COMMITTEE REPORT

Survey of the use of anticoagulation and anesthesia during cesarean section in patients with severe Pregnancy induced Hypertension (PIH) between 2010 and 2011 in Japan

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Aim: A survey of anticoagulation and anesthesia during cesarean section in patients with severe pregnancy induced hypertension (PIH) in Japan was conducted by a committee of the Japan Society for the Study of Hypertension in Pregnancy (JSSHP) to investigate 1) prophylactic anticoagulation for venous thromboembolism (VTE) after cesarean section in patients with PIH and 2) heparin treatment for disseminated intravascular coagulation (DIC) in patients with PIH and related disorders.

Methods: Surveys including questionnaires for obstetricians and anesthesiologists were separately conducted among 127 eligible regional leading institutes and hospitals of maternal-fetal medicine with neonatal intensive care units (NICUs) throughout Japan in order to analyze the participants' perspectives on anticoagulation for VTE and DIC in patients with PIH and related disorders.

Results: Sixty-six (52.2%) of the 127 eligible institutes and hospitals ultimately responded. Prophylactic anticoagulation after cesarean section was administered in 82% of the hospitals for patients without PIH to prevent various risks. However, the dose of prophylactic anticoagulation for VTE after cesarean section was not optimized for each patient with PIH in 73% of the hospitals. Anesthesiologists at approximately 74% of the hospitals used neuraxial regional anesthesia in patients with PIH who underwent cesarean section. They selected general anesthesia rather than regional anesthesia if they judged the effects of anticoagulation to be greater than the level indicated for regional anesthesia remaining during surgery. Approximately 30% of the hospitals used anticoagulants, including heparin and/or antithrombin, at the onset of DIC for prophylaxis of VTE after cesarean section in patients with PIH.

Conclusions: Most recommendations, worldwide as well as in Japan, in guidelines for prophylactic anticoagulation during cesarean section are based on observational studies and lack statements or recommendations on the use of anesthesia and appropriate anticoagulation during cesarean section in patients with PIH. The JSSHP needs to be encouraged to design studies to obtain better evidence for the use of anticoagulation in patients with severe PIH and to publish a clinical practice bulletin as soon as possible.
Introduction

Preeclampsia (PE) is a multiorgan complication of pregnancy characterized by high blood pressure and proteinuria. It occurs in 2–5% of all pregnancies and is a major cause of maternal and fetal morbidity and mortality. The pathophysiology observed during pregnancy and puerperium in patients with elevated critical maternal and fetal risks demonstrates dramatic changes in coagulation and the fibrinolytic system in those with severe pregnancy induced hypertension (PIH) and related diseases such as HELLP syndrome and abruptio placentae.

At the same time, pregnancy itself is widely recognized to be a major risk factor for venous thromboembolism (VTE). Pulmonary embolisms are a major cause of maternal death in the United States, Europe and Japan. The overall incidence of thromboembolic complications during pregnancy is increased another two to three times during puerperium. In particular, the risk of VTE after cesarean section is 10 times higher than that following vaginal delivery.

However, due to the lower incidence of congenital thrombophilia in the Japanese population compared with that observed in Caucasians, prophylaxis for VTE has not received attention over the past several decades in Japan. In 2004, a striking report based on a survey conducted by the Japanese Society for Obstetrics and Neonatal Hematology revealed that the incidence of VTE in obstetric and gynecologic patients in Japan is not less than that observed in the United States or European countries. Although the elevated risk of VTE observed during pregnancy appears to be due to a hypercoagulable state and increased static venous pressure induced by the enlarged uterus, the report also suggests that rapid Westernized changes in lifestyle, higher age at pregnancy and higher rates of cesarean section might be associated with the increasing incidence of VTE in Japan.

In response to this report, several Japanese societies relating to VTE (e.g., the Japanese Society on Thrombosis and Hemostasis, the Japan Society of Obstetrics and Gynecology, the Japanese Circulation Society, the Japanese Society on Thrombosis and Hemostasis, among others) have published the Japanese Guidelines for the Prevention of Venous Thromboembolism, referring to categorized risks, similar to the American College of Chest Physicians (ACCP) guidelines. Prophylactic anticoagulation for cesarean section in patients with a risk of VTE, even in those with PIH or a possible thrombophilia background, has been recommended and covered by government supported national health insurance since 2008 in Japan.

