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ORIGINAL ARTICLE

Peripartum management of hereditary thrombophilia: results of primary surveillance in Japan

Takao Kobayashi[1] · Kazuko Sugiura[2] · Toshiyuki Ojima[3] · Kyuya Hirai[1] · Eriko Morishita[4]

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Abstract

This study investigated patients with thrombophilia and current peripartum management practices based on national surveillance in Japan. Between 2014 and 2018, antithrombin (AT), protein C (PC) and protein S (PS) deficiency were observed in 84, 67, and 443 pregnancies, respectively, with incidence rates among total deliveries at 0.012%, 0.009%, and 0.061%. The percentage of institutions that measured both antigens and AT, PC, and PS activity for the diagnosis of thrombophilia was 50.2%, and 46.9% of institutions did not perform gene analysis. Prophylactic anticoagulation therapy was used in the ante- and postpartum management of patients with AT deficiency at 67.1% and 66.3% of institutions, most commonly with 10,000 units of unfractionated heparin. Ante- and postpartum management of PC and PS deficiency was performed at 75.3% and 67.1% of institutions. Approximately half of the institutions performed peripartum prophylactic AT supplementation for AT deficiency. Low trough AT activity before supplementation was most commonly $50 \leq < 70\%$, and the highest AT supplementation was $1500 \leq < 3000$ units. The number of pregnancies with AT, PC and PS deficiency might be as many as 29, 23 and 151 every year in Japan if complete answers were provided.

Keywords Antithrombin deficiency · Hereditary thrombophilia · Peripartum management · Protein C deficiency · Protein S deficiency

Abbreviations

AT	Antithrombin
DVT	Deep vein thrombosis
FV	Factor V
JSOG	Japan Society of Obstetrics and Gynecology
LDA	Low dose aspirin
LMWH	Low molecular weight heparin
PC	Protein C
PE	Pulmonary embolism
PS	Protein S
UFH	Unfractionated heparin
VTE	Venous thromboembolism

Co-first author: Takao Kobayashi and Kazuko Sugiura.

Contributed equally to this work with: Takao Kobayashi and Kazuko Sugiura.

✉ Takao Kobayashi
tkoba@hmedc.or.jp

Kazuko Sugiura
sugiura@med.nagoya-cu.ac.jp

Toshiyuki Ojima
ojima@hama-med.ac.jp

Kyuya Hirai
kyuya@hmedc.or.jp

Eriko Morishita
eriko86@staff.kanazawa-u.ac.jp

[1] Director Emeritus, Department of Obstetrics and Gynecology, Hamamatsu Medical Center, 328 Tomitsuka-cho, Naka-ku, Hamamatsu, Shizuoka 432-8580, Japan

[2] Department of Reproductive Health Nursing/Midwifery, Nagoya City University Graduate School of Nursing, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan

[3] Department of Community Health and Preventive Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431-3192, Japan

[4] Department of Laboratory Sciences, College of Medical, Pharmaceutical and Health Sciences, Kanazawa University, 5-11-80 Kodatsuno, Kanazawa, Ishikawa 920-0942, Japan

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Introduction

Hereditary thrombophilia is a condition in which individuals are susceptible to the formation of thrombi due to a hereditary deficiency in anticoagulant factors such as antithrombin (AT), protein C (PC), or protein S (PS). It is a syndrome in which severe thrombosis may occur under 40 years of age [1–6]. In the neonatal stage and infancy, it may lead to cerebral hemorrhage, cerebral infarction, purpura fulminans or other conditions, and in children or adults it sometimes causes early onset of venous thromboembolism (VTE) or repeated recurrences of VTE, which can be fatal [7, 8]. VTE is usually either deep vein thrombosis (DVT) or pulmonary embolism (PE), but there are also cases of thrombosis in unusual sites. Therefore, when a woman with thrombophilia becomes pregnant, thrombosis may develop during pregnancy or after delivery [9–11].

Racial differences are well known in hereditary thrombophilia. Factor V (FV) Leiden mutation and prothrombin 20210G > A are major pathological variants of thrombophilia in Western countries, but there are still no reports of them in Japanese people [12–15]. Therefore, AT deficiency, PC deficiency and PS deficiency are the major types of thrombophilia in the Japanese population. Among them, PS Tokushima (PS p.K196E) is exclusive to the Japanese people, and thrombosis sometimes occurs during pregnancy [16–19].

