Thromboembolism following cesarean section: a retrospective study

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Introduction

Thromboembolism (TE) remains one of the leading causes of death in obstetrical patients and as the postpartum period is associated with the highest risk for TE, we sought to determine the risk factors associated with TE following cesarean section (CS).

Methods: A retrospective analysis of patients who had CS at a large tertiary referral center was conducted. Patients were identified through hospital medical records and were contacted approximately 1 year following their CS. Medical records and a questionnaire were used to identify features that were potentially associated with TE. Univariate analysis was used to determine the risk associated with these characteristics.

Results: A total of 2206 patients had a CS, of which 1377 (62%) participated. Of the respondents, 137 patients received heparin (94% received a prophylactic dose, 6% received a therapeutic dose) and the remainder, 1233 patients, did not receive heparin. Seven patients (0.5%) developed a TE and 86% developed a TE within 7 days of CS. The odds ratio (OR) for TE for women with hypertension prior to pregnancy compared to patients who did not receive anticoagulation was 21.28 [95% confidence interval (CI) 4.64–90.13] and for patients who had varicose veins with superficial thrombophlebitis when compared to patients who received heparin postpartum was 21.01 (95% CI 1.55–288.24).

Discussion: Hypertension and the presence of varicose veins were associated with TE following CS. Larger cohort analyses are required to confirm these associations so that risk scores incorporating these characteristics may accurately predict the occurrence of TE.

Recently, a prediction model for TE was developed for all postpartum women [6]. The model was derived from a large cohort that spanned over 17 years and determined the risk of TE for all women postpartum irrespective of whether they had vaginal deliveries or cesarean sections (CS). The model identified several characteristics predisposing to thrombosis. CS, however, is associated with an increased risk of postpartum venous TE compared to vaginal delivery [2,6–9] and risk factors following CS may differ than those following vaginal delivery. Thus, our objectives were to determine the postpartum rate of TE following CS and to examine the risk factors for TE (venous and arterial) to facilitate the future development of prediction scores for TE following CS.

Methods

Study design

We conducted a retrospective analysis of the frequency and risk factors of TE following CS at Mount Sinai Hospital, Toronto, Canada.
Hospital, a tertiary care center in Toronto, Canada. Mount Sinai Hospital is the largest maternal-fetal medicine center in Canada, with approximately 6000 deliveries yearly, and nearly 30% of these deliveries are by CS. Patients who had a CS at Mount Sinai Hospital between 1 March 2013 and 1 March 2014 were identified through hospital electronic records. The study population was limited to patients older than 18 years. All eligible patients were sent a prenotice letter to their home address informing them of the study. Patients were then contacted by telephone to complete a questionnaire and obtain consent to have their hospital records reviewed 1 year following their delivery. TE was defined as deep vein thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis (SVT), and cerebrovascular accident (CVA). This study was approved by the Mount Sinai Hospital Research Ethics Board.

The telephone questionnaire was developed according to established techniques [10,11]. Participants were asked when the TE occurred following pregnancy, to describe radiological investigations conducted for diagnosis, and whether anticoagulants were used after CS and prior to the TE.

Each patient was contacted to a maximum of five attempts over the course of 1 year, after which they were deemed as unable to be contacted and excluded from the study.

Retrospective review of hospital records

Hospital records were reviewed using Mount Sinai Hospital’s electronic database and clinic charts to identify characteristics that have previously been described in the pregnant and nonpregnant population to predispose to TE [2,6,12]. The characteristics considered are outlined in Table 1.

| Table 1. Variables included in the regression model. |
|------------------------------|---------------------------------|
| Variables                   |                                  |
| Age, pregnancy weight, height, and smoking | Obstetric variables              |
| Gravidaity, parity, spontaneous abortion, therapeutic abortion, ectopic pregnancy, and intrauterine death | Hereditary thrombophilia         |
| Antithrombin deficiency, protein C deficiency, protein S deficiency, Factor V Leiden mutation, and prothrombin gene mutation | Thrombosis history               |
| Personal history of thrombosis | Medical disorders associated with thrombosis |
| Antiphospholipid antibody syndrome, sickle cell disease, malignancy, smoking, varicose veins with history of superficial thrombophlebitis, hypertension prior to pregnancy, diabetes, pregnancy induced hypertension, preeclampsia, heart disease, systemic lupus erythematosus, hemorrhage, and transfusion | Obstetric outcomes               |
| The need for emergent CS, postpartum sepsis, and delivery outcome | Statistical analysis |

Continuous variables were summarized as means (with standard deviations) and medians (with interquartile ranges). Categorical variables were described as frequencies and percentages. To determine the characteristics that were associated with TE occurrence, univariate analysis was performed using logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The Firth method [13] was applied to reduce bias in the parameter estimates due to the small number of patients who developed TE. Because of zero or very small sample size cells, the univariate logistic regression model did not converge for varicose veins with superficial thrombophlebitis and yielded very wide confidence intervals for previous TE. For these variables, therefore, we only report the p-value from the Fisher’s exact test. All statistical tests were two-sided and significance was defined as p-values of less than 0.05.