On the other hand, differences remain in recommendations in the guidelines on the prevention of VTE between the United Kingdom and the United States regarding the use of prophylactic anticoagulation after cesarean section in high-risk patients. The 9th edition of the ACCP guidelines discourages the use of thrombosis prophylaxis other than for early mobilization in females undergoing cesarean section without additional thrombosis risk factors. The British Green-top guidelines of the Royal College of Obstetrics and Gynecology (RCOG) recommend at least five days of postnatal prophylactic low-molecular-weight heparin during the postpartum period for females with postnatal risk factors that are not sufficient risks for thromboprophylaxis according to the ACCP guidelines.

In the Japanese guidelines for the prevention of venous thromboembolism published in 2004, mechanical and/or pharmacological thromboprophylaxis is recommended after cesarean section in patients with additional risks. The differences in the approaches to patients who have undergone cesarean section are most likely due to the lack of high quality evidence for prophylactic anticoagulation.

Under these circumstances, the Japan Society for the Study of Hypertension in Pregnancy (JSSHP) should be encouraged to publish comments or a clinical bulletin because prophylactic anticoagulation after cesarean section in patients with PIH might increase the risk of postsurgical hemorrhage, including serious complications of subdural hematoma formation resulting in paralysis due to regional neuroaxial anesthesia. Impaired renal clearance in patients with PIH may lead to a delay of the Time at 1/2 and the enhancement of Concentration at max, followed by an increased risk of hemorrhage.

However, at present, due to the lack of data regarding clinical practice in Japan, this committee investigated 1) prophylactic anticoagulation for VTE after cesarean section in patients with PIH and 2) heparin treatment for disseminated intravascular coagulation (DIC) in patients with PIH and related disorders for future research.

Materials and methods

Between January and June 2011, surveys including questionnaires (Table 1) for obstetricians and anesthesiologists were separately conducted among leading regional institutes and hospitals of maternal-fetal medicine with tertiary neonatal intensive care units (NICUs) throughout Japan in order to analyze the participants’ perspectives on anticoagulation for VTE and DIC in patients with PIH and related disorders. The institutes and hospitals were arbitrarily selected from all over Japan by the Committee of JSSHP to receive a survey on anticoagulation and anesthesia during cesarean section in patients with severe PIH. The survey was limited to the clinical practice observed for the past two years at each hospital.
Table 1. Questionnaire questions for survey of the use of anticoagulation and anesthesia during cesarean section in patients with severe pregnancy induced hypertension (PIH)

Category A. Questionnaires for you and your hospitals
1) Are you (board certified obstetrician, board certified perinatologist, board certified anesthesiologist, consultant anesthesiologist, none of others)?
2) Is type of your hospital (perinatal center with tertiary NICU, perinatal center with primary or secondary NICU, none of others)?
3) Number of obstetrician (full-time: , part-time: )
4) Total number of delivery a year ( )
5) Cesarean section rate a year ( )
6) Number of anesthesiologist (full-time: , part-time: )
7) Total number of operation a year ( )
8) At your department, anticoagulation is a) documented and standardized b) not documented but standardized c) not standardized
9) For the past two years, at your department, you have had a) accident or complication with permanent disorder related to anticoagulation b) accident or complication with temporary disorder related to anticoagulation c) accident or complication with temporary disorder on anticoagulation with unknown relation d) no accident or complication reported e) none of others

Category B. Survey of the use of anticoagulation during and after cesarean section in patients with severe PIH at your department between 2010 and 2011.
I. Concerning with prophylactic anticoagulation during and after cesarean section in patients with severe PIH,
1) are there any differences in prophylactic anticoagulation for VTE between patients with severe PIH and those without it? a) yes b) no if no, please go to 7.
2) what do you use as prophylactic anticoagulation in patients with severe PIH?
3) do you make prophylactic anticoagulation in patients without PIH? if yes,
4) what do you use as prophylactic anticoagulation in patients without PIH?
5) if no in 3), do you make thromboprophylaxis except anticoagulation?
6) if yes in 5) please describe it.
7) if no in 1), do you make prophylactic anticoagulation in patients with cesarean section? if yes in 1), do you make thromboprophylaxis except anticoagulation?
8) if no, why?
9) if no in 7), do you make thromboprophylaxis except anticoagulation?
10) if yes in 9), please describe it.
11) do you make thrombophilia screening test at first visit of patient at your department?
II. Survey of the therapeutic anticoagulation at the onset of DIC in patients with HELLP syndrome or patients with abruption placenta in PIH.
1) How do you diagnose as DIC?
2) How do you treat with DIC?
3) When do you make a blood test for coagulation and fibrinolytic markers and variables?
4) Do you make prophylactic anticoagulation in patients with past history of severe PIH?