Recently, we developed clinical guidance for peripartum management of patients with hereditary thrombophilia, referring to research articles and guidelines in Japan and other countries [1]. In past articles, however, the reported number of pregnant patients with thrombophilia is limited, and no large-scale surveillance has been carried out. This study aimed to investigate the number of patients with thrombophilia and their current peripartum management in Japan.

Materials and methods

National surveillance questionnaire

This national surveillance was conducted in June 2019. We sent paper surveillance questionnaires to 415 perinatal medical centers and general hospitals that have the ability to manage pregnant women with thrombophilia, listed as registered institutions by the perinatal committee of Japan Society of Obstetrics and Gynecology (JSOG). Institutions were asked to provide information regarding all deliveries and the number of pregnant women with thrombophilia between January 1, 2014 and December 31, 2018. They were also asked how such cases were diagnosed and managed during pregnancy and after delivery. The questionnaire included questions on antigen and/or activity measurements, gene analysis, peripartum prophylactic anticoagulation or prophylactic supplementation. As for peripartum prophylactic anticoagulation, the questionnaire asked about two groups, one of patients with AT deficiency, and one of patients with PC deficiency and PS deficiency (PC/PS deficiency), because peripartum VTE risk in patients with AT deficiency was reported to be higher than that with PC/PS deficiency [1]. All personal information were anonymized in this surveillance.

Diagnosis of hereditary thrombophilia

In this primary survey, hereditary thrombophilia was diagnosed according to the criteria of each institution, based on things such as low activities of AT, PC and PS, and family history and previous history of thrombosis (early onset in younger age, recurrence or unusual site of thrombosis). The lower limits of the adult reference values are generally about 70% for AT, 55–70% for PC, and 60–70% for PS [1]. The final diagnoses were confirmed by gene analyses.

Statistical analysis

The differences among antepartum, intrapartum and postpartum prophylactic anticoagulation, both in patients with AT deficiency and in those with PC/PS deficiency, were assessed by the chi-square test. The differences in peripartum prophylactic anticoagulation between patients with AT deficiency and those with PC/PS deficiency were also assessed. Statistical analysis was done using SPSS version 25. In these analyses, a p value of less than 0.05 indicated statistical significance.

Details of ethics approval

The study was approved by the Ethics Committee of Kanazawa University (approval number 890-1) and Hamamatsu Medical Center (rapid approval number 78, 2018). It was performed in compliance with the Declaration of Helsinki. Consent was not obtained, but the presented data are anonymized and there is no risk of identification.

Results

Participants

A flowchart of this study is shown in Fig. 1. Among the 415 institutions to which we sent a paper surveillance questionnaire, 2 institutions were excluded from the study

