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Pregnancy-related thromboembolism and contributing risk factors: From 10 years of experience at a Japanese tertiary obstetrics institute

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Aim: To determine the association between pregnancy-related thromboembolism and pre-existing risk factors, as well as the association between its severity and risk factors, among Japanese women.

Methods: We retrospectively analyzed cases of pregnancy-related thromboembolism over 10 years at a single Japanese tertiary obstetrics institute. Patients were divided into two groups based on thromboembolism severity.

Results: Our 22 thromboembolic patients had an incidence/detection rate of 0.18% (22/12,500). Deep venous thrombosis (DVT), PE, and DVT + PE occurred in 15 (68%), 3 (14%), and 4 (18%) patients, respectively. Of the 22 patients, 20 (91%) had pre-existing risk factors. Thrombophilia and bed rest were the most common, with each at 8/22 (36%). Of the 8 with thrombophilia, anti-phospholipid antibody syndrome (APS) and protein S (PS) deficiency accounted for 5 and 3 patients, respectively. Thrombophilia was detected in 7/15 (47%) and 1/7 (13%) in the severe and mild groups, respectively, showing that thrombophilia was more likely to accompany severe thromboembolism. All APS patients suffered severe thromboembolism.

Conclusions: Thrombophilia and bed rest were the most common risk factors for thromboembolism in a Japanese tertiary perinatal center. The most important thrombophilic factors accompanying thromboembolism were APS and PS deficiency. Patients with thrombophilia were likely to show severe thromboembolism.

Introduction

Thromboembolism (deep venous thrombosis (DVT) + pulmonary embolism (PE)) is the leading cause of maternal death.1–3) Venous stasis due to enlarged uterine caval compression and pregnancy-related hypercoagulability increase thromboembolic diathesis, which is aggravated by coexisting risk factors including thrombophilia,4–6) bed rest,7) obesity,5,7) and cesarean section (CS).5,7) Thus, determination of the risk factors of pregnancy-related thromboembolism is clinically important.

Two aspects should be taken into account when characterizing pregnancy-related thromboembolism, especially pre-existing risk factors. The first is racial or national differences. The Factor V Leiden mutation is a frequently detected cause of congenital thrombophilia in Caucasians8,9) that has yet to be reported in Japan.9) In addition, bed rest is employed in a different manner/frequency, depending mainly on health insurance coverage. Japanese insurance covers bed rest, enabling a higher rate of those admitted for bed rest, as patients with threatened preterm delivery are also admitted for long-term bed rest. Pregnancy-related thromboembolism has thus far been characterized mainly in Caucasian populations. Further insight on the two above-mentioned factors specific to Japan, i.e., the absence of a Leiden mutation and easier accessibility to admission for bed rest among Japanese women, would be useful. The second aspect that must be considered when examining pregnancy-related thromboembolism is the wide variation...
Pregnancy-related thromboembolism

in severity of thromboembolism. For example, PE or extensive DVT is life-threatening, whereas a lone
organized DVT in the extremities may not be. The effects
of these various factors on the severity of pregnancy-
related thromboembolism have not yet been clarified,
especially in Japanese women.

Against this backdrop, the present study aimed to
determine the association between pregnancy-related
thromboembolism and its pre-existing risk factors, as
well as the association between severity and risk factors,
in Japanese women. We retrospectively analyzed cases of
pregnancy-related thromboembolism at a single Japanese
tertiary obstetrics institute over 10 years.

Methods

This study was approved by the Ethics Committee of
our institute. We reviewed all the medical charts of all
deliveries at this institute from January 2005–August
2016. One of the largest in Japan, this institute handles
approximately 1,100 deliveries annually, and managed
12,500 deliveries during the present study period. Of the
12,500, 22 patients in whom thromboembolism (DVT or PE) was detected and treated during pregnancy or
postpartum were retrieved. These 22 did not have a prior
history of thromboembolism.

