Early detection of thrombosis after cesarean section using changes in D-dimer levels

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Aim: To identify important factors that can be used to predict the presence of venous thromboembolism (VTE) or pulmonary embolism (PE) after cesarean section.

Methods: This retrospective study was conducted at Juntendo University Hospital from January to December in 2012. A total of 313 patients who underwent cesarean section were included. Complete blood count, biochemistry parameters, and parameters of coagulation-fibrinolysis, such as D-dimer levels, were examined on the day before cesarean section and on postoperative days 1, 3, and 5.

Results: Six cases of VTE and/or PE were identified. We designed an equation that incorporates changes in D-dimer levels for predicting the presence of thrombosis, as follows: $y = (D1 - D-dimer) \times 1.263 - (D3 - D-dimer) \times 1.741 + (D3 / D1 - D-dimer) \times 6.42 + (D5 - D-dimer) \times 4.029 - 53.248$. When the resulting value is $> 20$, the patient is considered likely to have thrombosis.

Conclusions: This study showed that rate of change in D-dimer levels from postoperative day 1 to day 3, and D-dimer level itself on postoperative day 5, are important factors for predicting the presence of VTE or PE.

Introduction

Venous thromboembolism (VTE) in pregnancy is a major cause of maternal morbidity and mortality in developed countries. Pregnancy is associated with an overall 5–10-fold increased risk of VTE due to various factors such as maternal physiological changes and maternal compressed circulation associated with an enlarged uterus. The incidence of VTE is reportedly 85 in 100,000 pregnant women in London and 47 in 100,000 pregnant women in Japan. Many prophylactic strategies, such as the use of compression stockings, applying intermittent positive pressure to the legs, and the use of low molecular weight heparin (LMWH), aim to prevent the occurrence of VTE, particularly in patients who undergo cesarean section. If it were clear which patients were at higher risk for VTE, it would be possible to select the appropriate prophylactic strategy. However, at present, it is difficult to identify those with early stage VTE without symptoms, since D-dimer levels gradually increase during the course of pregnancy and increase further during the postpartum period.

Although some studies have reported on D-dimer levels before and after cesarean section, we do not know which D-dimer level is considered safe when we test it at only one point after operation. This study aimed to identify important factors for predicting the presence of VTE or pulmonary embolism (PE) after cesarean section.

Methods

This retrospective study was conducted at Juntendo University Hospital from January to December in 2012. A total of 313 patients who underwent both elective and emergency cesarean section were included (Figure 1). Indications for elective cesarean section were breech presentation, past history of cesarean section, or past history of uterine myomectomy. Emergency cesarean sections were performed for fetal distress and maternal indications. In order to minimize the influence on changes in D-dimer levels, patients with coagulation factor deficiency, antiphospholipid antibody syndrome, or hemorrhage over 2,000 ml at the time of cesarean section were excluded. The final study population included...
Longitudinal data were collected, including a complete blood count, biochemistry parameters, and parameters of coagulation-fibrinolysis, such as D-dimer levels, on the day before cesarean section and on postoperative days 1, 3, and 5. The normal D-dimer range in general at our institute was 0.0\( \mu \)g/ml to 0.99\( \mu \)g/ml (Nanopia D-dimer, SEKISUI MEDICAL Co., Ltd., Tokyo, Japan). When D-dimer levels were abnormally elevated, we first checked clinical symptoms and SpO\(_2\). We also performed compression ultrasound on the femur and enhanced CT scans to confirm the venous embolism. At our institute, patients who underwent cesarean section are provided with elastic compression stockings and administered LMWH (5000 IU/12h) from postoperative day 1 to day 5 for prophylaxis, unless there were postoperative bleeding complications.

**Statistical analysis**

Data are presented as mean ± SD. Discrimination analysis was performed with multiple variables to identify important factors for predicting VTE or PE. Assessed variables included the following: height, body weight before and after pregnancy, gained body weight, body mass index, D-dimer levels before cesarean section and on postoperative days 1, 3, and 5, D3/D1, and D5/D3. Using stepwise forward selection, we designed an equation that incorporates the important variables, and the multiplication factor in the equation reflects the importance of the variable.