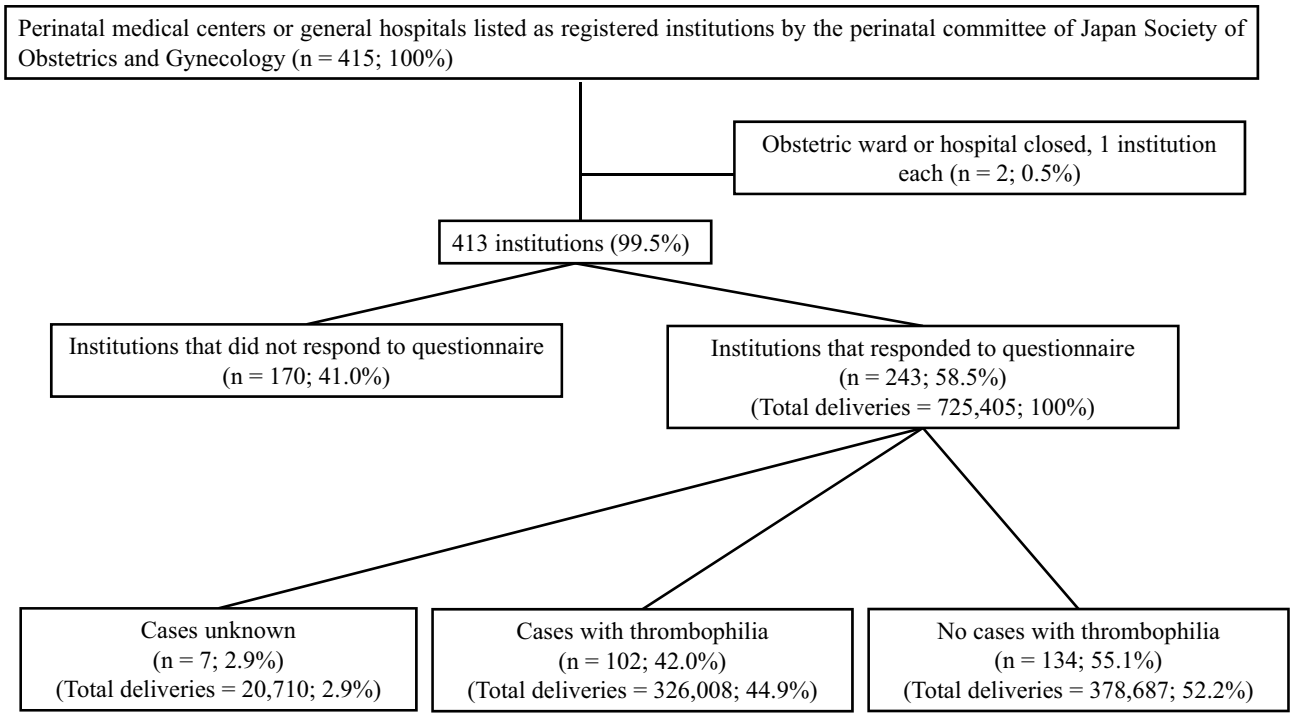

Fig. 1 Flowchart of this study

because their obstetric ward or hospital was closed, and 243 (58.5%) responded to the questionnaires. At these institutions, 725,405 women delivered after 22 gestational weeks; their infants represented 15.0% of all Japanese live births between January 1, 2014 and December 31, 2018 [20]. Among the 243 responding institutions, 134 (55.1%, total deliveries; 378,687, 52.2%) had no cases of thrombophilia, 102 (42.0%, total deliveries; 326,008, 44.9%) had cases of thrombophilia, and 7 did not know (2.9%, total deliveries; 20,710, 2.9%).

Reported cases and prevalence of pregnant women with thrombophilia

The number of reported cases and the prevalence of thrombophilia in pregnant women from 2014 to 2018 are shown in Table 1. The number of cases of thrombophilia was counted as one each when one woman delivered several times, or when one woman had combined thrombophilia deficiencies. In cases of multiple pregnancy, however, the number of cases of thrombophilia was counted as one case. The numbers of cases with AT deficiency, PC deficiency, PS

Table 1 Reported cases and prevalence of pregnant women with thrombophilia from 2014 to 2018

Type of thrombophilia	Cases of thrombophilia (from Jan 1, 2014 to Dec 31, 2018)						Prevalence in total deliveries (%)**
	2014	2015	2016	2017	2018	Total	
Antithrombin deficiency	14	12	22	17	19	84	0.012
Protein C deficiency	11	14	8	13	21	67	0.009
Protein S deficiency	71	83	87	81	121	443	0.061
Others*	1	2	0	0	2	5	0.001
Total	97	111	117	111	163	599	0.083

The number of cases of thrombophilia was counted as one each when one woman delivered several times, or when one woman had combined thrombophilia deficiencies. In cases of multiple pregnancies, however, the number of cases of thrombophilia was counted as one case

*One case each of methylenetetrahydrofolate reductase gene polymorphism, factor V Leiden (a Russian woman), Upshaw–Schulman syndrome, plasminogen deficiency, and essential thrombocythemia

**The number of total deliveries in this survey was 725,405

Table 2 Thrombophilia diagnosis: antigen and/or activity measurement

Measurement	Institution	%
Measurement of both antigen and activity	122	50.2
Measurement of antigen only	7	2.9
Measurement of activity only	76	31.3
Measurement of antigen and/or activity	8	3.3
No answer	30	12.3
Total	243	100

Table 3 Thrombophilia diagnosis: gene analysis

Gene analysis	Institution	%
Analysis in all cases	6	2.5
Analysis if possible	102	42.0
No analysis	114	46.9
No answer	21	8.6
Total	243	100.0

Among 108 institutions that used gene analysis, 68 (63.0%) outsourced it to other institutions, and only 24 (22.2%) performed it in their own institutions. The remaining 16 institutions (14.8%) did not answer

deficiency and other abnormalities were 84, 67, 443 and 5 (599 in total), respectively. The prevalence of AT deficiency, PC deficiency, PS deficiency and other abnormalities among total deliveries was 0.012%, 0.009, 0.061% and 0.001% (0.083% in total), respectively. Other reported abnormalities were one case each of methylenetetrahydrofolate reductase gene polymorphism, factor V Leiden (a Russian woman), Upshaw–Schulman syndrome, plasminogen deficiency, and essential thrombocythemia.

