = hematocrit, EBL = estimated blood loss, Tmax = maximum temperature, pp = postpartum, DVT = deep vein thrombosis.
aged 35–39 and 40–44 have increased to the highest reported levels in 40 years, and births to women aged 50 and over have increased by more than 250% since 1997. Cesarean rates increased by 53% from 1996 to 2007, and this rate rose in women of all age, racial/ethnic, and gestational age groups. Cesarean section is associated with 8–10 times higher maternal mortality risks as compared to vaginal delivery. The confluence of these factors provides a strong theoretical basis for significant increases in the rate and absolute number of postpartum VTE in the coming years.

Reducing maternal mortality has been prioritized by both national and international health organizations for decades, and Healthy People 2020 has set a 10% reduction in the maternal mortality rate as its goal. The World Health Organization has targeted reducing the maternal mortality rate by including maternal health as one of its eight Millennium Development Goals. Although VTE is not a major cause of maternal mortality in the developing world, further development of best practices in the developed world can serve as a blueprint for the future.

Although relatively little quality data exists detailing the safety of heparin thromboprophylaxis protocols in the United States, this study contributes further evidence. It builds upon information detailing thromboprophylaxis’ modest mortality benefits with risk reductions in VTE. Although current ACOG practice guidelines recommend thromboprophylaxis in patients with risk factors, higher complication rates were not observed when all women undergoing cesarean section were administered unfractionated heparin within 6 hours of delivery. Other studies have attempted to assess the effects on risk of developing deep venous thrombosis or pulmonary embolism after cesarean section with or without thromboprophylaxis, but they were “small and not adequately powered.”

The limitations of this study were consequences of the study design and the rarity of VTE. This type of study does not have the benefit of controlling for bias and confounding through randomization and blinding. Even though the risk of VTE is doubled in cesarean delivery versus vaginal delivery, the overall risk is still low (approximately 1 per 1,000 patients). Here, experimental results were as expected, with only 1 case in 1,001 patients. Ideally, a large multicenter randomized controlled trial would be conducted to reduce these limitations.

This is the best information available thus far demonstrating a failure to identify differences in complication rates in groups of women undergoing cesarean section with and without postoperative heparin thromboprophylaxis. More research is required to determine the generalizability of these results on a population level, and, should heparin thromboprophylaxis become the standard of care post–cesarean section, continued analysis should focus on comparing and contrasting the risk profiles, safety, and effectiveness of heparin protocols.

References