Category C. Survey of the use of anticoagulation and anesthesia during cesarean section in patients with severe PIH at your department between 2010 and 2011.
I. Concerning with anesthesia during cesarean section with prophylactic anticoagulation for VTE in patients with PIH in your department of anesthesiology,
1) do you have any standardized protocol for selection of regional anesthesia with or without PIH under prophylactic anticoagulation for VTE? a) if yes, what kind of guidelines do you refer to? b) if no, why?
2) do you have any standardized protocol for selection of regional anesthesia in patients with severe PIH? a) if yes, what kind of guidelines do you refer to? b) if no, why?
Results

1) Background
The questionnaires were sent to 127 eligible institutes and hospitals, 66 (52.2%) of which ultimately responded. The annual total number of deliveries at the institutes and hospitals was approximately 48,000 with a cesarean section rate of 31.8%, as shown in Table 2. Sixty-seven percent of the responding institutes were categorized as hospitals with a tertiary NICU, as shown in Figures 1A and B. Although anticoagulation therapy was standardized at 63% of the reporting hospitals, it was not standardized, but rather individualized for each patient, at 37% of the hospitals, as shown in Figure 1C. Seventeen percent of the hospitals reported accidental complications associated or possibly associated with anticoagulation, as shown in Figure 1D.

2) Prophylactic anticoagulation for VTE after cesarean section in patients with PIH
The dose of prophylactic anticoagulation for VTE after cesarean section was not optimized for each patient with PIH in 73% of the hospitals (Figure 2A). The hospitals reduced the amount of heparin administered per day in postsurgical patients with PIH, as shown in Figure 2B.

Prophylactic anticoagulation after cesarean section was administered in patients without PIH for various reasons in 82% of the hospitals, as shown in Figure 2C and Table 3. However, various types, durations and doses of anticoagulants were used. The anticoagulants used included unfractionated heparin, low-molecular-weight heparin and synthetic coagulation factor Xa inhibitor. Only 17% of the hospitals optimized prophylactic anticoagulation after cesarean section for patients with PIH.

Table 2. Background of hospital that questionnaire was sent arbitrary

| Questionnaire sent (number of hospital) | 127 |
| Responded (number) | 66 |
| Response rate (%) | 52.2 |
| Average number of Obstetrician/hospital (full-time) | 10.2 ± 5.0 |
| Average number of Anesthesiologist/hospital (full-time) | 10.7 ± 8.3 |
| Total summed number of delivery at responded hospitals | 48,271/a year |
| Total summed number of cesarean section | 15,326/a year |
| Cesarean section rate (%) | 31.8 |
3) Anesthesia and prophylactic anticoagulation for VTE after cesarean section in patients with PIH

Anesthesiologists at approximately 74% of the hospitals used combined spinal and epidural anesthesia (CSEA) in patients with PIH who underwent cesarean section (Figure 3A). However, they selected general anesthesia rather than regional anesthesia if they judged the effects of anticoagulation to be greater than the level indicated for regional anesthesia remaining during surgery according to various recommendations, as shown in Figures 3B and C. The anesthesiologists used various coagulation markers and cut-off values as indicated at each department when choosing regional anesthesia in patients with or without PIH who underwent cesarean section, as shown in Figures 4A–C and Table 4. In addition, they tended to use individualized timing when setting up and removing the epidural catheter for anticoagulation, although the catheters were set up and removed according to the manufacturer’s instructions.

The results of the survey indicate that anesthesiologists follow guidelines based on the manufacturer’s instructions; however, there are no standardized methods of using regional anesthesia in each department.