How thrombophilia was diagnosed—antigen and/or activity measurement, gene analysis

The methods of diagnosing thrombophilia are shown in Table 2 (antigen and/or activity measurement) and in Table 3 (gene analysis). Effective answers for antigen and/or activity measurement were provided by 87.7% of institutions. To diagnose thrombophilia, 122 institutions (50.2%) measured both antigen and activity, 76 (31.3%) measured activity only, 8 (3.3%) measured antigen and/or activity, and 7 (2.9%) measured antigen only (Table 2). Effective answers for gene analysis were provided by 91.4% of institutions. One hundred fourteen institutions (46.9%) did not perform gene analysis, 102 (42.0%) performed it if possible, and 6 (2.5%) performed it in all cases. Among 108 institutions, 68 (63.0%) outsourced gene analysis to other institutions, and only 24 (22.2%) performed it in their own institutions (Table 3).

Peripartum prophylactic anticoagulation therapy

Prophylactic anticoagulation in patients with AT deficiency is shown in Table 4 and Supplemental Table 1. In antepartum management, 100 institutions (41.2%) performed anticoagulation on a case by case basis, 63 (25.9%) performed it in all cases, 22 (9.1%) performed only clinical vigilance, and 58 institutions (23.9%) did not respond and/or had no experience of thrombophilia. Unfractionated heparin (UFH) combined with low dose aspirin (LDA) was seen in 6 institutions. In intrapartum management, 93 institutions (38.3%) performed only clinical vigilance, 70 (28.8%) performed anticoagulation on a case by case basis, 21 (8.6%) performed it in all cases, and 59 (24.3%) did not respond and/or had no experience. In postpartum management, 100 institutions (41.2%) performed anticoagulation on a case by case basis, 61 (25.1%) performed it in all cases, 22 (9.1%) performed only clinical vigilance, and 60 (24.7%) did not respond and/or had no experience. UFH combined with warfarin was seen in 22 institutions. During peripartum management, 10,000 units of UFH were used the most often. Low molecular weight heparin (LMWH) was used after cesarean section in many institutions. In prophylactic anticoagulation, there were significant differences between the antepartum and intrapartum periods, and between the intrapartum and postpartum periods (both $p < 0.001$ by the chi-square test). However, the difference between antepartum and postpartum was not significant (ns).

Table 4 Prophylactic anticoagulation in patients with antithrombin (AT) deficiency. Proportion of institutions that performed prophylactic anticoagulation

Prophylaxis	Antepartum		Intrapartum		Postpartum	
	Institution	%	Institution	%	Institution	%
Anticoagulation	163[a]	67.1	91[b]	37.4	161[c]	66.3
In all cases	63	25.9	21	8.6	61	25.1
Case by case	100	41.2	70	28.8	100	41.2
Clinical vigilance	22[a]	9.1	93[b]	38.3	22[c]	9.1
No answer/no experience	58	23.9	59	24.3	60	24.7
Total	243	100.1	243	100	243	100.1

a vs. b; $p < 0.001$, a vs. c; not significant, b vs. c; $p < 0.001$ by the chi-square test

Prophylactic anticoagulation in patients with PC/PS deficiency is shown in Table 5 and supplemental Table 2. In antepartum management, 132 institutions (54.3%) performed anticoagulation on a case by case basis, 51 (21.0%) performed it in all cases, 19 (7.8%) performed only clinical vigilance, and 41 (16.9%) did not respond and/or had no experience of thrombophilia. UFH combined with LDA was seen in 17 institutions. In intrapartum management, 109 institutions (44.9%) performed only clinical vigilance, 75 (30.9%) performed anticoagulation on a case by case basis, 17 (7.0%) performed it in all cases, and 42 (17.3%) did not respond and/or had no experience. In postpartum management, 113 institutions (46.5%) performed anticoagulation on a case by case basis, 50 (20.6%) performed it in all cases, 39 (16.0%) performed only clinical vigilance, and 41 (16.9%) did not respond and/or had no experience. During peripartum management, 10,000 units of UFH were used the most. LMWH was used after cesarean section in many institutions. In prophylactic anticoagulation, there were significant differences between the antepartum and intrapartum periods, between the intrapartum and postpartum periods (both $p < 0.001$), and between the antepartum and postpartum periods ($p < 0.01$). Postpartum anticoagulation only was marginally significant lower ($p = 0.0506$) in patients with PC/PS deficiency than in patients with AT deficiency.