As routine universal screening of DVT or PE was not
employed, thromboembolism was detected based on the
following: 1) clinical findings leading to a suspicion of
thromboembolism (e.g., leg edema, leg pain, Homan’s
sign positive) triggering the examination described below,
which confirmed the presence of thromboembolism, or 2) incidental detection during work-ups for other conditions
(e.g., massive postpartum bleeding, placental abruption,
post-CS). Thromboembolism work-up was performed for
i) women with D-dimer concentrations ≥ 5 μg/ml, a
parameter of thromboembolism, and ii) those with clinical
findings leading to the suspicion of thromboembolism,
even with D-dimer concentrations < 5 μg/ml. DVT was
initially diagnosed by ultrasound. Enhanced computed
tomography (CT) confirmed the diagnosis and magnetic
resonance angiography was also used in some cases.
PE was diagnosed by enhanced CT. In before-delivery
cases, enhanced CT was performed with sufficient
informed consent. Experienced radiologists made the
diagnoses. D-dimer levels were serially measured in all cases. Peri-delivery/peri-surgical (both vaginal and
cesarean) thrombophylaxis was performed as necessary.
Briefly, anti-coagulative agents were not administered
to a woman undergoing a vaginal delivery. Intermittent
pneumatic compression was performed in women with
CS. In addition, beginning in 2009, low-molecular-weight
heparin (2,000 U × 2 times/day) was subcutaneously
administered until 2 days after a CS. In women with
a high risk of thromboembolism (e.g., history of
thromboembolism, thrombophilia, advanced obesity),
unfractionated or low-molecular-weight heparin was
administered after delivery. Thus, although we employed
this thrombophylaxis protocol before the publication of
Guidelines for Obstetrical Practice in Japan (2014), our
present protocol was consistent with the guidelines.

Presence/absence of thrombophilia was determined for
all 22 patients using the following parameters: activated
partial thromboplastin time, prothrombin time,
fibrinogen, protein C, protein S (PS), antithrombin, lupus
anticoagulant, anti-cardiolipin IgG antibody, and beta 2
glycoprotein-1 antibody. Factor V Leiden mutation and
prothrombin gene mutation were not investigated because
these types of thrombophilia have not been reported in
Japan. Since PS activity markedly changes during
pregnancy (making it difficult to determine PS deficiency
during pregnancy), PS deficiency was diagnosed
postpartum by measuring PS activity, PS antigen,
and free PS. Anti-phospholipid antibody syndrome
(APS) was diagnosed using the Sapporo criteria.

Other thrombophilias and maternal complications were
diagnosed and followed by specialists according to
general criteria.

We also examined pre-existing risk factors of
thromboembolism, including age, preconceptional body
mass index, race, smoking, mode of conception, maternal
complication, obstetrical complication, pregnancy
course, delivery week, mode of delivery, and birth
weight. Pregnancy is a pre-existing risk factor for
thromboembolism. However, as this study was limited
to pregnant women, we excluded “pregnancy” from
the pre-existing risk factors for the present study. The
thrombosis regions/parts/areas were fundamentally
assigned to one of 5 categories: crural, femoral, pelvic,
caval, and pulmonary. The patients were divided into
two groups based on the severity of thromboembolism.
Severe thromboembolism (15 patients) was defined as a
thromboembolism manifesting in more than 2 regions,
caval thromboembolism, or PE. Mild thromboembolism
(7 patients) was defined as thrombosis limited to one part
of a unilateral extremity.

For patients with thromboembolism, unfractionated
heparin was initially administered under hospitalization.
Low-molecular-weight heparin was also used if
appropriate. A temporary vena cava filter was applied when
there was 1) impending PE occurrence (e.g., thrombosis
formation across a wide area) as judged by the specialists,
2) suspected/definite presence of contraindication
for heparin (e.g., heparin-induced thrombocytopenia,
heparin-induced liver enzyme elevation). At postpartum,
warfarin sodium was administered instead of heparin over
one month and specialists decided on its tapering time.
Warfarin was not used during pregnancy. Thrombolytic
treatment was not employed. Fisher’s exact test and the chi-square test were applied using JMP version 10 (SAS Institute, Tokyo, Japan) for statistical analysis, with a value of $P < 0.05$ considered statistically significant.