Unpaired t-tests were used to compare two variables. \( P < 0.05 \) was considered statistically significant. Statistical analysis was conducted with SPSS 18 (IBM Japan, Ltd., Tokyo, Japan).

**Results**

We identified six patients with VTE and/or PE during the study period. Four patients had PE, one had deep vein thrombosis, and one had both PE and deep VTE. Patient characteristics are presented in Table 1. Maternal age, gestational age, body mass index, gained body weight, smoking, and hemorrhage did not significantly differ between groups with and without VTE or PE. Detailed characteristics of the thrombosis group are shown in Table 2. While two patients had edema, the other four patients did not present with typical symptoms such as dyspnea or chest pain. PE and VTE were diagnosed based on enhanced CT after observing increased D-dimer levels on postoperative day 1 or day 5.

Baseline assessments of D-dimer levels before and after cesarean section are shown in Table 3. Mean D-dimer level increased immediately after cesarean section (11.7 ± 12.8), and gradually decreased toward day 5 (3.53 ± 1.80). Mean levels on postoperative day 1 and day 5 were high (34.4 ± 31.6 and 19.7 ± 13.6).
Prediction of thrombosis with D-dimers

Table 2. Clinical characteristics of patients with VTE or PE

<table>
<thead>
<tr>
<th>VTE</th>
<th>PE</th>
<th>Symptom</th>
<th>Complication</th>
<th>Hemorrhage (ml)</th>
<th>Day of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>—</td>
<td>Rt pulmonary artery</td>
<td>edema</td>
<td>—</td>
<td>1,050</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ramus descendens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>—</td>
<td>Rt pulmonary artery</td>
<td>—</td>
<td>—</td>
<td>1,040</td>
</tr>
<tr>
<td>Case 3</td>
<td>Rt internal iliac vein</td>
<td>Rt pulmonary artery</td>
<td>—</td>
<td>—</td>
<td>1,705</td>
</tr>
<tr>
<td>Case 4</td>
<td>Lt femoral vein</td>
<td>—</td>
<td>edema</td>
<td>—</td>
<td>1,330</td>
</tr>
<tr>
<td>Case 5</td>
<td>—</td>
<td>Rt inferior lobar branch</td>
<td>IVC</td>
<td>—</td>
<td>500</td>
</tr>
<tr>
<td>Case 6</td>
<td>—</td>
<td>Rt pulmonary artery</td>
<td>—</td>
<td>—</td>
<td>1,200</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; PE, pulmonary embolism; IVC, inferior vena cava; Rt, right; Lt, left.

Table 3. Changes in D-dimer levels before and after cesarean section

<table>
<thead>
<tr>
<th></th>
<th>VTE or PE</th>
<th>Without VTE or PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>At term</td>
<td>3.38 ± 0.84</td>
<td>4.4 ± 5.46</td>
</tr>
<tr>
<td>PO Day 1</td>
<td>34.4 ± 31.6</td>
<td>11.7 ± 12.8</td>
</tr>
<tr>
<td>PO Day 3</td>
<td>6.5 ± 2.7</td>
<td>7.66 ± 6.68</td>
</tr>
<tr>
<td>PO Day 5</td>
<td>19.7 ± 13.6</td>
<td>3.53 ± 1.80</td>
</tr>
</tbody>
</table>

In patients without VTE or PE, D-dimer levels increased rapidly on postoperative day 1, then gradually decreased to day 5. However, in those with VTE or PE, there was a large increase in D-dimer levels on postoperative day 1 or day 5.

VTE, venous thromboembolism; PE, pulmonary embolism; PO, postoperative.

Figure 2. Changes of D-dimer levels in those with and without VTE or PE.

Two notable changes in D-dimer levels were observed in the group with VTE or PE. An acute and substantial increase in D-dimer levels was noted immediately after cesarean section, and an abnormal increase in D-dimer level on postoperative day 5. The dotted line indicates those without VTE or PE. The gray zone indicates the standard deviation of those without VTE or PE. C/S, cesarean section.

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VTE, venous thromboembolism; PE, pulmonary embolism; PO, postoperative.