Peripartum prophylactic supplementation

Peripartum prophylactic AT supplementation in patients with AT deficiency is shown in Table 6. In antepartum management, 80 institutions (33.3%) performed supplementation in cases of lower activity, 50 (20.6%) performed clinical

Table 5 Prophylactic anticoagulation in patients with protein C and protein S (PC/PS) deficiency. Proportion of institutions that performed prophylactic anticoagulation

Prophylaxis	Antepartum		Intrapartum		Postpartum	
	Institution	%	Institution	%	Institution	%
Anticoagulation	183[d]	75.3	92[e]	37.9	163[f]	67.1
In all cases	51	21.0	17	7.0	50	20.6
Case by case	132	54.3	75	30.9	113	46.5
Clinical vigilance	19[d]	7.8	109[e]	44.9	39[f]	16.0
No answer/no experience	41	16.9	42	17.3	41	16.9
Total	243	100	243	100.1	243	100

d vs. e; $p < 0.001$, d vs. f; $p < 0.01$, e vs. f; $p < 0.001$ by the chi-square test. a vs. d; not significant, b vs. e; not significant, c vs. f; $p = 0.0506$ (marginally significantly lower) compared to AT deficiency (Table 4)

Table 6 Prophylactic antithrombin (AT) supplementation in patients with AT deficiency

Supplementation	Antepartum		Intrapartum		Postpartum	
	Institution	%	Institution	%	Institution	%
Supplementation in all cases	41	16.5	49	19.8	40	16.1
Supplementation in cases of lower activity	80	33.3	79	32.5	77	31.7
Clinical vigilance	50	20.6	45	18.5	55	22.6
No answer/no experience	72	29.6	70	29.2	71	29.6
Total	243	100	243	100	243	100
Trough AT activity before supplementation in cases of lower activity (%)						
< 50	8	10	6	7.6	6	7.8
50 ≦ < 70	17	21.3	13	16.5	16	20.8
70 ≦	10	12.5	16	20.3	14	18.2
Undetermined (case by case)	2	2.5	4	5.1	2	2.6
No answer/no experience	43	53.8	40	50.6	39	50.6
Total	80	100.1	79	100.1	77	100
Amount of AT supplementation (units)						
< 1500	2	0.8	0	0	2	0.8
1500 ≦ < 3000	20	8.2	3	1.2	21	8.6
3000 ≦	8	3.3	2	0.8	8	3.3
Undetermined (case by case)	2	0.8	1	0.4	2	0.8
No answer/no experience	211	86.8	237	97.5	210	86.4
Total	243	99.9	243	99.9	243	99.9

vigilance only, 41 (16.5%) performed supplementation in all cases, and 72 (29.6%) did not respond and/or had no experience. In intrapartum management, 79 institutions (32.5%) performed supplementation in cases of lower activity, 49 (19.8%) performed supplementation in all cases, 45 (18.5%) performed clinical vigilance only, and 70 (29.2%) did not respond and/or had no experience. In postpartum management, 77 institutions (31.7%) performed supplementation in cases of lower activity, 55 (22.6%) performed clinical vigilance only, 40 (16.1%) performed supplementation in all cases, and 71 (29.6%) did not respond and/or had no experience. The most common answer for the low trough AT activity criterion for the use of supplementation was $50 \leq < 70\%$, and the most common amount of AT supplementation was $1500 \leq < 3000$ units among institutions that provided valid answers. No cases of supplementation with freeze-dried concentrated human activated protein C were reported in PC deficiency.

Discussion

In this study, we conducted the first national surveillance of peripartum management of hereditary thrombophilia in Japan. Between 2014 and 2018, AT, PC and PS deficiency were observed in 84, 67, and 443 pregnancies, respectively, with incidence rates among total deliveries at 0.012%, 0.009%, and 0.061%.