**Results**

Table 1 shows the backgrounds of the 22 thromboembolic patients, for whom the incidence/detection rate was 0.18% (22/12,500). The median body mass index was 20.1 kg/m². All were Japanese. Two (9%) had medical complications (breast cancer, $n = 1$; idiopathic thrombocytopenic purpura (lupus anticoagulant +), $n = 1$). One patient underwent pregnancy termination because of PE occurring at 6 gestational weeks. No patient died.

Table 2 shows the patient characteristics. DVT, PE, and DVT + PE occurred in 15 (68%), 3 (14%), and 4 (18%) patients, respectively. Half had a thrombus in crural and femoral regions. Thromboembolisms were detected in 13/22 patients (59%) in the antepartum period. Leg pain/swelling was the most common symptom. In all but one, D-dimer concentrations increased at DVT/PE detection with a median concentration of 14.2 μg/ml (interquartile range: 5.5–36 μg/ml, normal range < 5 μg/ml). In the one patient, this concentration was 0.7 μg/ml.

Table 3 shows the pre-existing risk factors for thromboembolism. Twenty of 22 (91%) patients had pre-existing risk factors, of which thrombophilia and bed rest were the most common, with each observed in 8/22 (36%) patients. Of the 8 with thrombophilia, APS and PS deficiency accounted for 5 and 3 patients, respectively. Eight of the 22 (36%) patients had more than 2 pre-existing risk factors, whereas 2/22 (9%) patients had no identifiable risk factors.

Table 4 shows the relationship between disease severity and background/risk factors. Thrombophilia was detected in 7/15 (47%) and 1/7 (13%) in the severe and mild groups, respectively, showing that thrombophilia was more likely to accompany severe thromboembolism. Notably, this difference was not statistically significant.
### Table 3. Pre-existing risk factors of thromboembolism

<table>
<thead>
<tr>
<th>Pre-existing risk factors, n (%)</th>
<th>Present</th>
<th>Absent</th>
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<tbody>
<tr>
<td>Details</td>
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<tr>
<td>Thrombophilia</td>
<td>8 (36)</td>
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</tr>
<tr>
<td>APS</td>
<td>5</td>
<td>2 (9)</td>
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<tr>
<td>PS deficiency</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Bed rest</td>
<td>8 (36)</td>
<td></td>
</tr>
<tr>
<td>CS†</td>
<td>5 (23)</td>
<td></td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>3 (14)</td>
<td></td>
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<tr>
<td>HDP</td>
<td>3 (14)</td>
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</tr>
<tr>
<td>Massive PPH</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>Maternal complication*</td>
<td>2 (9)</td>
<td></td>
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<tr>
<td>Smoking</td>
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<td></td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>1 (5)</td>
<td></td>
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<tr>
<td>Chorioamnionitis</td>
<td>1 (5)</td>
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<tr>
<td>Severe varix</td>
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The number of pre-existing risk factors in one patient

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<table>
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<tr>
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<td>3</td>
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<td>4</td>
<td>1 (5)</td>
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<tr>
<td>5</td>
<td>1 (5)</td>
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</tbody>
</table>

* Abbreviations: APS, anti-phospholipid antibody syndrome; BMI, body mass index; CS, cesarean section; HDP, hypertensive disease of pregnancy; PPH, postpartum hemorrhage; PS, protein S; *One woman was complicated by breast cancer, and the other was complicated by idiopathic thrombocytopenic purpura and lupus anti-coagulant-positive, †limited to cases with thromboembolism occurring postpartum

(P = 0.19), possibly due to the small sample size. All APS patients suffered severe thromboembolism. The other pre-existing risk factors showed no differences between the two groups. Two of the 22 (9%) patients without risk factors had severe thromboembolism: one with PE, left common iliac vein thrombosis, and extensive thrombosis in the left lower extremity, and the other with bilateral extensive lower-extremity thrombosis.