Results

Over the 1-year interval, 2207 patients were identified to have had a CS (Figure 1). Within this cohort, 1445 (66%) were contacted. Among the patients who were contacted, 1377 (95%) agreed to participate in the telephone questionnaire and consented for review of their hospital records.

The characteristics of the patients are displayed in Table 2. Seven patients (0.5%) developed a TE postpartum. Two patients had a DVT, three had a PE, and one had each of an SVT and a CVA. All except one event occurred within 7 days of delivery and were confirmed by radiological investigation. None had hereditary thrombophilia. Three did not have sickle cell disease and four patients were not screened for a hemoglobin disorder. Only one individual was screened but did not have antiphospholipid syndrome.

Among patients who did not develop a TE, 137 patients received heparin (low-molecular-weight or unfractionated heparin, 94% received a prophylactic dose and 6% received a therapeutic dose) and the remainder, 1233 patients, did not receive heparin. Women who developed TE had a higher rate of smoking, varicose veins with a history of superficial thrombophlebitis, previous TE, preterm delivery, intrauterine growth restriction, and hypertension prior to and during pregnancy (Table 2).

Table 3 describes the odds of developing a TE according to whether patients received prophylactic anticoagulation postpartum. Hypertension prior to pregnancy (Table 3) and a prior history of TE (p = .0003) were risk factors for TE compared to patients who did not receive postpartum prophylactic anticoagulation. Prior TE was associated with the highest risk for TE (p = .0003) as has been previously established.
Maternal age, body mass index (BMI), gravidity, smoking and preterm delivery were potential risk factors that did not reach predefined statistical significance (Table 3).

The presence of varicose veins with superficial thrombophlebitis was the only statistically significant risk for the development of TE when compared to patients who had received postpartum anticoagulation; hypertension prior to pregnancy did not reach statistical significance in the presence of prophylactic heparin [OR 4.46 (95% 0.94–19.73)].

Comment

Using hospital medical records and patient questionnaires, clinical characteristics potentially associated with TE were acquired from a large population (n = 1377) all of whom delivered by CS. The use of patient interviews enhanced the observational nature of this study by emphasizing the relevant aspects of care that may not be easily captured using large database studies or reviews of hospital records, and permitted incorporating all potential risk factors. Patients who had a TE were compared not only to patients who did not receive prophylactic anticoagulation following CS but also to patients who did receive thromboprophylaxis to enable the identification of characteristics that may need more active surveillance/escalating doses of anticoagulants because of higher risk of TE. The presence of varicose veins with a history of superficial thrombophlebitis was such a characteristic [12,15].

There is limited guidance for anticoagulation for superficial thrombosis during pregnancy or prophylaxis in subsequent pregnancies. Low-molecular-weight heparin has been suggested at an intermediate or prophylactic dose and for a brief duration to reduce the risk of TE for symptomatic superficial thrombosis, superficial thrombosis of 5 cm or more, bilateral superficial thromb, and superficial thrombi less than 5 cm from the deep venous system [16], but the effectiveness of these regimens has not been adequately assessed in pregnancy. As we found that superficial thrombosis is a risk for TE in patients with varicose

Figure 1. Flowchart of the included patients.
veins, we feel that intermediate dose heparin should be a consideration for these women, particularly those with characteristics as described by Chan et al. [16].

Our study demonstrated that previous TE was a risk factor for subsequent TE. A history of TE has been shown to be a risk factor of TE in a subsequent pregnancy previously and prophylactic anticoagulation in a subsequent pregnancy antepartum and postpartum is suggested [17]. The signficance of the prior history of a TE in predisposing to a TE in the following pregnancy cannot be underscored as 79–89% of women who died from PE in the United Kingdom between 2003 and 2005 and between 2006 and 2008 had identifiable risk factors [18]; yet, only 73% of patients who have had a previous TE had received prophylaxis [19].

Although the association of preeclampsia/eclampsia with thrombosis has been described [6,17], as far as we are aware, hypertension predating pregnancy has not been previously identified as a risk factor for thrombosis in obstetrical patients nor has hypertension been incorporated into risk stratification models [20]. Hypertension has been identified though as a risk factor for thrombosis for women. The Nurse’s Health Study, a cohort of 112,822 registered female nurses, demonstrated that hypertension was associated with a relative risk of PE of 1.5 (95% CI 1.2–2.0) [21]. A diastolic blood pressure (DBP ≥ 100 mm Hg compared to a DBP < 80 mmHg) has also been shown recently to be associated with TE in a retrospective study of 10,153 women [hazard ratio 1.43 (95% CI 1.05–1.95)] [22]. Our results

Table 2. Characteristics of the cohort of patients who had a cesarean section.