AT deficiency, PC deficiency and PS deficiency are the major types of thrombophilia in the Japanese population [1–6, 15]. In this surveillance, 243 institutions (58.5%) responded to the questionnaire and 102 (42.0%) of them had cases with thrombophilia (Fig. 1). The number of pregnant women with AT, PC and PS deficiency was reported to be 84, 67, and 443, respectively (Table 1). Though the number of reported cases fluctuated every year, the reason why it was the highest in 2018 may be because that was the year nearest to the year of the surveillance. At these institutions, 725,405 women delivered, representing 15.0% of all Japanese live births between 2014 and 2018. As we sent a paper surveillance questionnaire to all perinatal medical centers and general hospitals that have the ability to manage pregnant women with thrombophilia throughout Japan, there might have been up to 144 cases of AT deficiency, 115 of PC deficiency and 757 of PS deficiency in these 5 years if 100% of institutions had responded. Specifically, there could have been up to 29 cases of AT deficiency, 23 of PC deficiency and 151 of PS deficiency every year. National surveys by Ministry of Health, Labour and Welfare research groups and academic societies have found that there are about 2,000 individuals with AT, PC, and PS deficiencies in all of Japan (total population was estimated at 124.2–125.4 million between 2014 and 2018 [20]). The number of patients in whom these conditions newly develop annually is estimated to be less than 100 among neonates and infants, and about 500 among adults [21–23]. Accordingly, looking only at women of reproductive age who hope to bear children, the estimated annual number of pregnant women with thrombophilias obtained from this surveillance (29 with AT deficiency, 23 with PC deficiency, 151 with PS deficiency, and 203 in total) would seem to be reasonable and to reflect the current situation of Japan. The prevalence of AT, PC and PS deficiency among total deliveries was 0.012%, 0.009% and 0.061%, respectively (Table 1). In the general Japanese population, AT, PC and PS deficiency are thought to be present in about 1 person per 650 people (0.15%), about 1 person per 750 people (0.13%) [24], and about 10–20 persons per 1,000 people, respectively. Only PS deficiency is roughly 10 times higher than the 0.16–0.21% in Caucasians [25, 26]. The main reason for that is thought to be the PS gene polymorphism, PS p.K196E, which is exclusive to Japanese [16, 18, 19]. A mutant allele of PS p.K196E is seen in 1 of about 55 people (about 2%) in the general population [17].

Only about a half of institutions (50.2%) measured both antigen and activity for a diagnosis of thrombophilia; however, more than 80% of institutions measured at least activity (Table 2). The best way to diagnose thrombophilia is to measure both antigen and activity, which leads to distinguishing between type I and type II subtypes of thrombophilia. However, this surveillance revealed that subtype diagnosis of thrombophilia is difficult even if thrombophilia itself can be diagnosed in Japan today. We recommend the measurement of both antigen and activity to diagnose thrombophilia at more institutions in the near future. Gene analysis is the ultimate diagnosis of thrombophilia, however, this surveillance revealed that among the 108 institutions that used gene analysis, only 22.2% could perform gene analysis in their own institutions (9.9% of the whole) (Table 3). Although genetic screening is currently very difficult in Japan, gene analysis for thrombophilia is expected to become widespread in the near future as AT, PC, and PS deficiency were added to the diseases targeted for genetic testing in the 2020 revision of the medical payment system in Japan [1].

In peripartum prophylactic anticoagulation in patients with AT deficiency (Table 4), about two-thirds of institutions performed anticoagulation in the antepartum and postpartum periods (67.1% antepartum and 66.3% postpartum; ns), while 37.4% did in the intrapartum period ($p < 0.001$ vs. antepartum and postpartum). As VTE risks differ with factors such as type I deficiency, past history or family history of thrombosis, prophylactic anticoagulation depends on individual VTE risk. According to clinical guidance for peripartum management of patients with hereditary thrombophilia [1], both antepartum and postpartum prophylactic doses of anticoagulation are

suggested. However, it is recommended that they be discontinued with the onset of labor pains in cases of vaginal delivery and 6 h before the start of delivery in cases of planned delivery or cesarean section. Although the proportion of institutions with postpartum prophylactic anticoagulation was not so high, the obtained data seem to be satisfactory. The anticoagulation was stopped during labor in all institutions even when it was performed on the date of delivery. UFH was used during pregnancy because LMWH, which is widely used in Western countries, is not covered by health insurance in Japan for either prophylaxis or treatment of VTE, except for postoperative prophylactic use for VTE. In the peripartum period, 10,000 units of UFH was the most common dose for prophylactic anticoagulation. For the postpartum period only, UFH combined with warfarin was seen in some institutions and LMWH was used after cesarean section in many institutions (supplemental Table 1). These data are thought to be in accordance with the abovementioned clinical guidance [1].