4) Administration of heparin for DIC in patients with PIH

DIC was diagnosed at onset based on the obstetric scoring system used in Japan at 87% of the hospitals. Approximately 30% of the hospitals used anticoagulants, including heparin and/or antithrombin, after cesarean section at the onset of DIC for prophylaxis of VTE and treatment for DIC in patients with PIH, as shown in Figures 5A and B. Although patients with a past history of severe PIH or severe fetal growth restriction (FGR) are often treated with prophylactic heparin during pregnancy in North America, patients with a similar past history tend to be managed without anticoagulation in Japan, most likely due to the low prevalence of congenital thrombophilia, as shown in Figure 5C.
Survey of anticoagulation and anesthesia in severe PIH

Figure 2. Anticoagulation for VTE after cesarean section
A. Optimized anticoagulation for VTE after cesarean section in each patient with severe PIH or preeclampsia
B. Optimized modification of prophylactic anticoagulation in patients with severe PIH or preeclampsia
C. Prophylactic anticoagulation for VTE after cesarean section for all patients

Table 3. Background of patient for thromboprophylaxis

<table>
<thead>
<tr>
<th>Factor</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity*</td>
<td>26</td>
</tr>
<tr>
<td>Past history of VTE**</td>
<td>11</td>
</tr>
<tr>
<td>Hospitalization***</td>
<td>10</td>
</tr>
<tr>
<td>Age</td>
<td>8</td>
</tr>
<tr>
<td>No descriptive indication</td>
<td>7</td>
</tr>
<tr>
<td>Family history of thrombophilia</td>
<td>6</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>6</td>
</tr>
<tr>
<td>APS</td>
<td>5</td>
</tr>
<tr>
<td>Past history of abruption placentae</td>
<td>3</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>3</td>
</tr>
<tr>
<td>Elevated D-dimer value</td>
<td>2</td>
</tr>
<tr>
<td>PIH</td>
<td>2</td>
</tr>
<tr>
<td>Coagulation disorder</td>
<td>1</td>
</tr>
<tr>
<td>Severe varicose</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
</tr>
<tr>
<td>Swelling in lower extremity</td>
<td>1</td>
</tr>
<tr>
<td>Huge postpartum hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>DVT</td>
<td>1</td>
</tr>
<tr>
<td>Polymydrarnios</td>
<td>1</td>
</tr>
<tr>
<td>Maternal fever (suspected CAM)</td>
<td>1</td>
</tr>
<tr>
<td>Dehydration</td>
<td>1</td>
</tr>
<tr>
<td>Dystocia</td>
<td>1</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>As indicated in Japan Society of Thrombosis Hemostasis</td>
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<tr>
<td>DM</td>
<td>1</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>1</td>
</tr>
<tr>
<td>Doctor’s judgment</td>
<td>1</td>
</tr>
<tr>
<td>As indicated in Obstetrical guideline of Japan Society of Obstetrics Gynecology</td>
<td>1</td>
</tr>
</tbody>
</table>

* Obesity: 13, severe Obesity: 1, BMI more than 25: 2, more than 27: 2, more than 28: 2, more than 30: 4, more than 35: 2
** Long hospitalization: 7, Hospitalization for more than 2 wks.: 2, more than 48 hrs: 1
*** Age more than 35: 4, more than 40: 3, Elderly: 1
**Figure 3.** Type of anesthesia used for anticoagulation and guidelines for use at or after cesarean section in patients with PIH
A. Type of anesthesia
B. Guidelines for regional anesthesia during anticoagulation in each department
C. Recommendations used

**Figure 4.** Comparison of the type of anesthesia used for anticoagulation after cesarean section and preoperative examinations in patients with or without PIH
A. Changes in the type of anesthesia used in patients with PIH compared with that used in patients without PIH
B. Comparison of the type of anesthesia used in patients with or without PIH
C. Selected preoperative laboratory examinations for the use of regional anesthesia during cesarean section
**Table 4.** Cut-off value of pre-operative laboratory examinations for regional anesthesia (numbers of hospital)

<table>
<thead>
<tr>
<th>Examination</th>
<th>Platelet counts [1 × 10^4/μl] (41)</th>
<th>APTT [sec] (21)</th>
<th>PT [sec] (17)</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3～10</td>
<td>23～50</td>
<td>10～14.5</td>
<td>1.15～1.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding time [min]</th>
<th>Fibrinogen [mg/dl]</th>
<th>FDP [μg/ml]</th>
<th>ATIII [%]</th>
<th>D-Dimer [μg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3～8</td>
<td>100～400</td>
<td>5</td>
<td>84～117</td>
<td>1</td>
</tr>
</tbody>
</table>

**Discussion**

The mechanisms of onset of PIH and VTE have been investigated for more than 100 years, and the pathophysiology of PIH and VTE share a similar thrombophilic background in some patients. A review of three studies demonstrated that the risk of VTE in females who develop preeclampsia is elevated compared with that observed in females without preeclampsia.