### Discussion

The present study demonstrated that almost all patients with thromboembolism had some pre-existing risk factors: thrombophilia and bed rest were the most common, with APS and PS deficiency accounting for the former. All but one patient with thrombophilia had severe thromboembolism, and other known risk factors for thromboembolism did not affect the disease severity, although the small sample size prevented us from confirming whether thromboembolism was significantly associated with severe thromboembolism.

Thrombophilia and bed rest were the most common pre-existing risk factors. Approximately one-third of patients with thromboembolism had thrombophilia, which was roughly consistent with previous data from 50% of DVT patients with thrombophilia. In the present study, PS deficiency was identified in all patients with congenital thrombophilia-associated thromboembolism. In a Caucasian population, PS deficiency was reported to account for only 2–8% of thromboembolism cases, showing a marked contrast with the present study result. Odds ratios for thromboembolism occurrence were reported as 4.1 for PS deficiency, 5.5 for PC deficiency, and 49 for antithrombin deficiency. Thus, relative to PC-antithrombin-deficiency, PS deficiency showed a lower odds ratio; however, in the present study, PS deficiency was dominant. This may be due to two factors unique to this study population. First, the estimated rate of PS deficiency in Japan was 1.6%, which is much higher than the 0.03–0.12% reported in Caucasian populations. Second, among Japanese populations, there is a unique mutation of PS deficiency (K196E), for which the occurrence rate and odds ratio of venous thromboembolism are reportedly very high (5.8–10% and 3.74–8.56, respectively). For the latter, we did not identify this mutation, so the extent to which this affected the results remains unclear.

The data obtained from Caucasians are inconclusive and controversial with regard to screening for PS deficiency during pregnancy for thrombophilaxis. Because of the different/unique character of PS deficiency in Japan, the fact that the present study data showed that PS deficiency accounted for a significant fraction of thromboembolism cases, and since PS deficiency is an autosomal dominant trait, it may be prudent to screen for PS deficiency among pregnant Japanese patients with any family history of thromboembolism.

Nearly one-third of thromboembolism patients were on bed rest. The risk of thromboembolism is reportedly 4–12.2 times higher during hospitalization, which is why this may naturally increase the chance of bed rest. In Japan, because of the extensive coverage provided by public insurance, pregnant women can be hospitalized at a relatively low cost. Consequently, numerous women are hospitalized for bed rest, and are more likely to undergo bed rest as a result of admission (irrespective of the reason for admission). Obstetricians should consider the risk assessment of thromboembolism when patients are hospitalized and in a state of bed rest. We must...
Table 4. The severity of thromboembolism and its pre-existing risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Severe</th>
<th>Mild</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>More than 2 regions</td>
<td>11 (73)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>7 (47)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>34 (32−37)</td>
<td>32 (26−35)</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>20.7 (28.6−22.5)</td>
<td>19.5 (18.7−23.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>Timing of occurrence, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antepartum</td>
<td>9 (60)</td>
<td>4 (57)</td>
<td>1.00</td>
</tr>
<tr>
<td>Postpartum</td>
<td>6 (40)</td>
<td>3 (43)</td>
<td></td>
</tr>
<tr>
<td>D-dimer at detection, median (IQR) (µg/ml)</td>
<td>14.2 (5.9−42.7)</td>
<td>8.5 (4.5−29.3)</td>
<td>0.49</td>
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</table>