In peripartum prophylactic anticoagulation in patients with PC/PS deficiency (Table 5), two-thirds to three-fourths of institutions performed anticoagulation in the antepartum and postpartum periods (75.3% antepartum and 67.1% postpartum; $p < 0.01$), while 37.9% performed anticoagulation in the intrapartum period ($p < 0.001$ vs. antepartum and postpartum). Though the peripartum VTE risk in patients with AT deficiency is reported to be higher than that in patients with PC/PS deficiency [1], the proportion of institutions performing antepartum anticoagulation for PC/PS deficiency was slightly higher than that for AT deficiency. This data may seem strange. The reasons for this are thought to be the following: (1) The guideline for obstetrics practice in Japan recommends peripartum prophylactic anticoagulation equally in patients with thrombophilia, regardless of whether it is AT and PC/PS deficiency [27]. (2) Japanese physicians have more occasions to encounter patients with PS deficiency because of the higher prevalence of PS deficiency than of AT or PC deficiency in Japan [16–19, 25, 26]. (3) Prophylactic anticoagulation is suggested to prevent recurrent fetal loss in cases with PS deficiency [1]. Accordingly, physicians tend to perform prophylactic anticoagulation in patients with PS deficiency, especially in the antepartum period. Two statistical findings, i.e., that the proportion of institutions performing postpartum prophylactic anticoagulation was significantly lower than that performing antepartum prophylactic anticoagulation ($p < 0.01$), and that it was marginally significant lower ($p = 0.0506$) compared to AT deficiency, might demonstrate this tendency. In the peripartum period, doses of UFH were almost the same as for AT deficiency. However, UFH combined with low dose aspirin (LDA) was seen in some institutions. It is thought that LDA was used for the prevention of recurrent pregnancy loss in patients with PS deficiency.

Approximately half of institutions performed peripartum prophylactic AT supplementation in patients with AT deficiency (49.8% in the antepartum, 52.3% in the intrapartum and 47.8% in the postpartum period) (Table 6). According to the abovementioned clinical guidance [1], supplementation with an AT preparation is suggested in peripartum periods depending on individual VTE risk. Although there is no established opinion with regard to AT supplementation, it has been recommended in some reports in recent years [28, 29]. The reason that only half of institutions currently perform AT supplementation in the peripartum periods in Japan seems to be that there is no firm recommendation about it. In this survey, low trough AT activity before supplementation was most commonly $50\% \leq < 70\%$, and the highest AT supplementation was $1500 \leq < 3000$ units. Since administration of 1500 to 3000 units of AT concentrate are recommended so that AT activity levels are preferably maintained at 70% or higher if possible [1, 30], the obtained data seem satisfactory.

In conclusion, it is suggested that the number of pregnancies with AT, PC and PS deficiency might be as many as 29, 23 and 151 every year in Japan. More than 80% of institutions measured at least activity for the diagnosis of thrombophilia; however, only about 10% of institutions could perform gene analysis in their own institutions. The obtained data on peripartum prophylactic anticoagulation and AT supplementation are thought to be in accordance with clinical guidance.

Study limitations

We revealed the number of patients with thrombophilia and their current peripartum management in Japan for the first time; however, (i) The rate of responding institutions in this primary survey (243/415, 58.5%) was not very high. (ii) Reported cases of thrombophilia may not have been definitively diagnosed, since hereditary thrombophilia was diagnosed according to the criteria of each institution. In addition, there might be considerable pregnant women with false PS deficiency, especially if PS activities were measured during pregnancy. (iii) Since this study was a primary survey, detailed information other than the obtained data is unknown.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12185-022-03354-4.

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Author contributions TK wrote the manuscript and researched data. KS collected paper surveillance questionnaire and researched data. TO,

KH, and EM contributed to the discussion and reviewed or edited the manuscript.

Declarations

Disclosure No declaration.

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