In one study, severe preeclampsia was found to be associated with a higher risk of VTE later in life than mild preeclampsia.\(^{14}\) It is well known that patients with PIH, abruptio placentae and HELLP syndrome are at an increased risk of developing DIC. Therefore, clinical practice has paid attention to the management of patients with coagulation and hypertensive disorders.

A three- to four-fold increase in the incidence of VTE in Japan since 2000 has been reported.\(^{9}\) In addition to the congenital thrombophilic backgrounds present in Japan, an increasing percentage of older pregnant females in the childbearing population and the subsequent increasing rate of cesarean section have resulted in striking changes in the mechanism of onset of VTE. These observations indicate that recommendations for the management of patients with PIH who undergo cesarean section should be revised according to recent changes in the circumstances observed in Japan.

In this survey, we investigated the present situation regarding the use of anticoagulation and anesthesia after cesarean section in patients with severe PIH from the view of prophylaxis of VTE and the management with DIC at major hospitals with NICUs throughout Japan.
Surprisingly, concerning the prophylaxis of VTE, 37% of anticoagulation therapies are managed individually by obstetricians without standardization, although anticoagulation was taken into consideration in the prevention of VTE in 82% of the hospitals that responded to the questionnaires. Anticoagulation in patients with severe PIH or preeclampsia showing subclinical renal impairment and/or possible bleeding tendencies should be optimized by reducing the dose or discontinuing heparin. Twenty-seven percent of the hospitals estimated the adverse effects of PIH on anticoagulation; however, anticoagulation therapy was modified and optimized in half of the hospitals only. This is partly because no clinical bulletins or proposals from related societies, including the Japan Society of Hypertension in Pregnancy, have been presented with the aim to prevent major bleeding and VTE at the same time in postsurgical patients with PIH. Given the findings of major bleeding related to anticoagulation reported in 3% of hospitals in the present survey, further study of ways to reduce the risk of major bleeding is required.

Ninety-two percent of anesthesiologists reported selecting regional anesthesia for cesarean section and postsurgical anticoagulation taking into consideration the guidelines of the American Society of Anesthesia (ASA). However, general anesthesia instead of regional anesthesia was selected for thrombocytopenia, and varied from 30,000 to 100,000 [μl] at each department because the ASA guidelines are not intended to replace local institutional policies. Furthermore, the timing of epidural catheter removal is controversial because manufacturer guidelines refer to the standard time after the latest anticoagulant based on the estimated elimination time of the drug in nonsurgical patients with reference to various levels of creatinine clearance, age and body weight in Japan. Precise guidelines with strong evidence for optimized anticoagulation in surgical preeclampsia patients with or without renal impairment need to be presented. The ASA has proposed no standardized management guidelines for the use of regional anesthesia or anticoagulation after cesarean section in patients with PIH, most likely due to the lack of data regarding changes in the concentrations of anticoagulants and the risk of bleeding.

We found amazing results in the survey of the administration of heparin for DIC in patients with PIH in Japan. In the presence of adequate concentrations of antithrombin at the onset of DIC, heparin works properly as an inhibitor of thrombin generation and microthrombi formation. Intrinsic heparin or heparan sulphate located on the endothelial cell surface is provided at the site of thrombin generation and accelerates the inhibition of thrombin formation by inhibiting antithrombin. Therefore, for the last decade, it has become increasingly accepted for obstetricians in Japan to administer antithrombin only in patients with DIC because it reduces the risk of bleeding tendencies in patients with a shortage of antithrombin as a result of consumption by DIC. According to this survey, approximately 30% of hospitals use anticoagulants, including heparin and/or antithrombin, at the onset of DIC for prophylaxis of VTE after cesarean section in patients complicated with PIH.

Although patients with a past history of severe PIH or severe FGR are often treated with prophylactic heparin during pregnancy in North America, patients with a similar past history tend to be managed without anticoagulation in Japan, most likely due to the low prevalence of congenital thrombophilia.

In conclusion, most recommendations, worldwide as well as in Japan, in guidelines for prophylactic anticoagulation after cesarean section are based on observational studies and lack statements or recommendations on the use of anesthesia and appropriate anticoagulation during cesarean section in patients with PIH. The JSSHP is further encouraged to design studies to obtain better evidence for the use of anticoagulation in patients with severe PIH.

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Conflict of interest

None.

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