| Characteristic | Postpartum TE (N = 7) | Heparin postpartum (N = 137) | No heparin postpartum (N = 1233) |
|---------------|-----------------------|-----------------------------|----------------------------------|
| Age (years), median (IQR) | 38.0 (32.0–39.0) | 34.0 (31.0–38.0) | 34.0 (31.0–37.0) |
| BMI (kg/m²), median (IQR) | 31.7 (30.8–35.3) | 32.6 (28.3–42.2) | 29.2 (26.6–32.5) |
| Parity, mean ± SD | 3.0 ± 1.5 | 2.5 ± 1.6 | 2.3 ± 1.4 |
| Smoking > 10 cigarettes/day, n (%) | 1 (14.28) | 13 (9.49) | 32 (2.60) |
| Parity, mean ± SD | 1.10 ± 0.87 | 0.74 ± 0.16 | 0.7 ± 0.9 |
| Age (years), median (IQR) | 38.0 (32.0–39.0) | 34.0 (31.0–38.0) | 34.0 (31.0–37.0) |
| BMI (kg/m²), median (IQR) | 31.7 (30.8–35.3) | 32.6 (28.3–42.2) | 29.2 (26.6–32.5) |
| Parity, mean ± SD | 3.0 ± 1.5 | 2.5 ± 1.6 | 2.3 ± 1.4 |
| Smoking > 10 cigarettes/day, n (%) | 1 (14.28) | 13 (9.49) | 32 (2.60) |
| Parity, mean ± SD | 1.10 ± 0.87 | 0.74 ± 0.16 | 0.7 ± 0.9 |

Notes: Missing data were as follows: BMI, n = 292; gravidity, n = 1; parity, n = 1; spontaneous abortion, n = 7; therapeutic abortion, n = 7; ectopic pregnancy, n = 9; intraterine fetal demise (IUFD), n = 9.

HELLP: hemolytic anemia, elevated liver enzymes, low platelets; HTN: hypertension; SD: standard deviation; SLE: systemic lupus erythematosus; IUGR: intrauterine growth restriction.

Table 3. Logistic regression comparing patients who developed venous TE with patients who did not develop venous TE and did/did not receive heparin postpartum.

| Characteristic | Patients who did not develop venous TE and did not receive heparin postpartum Odds ratio (95% confidence interval) | Patients who did not develop venous TE and did receive heparin postpartum Odds ratio (95% confidence interval) |
|---------------|-------------------------------------------------|-------------------------------------------------|
| Age (years)   | 1.12 (0.96–1.27) | 1.08 (0.93–1.25) |
| BMI (kg/m²)   | 1.10 (0.96–1.21) | 0.98 (0.87–1.06) |
| Gravidity     | 1.34 (0.89–1.75) | 1.20 (0.77–1.72) |
| Parity        | 1.65 (0.86–2.46) | 1.40 (0.70–2.59) |
| Smoking       | 8.53 (0.87–42.27) | 2.13 (0.21–11.30) |
| Varicose veins with superficial thrombophlebitis | p = .0056* | 21.01 (1.53–286.24) |
| Hypertension prior to pregnancy | 21.28 (4.64–90.13) | 4.46 (0.94–19.73) |
| Preterm delivery | 3.94 (0.88–16.29) | 1.69 (0.36–7.24) |
| Previous venous TE | p = .0003* | 3.35 (0.57–15.26) |
| Emergent CS   | 0.74 (0.16–3.04) | 0.59 (0.13–2.51) |

*Because of zero or very small sample size cells, the logistic regression model did not converge for variceous veins with superficial thrombophlebitis and yielded very wide CIs for previous venous TE. For these variables, therefore, we only report the p-value from the Fisher’s exact test.
suggest that prepregnancy hypertension should be considered in risk models of TE and pregnancy.

The relatively few number of patients who developed TE in this study is a potential limitation which may have limited the ability to describe an association of risk with maternal age, BMI, gravidity, smoking, or preterm delivery. The frequency of TE in this study though is similar to what has been described [23] and reflects the rate of TE in this population. We were selective about the inclusion of factors to develop estimates by univariate analysis because TE was anticipated to be infrequent. Although we were unable to contact all patients, 62% of patients were contacted, and thus we think the results are generalizable. Recall bias is considered a limitation to surveys; however, we did not think that recall bias influenced our results as patients were contacted within a short interval following their delivery. We included patients with SVT and CVA as we considered all patients with TE.

Factors that have been associated with TE in all obstetrical patients were also found to be associated with TE after CS. Hypertension, however, has not been previously identified as a risk factor for TE following delivery and may be a risk only for patients undergoing CS. Hypertension as a predisposition for TE needs to be further investigated to confirm the findings in this study. Analysis of characteristics incorporated in this study in larger cohorts may aid in the development of risk stratification models for patients undergoing CS so that prophylactic anticoagulation is instituted to reduce the morbidity and mortality secondary to TE.

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No potential conflict of interest was reported by the authors.

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