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Severe</th>
<th>Mild</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia</td>
<td>7 (47)</td>
<td>1 (13)</td>
<td>0.19</td>
</tr>
<tr>
<td>APS</td>
<td>5 (33)</td>
<td>0 (0)</td>
<td>0.14</td>
</tr>
<tr>
<td>PS deficiency</td>
<td>2 (13)</td>
<td>1 (13)</td>
<td>1.00</td>
</tr>
<tr>
<td>Bed rest</td>
<td>6 (40)</td>
<td>2 (29)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multiple gestations</td>
<td>1 (7)</td>
<td>2 (29)</td>
<td>0.23</td>
</tr>
<tr>
<td>HDP</td>
<td>1 (7)</td>
<td>2 (29)</td>
<td>0.23</td>
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</tbody>
</table>

The number of pre-existing risk factors, n (%)*

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Severe</th>
<th>Mild</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (47)</td>
<td>5 (71)</td>
<td></td>
</tr>
<tr>
<td>2 ≤</td>
<td>6 (40)</td>
<td>2 (29)</td>
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</table>

* Abbreviations: APS, anti-phospholipid antibody syndrome; BMI, body mass index; HDP, hypertensive disease of pregnancy; IQR, interquartile range; PS, protein S; * We did not perform statistical analysis because of the small sample sizes of the 3 groups (0, 1, and 2 ≤).

re-consider bed rest as a pre-existing risk factor for thromboembolism.

Another major finding was that “severe” thromboembolism is likely to accompany thrombophilia: all but one “severe” case had thrombophilia, with “severe” being defined as the extensive spread of thrombosis, caval thromboembolism, or PE. Mortality increased in patients with PE19) and those with thrombosis of both the arms and legs.10) There were no other risk factors predicting “severe” thromboembolism. Although the small sample size prevents us from confirming the significance, thrombophilia may be the most important pre-existing risk factor of severe thromboembolism.

All patients with APS (acquired thrombophilia) also showed severe thromboembolism. The imbalance between coagulants and anticoagulants occurs throughout the body of a patient with thrombophilia. As a result, extensive (“severe”) thromboembolism is likely to occur. A large prospective study16,20) showed that if thrombophylaxis was performed, thromboembolism was not significantly more frequent in APS patients than control subjects (occurrence: 2.3 vs. 1.9%, respectively); this contradicts the present study findings. In the present study, all APS cases were identified during the examination for thromboembolism; i.e., thromboembolism was the first to be detected and APS was the second. This means that the treatment began after thromboembolism detection, and thus, multiple occurrences of thrombus were noted. APS also causes severe obstetrical complications such as fetal growth restriction and preeclampsia. Taken together, this indicates that screening for APS during the first trimester may be ideal. However, Asian people are considered to show a low prevalence compared with Caucasians,21–23) so a cost-benefit evaluation may be needed.

This study had some limitations. First, pre-existing risk factors were not analyzed in patients without thromboembolism, which prevented us from calculating cut-off values and performing multivariate analysis of the thromboembolism-related parameters including D-dimer concentrations. Second, only some well-known thrombophilias were examined, while other thrombophilias including plasminogen abnormalities remained unexamined, so we could not rule out the possibility of some other underlying thrombophilic diathesis. Third, as thromboembolism was diagnosed based on symptom manifestations, ‘no’ or ‘mild’
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Symptoms may have gone undetected. These weaknesses may be inherent to retrospective studies.

In conclusion, thrombophilia and bed rest were the most common pre-existing risk factors for thromboembolism among patients at a Japanese tertiary perinatal center. The most important thrombophilic factors accompanying thromboembolism were PS deficiency and APS. Patients with thrombophilia were likely to show severe thromboembolism. Based on this study, screening may be recommended to identify patients with PS deficiency and APS in Japan; however, the balance with cost-effectiveness should be determined before its actual employment. It is noteworthy that severe thromboembolism was detected in two patients without pre-existing risk factors. A well-designed prospective cohort study targeting pregnant Asian women may be required to characterize more definitively the rates of pregnancy-related thromboembolism in this specific population.

Acknowledgements

None.

Conflict of interest

The authors declare no conflicts of interest.

References