Discrimination analysis was used to identify factors that are important for predicting VTE; important factors were incorporated into an equation for predicting VTE. In the equation, greater weight was placed on factors with more importance. The equation determined from our analysis was: \[ y = (D1 \text{ D-dimer}) \times 1.263 - (D3 \text{ D-dimer}) \times 1.741 + (D3/D1 \text{ D-dimer}) \times 6.42 + (D5 \text{ D-dimer}) \times 4.029 - 53.248. \]

When the resulting value was > 20, the patient was likely to have VTE or PE. The equation accounts for the important factors of rate of change in mean D-dimer levels from postoperative day 1 to day 3, and mean D-dimer level on postoperative day 5, for predicting the presence of VTE or PE after cesarean section.

Discussion

The major finding of this study was the importance of the rate of change in mean D-dimer levels from postoperative day 1 to day 3, and mean D-dimer level on postoperative day 5, in predicting the presence of VTE or PE. We also decided the equation to predict the presence of VTE or PE. Regarding these two important factors, it is necessary to know baseline changes in D-dimer levels during pregnancy and after cesarean section. During pregnancy, D-dimer levels slightly increase relative to those in non-pregnant women. Indeed, D-dimer levels have been shown to exhibit a linear and positive correlation with gestational age. A number of studies have assessed changes in D-dimer levels after operative delivery. These studies reported a significant increase in D-dimer level on postoperative day 1, a decrease on postoperative day 3, and an increase again on postoperative day 5. This pattern differs slightly from our results. D-dimer levels are known to rapidly increase due to secondary
fibrinolysis following an increase in plasmin activity. Plasminogen activator inhibitor-1 (PAI-1) subsequently increases in order to prevent re-bleeding and heal the injury after trauma. After several days from trauma which is called as a proliferation stage which starts filling in the wound with new tissue, D-dimer levels slightly increase again due to a decrease in PAI-1 levels. In the present study, we observed the same trend in changes in D-dimer levels after cesarean section, with the exception of postoperative day 5. The discrepancy of the change in D-dimer level after cesarean section may be due to the differences in the baseline value for each postoperative day such as a higher D-dimer level on postoperative day 3 or a lower D-dimer level on postoperative day 5, relative to other studies.

Discrimination analysis revealed that changes in D-dimer levels from postoperative day 1 to day 3, and D-dimer level on postoperative day 5, are important factors for predicting VTE after cesarean section. This highlights the clinical importance of continuously monitoring D-dimer levels until postoperative day 5. A significant increase in D-dimer level on postoperative day 5 suggests a high probability of VTE. Although our findings support the importance of serial assessments of D-dimer levels postoperatively, prospective studies will be needed to confirm the accuracy of the equation. At present, not many physicians take three D-dimer readings from the period after cesarean section to postoperative day 5.

There are some limitations to this study. First, an enhanced CT scan was performed only for patients with increased D-dimer levels, which may have introduced selection bias. Thus, we may have missed patients with asymptomatic PE or VTE. Second, patients with hemorrhage over 2,000 ml were excluded. Some studies with asymptomatic PE or VTE. Second, patients with selection bias. Thus, we may have missed patients increased D-dimer levels, which may have introduced enhanced CT scan was performed only for patients with increase again due to a decrease in PAI-1 levels. In the wound with new tissue, D-dimer levels slightly increases in order to prevent re-bleeding and heal the injury after trauma. After several days from trauma which is called as a proliferation stage which starts filling in the wound with new tissue, D-dimer levels slightly increase again due to a decrease in PAI-1 levels. In the present study, we observed the same trend in changes in D-dimer levels after cesarean section, with the exception of postoperative day 5. The discrepancy of the change in D-dimer level after cesarean section may be due to the differences in the baseline value for each postoperative day such as a higher D-dimer level on postoperative day 3 or a lower D-dimer level on postoperative day 5, relative to other studies.

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In conclusion, we found that the rate of change in D-dimer levels from postoperative day 1 to day 3, and D-dimer level on postoperative day 5, are important factors for predicting the presence of VTE or PE. This highlights the importance of serial assessments of D-dimer levels until postoperative day 5. Prospective studies will be needed to determine the utility of the equation for predicting VTE or PE after cesarean section.

**Conflict of interest**

None.

**References**