

Characteristics of Maternal Venous Thromboembolism in Japan, 2018: A Retrospective Cohort Study with National Surveillance Questionnaire Conducted in Maternity Hospitals

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Abstract

Background: In Japan, deliveries by women of older maternal age and by women with overweight or obesity have recently increased. While, since 2008, the guidelines and practices to prevent the maternal VTE have been recommended. This study aims to clarify the incidence and characteristics of venous thromboembolism (VTE) in pregnant women in Japan to reduce the rate of mortality from VTE.

Methods: Of 2299 institutions sent the surveillance questionnaire, 666 (29.0%) responded, and data from 295,961 women who gave birth in those institutions in 2018 were analyzed. We calculated the incidence and characteristics of VTE before and after the deliveries in the three types of institutions (perinatal medical centers, general hospital with obstetric facilities, and maternal clinic with beds). To clarify the incidence and characteristics of VTE, and to clarify the relationship between the incidence of the VTE and the types of institutions in 2018 in Japan.

Results: At the responding institutions, 20 (0.0068%) died, and 243 women (0.082%) had VTE. Deep vein thrombosis was significantly more common (0.0053%) than pulmonary thromboembolism (0.0019%; $p < 0.0001$). The incidence of antepartum VTE (0.0055%) was significantly higher than that of postpartum VTE (0.0026%; $p < 0.0001$). Among the 165 women with antepartum VTE, perioperative pulmonary thromboembolism (30.0%) was more common than perioperative deep vein thrombosis (8.8%, $p = 0.0150$). The incidence of VTE after cesarean section (0.0074%) was significantly higher than that after vaginal delivery (0.0012%; $p < 0.0001$). After cesarean section, the incidence of pulmonary thromboembolism (46.4%) was significantly higher than that of deep vein thrombosis (10.8%; $p < 0.0001$). Of the women with VTE, four (1.6%) died.

Conclusions: Obstetricians should be strongly encouraged to administer thromboprophylaxis to decrease the incidence of VTE because among women thought to have low risk of VTE, the incidence might have increased in Japan.

Background

Pregnant women and women who have recently given birth are in states of hypercoagulability [1] and are thus at increased risk of venous thromboembolism (VTE) [2], one of the leading causes of maternal death in developed countries [3, 4].

Women who have delivered by cesarean section are at increased risk of VTE [5–7]. In the United States [8], the incidence of VTE among pregnant and postpartum women is four to five times higher than that among nonpregnant women.

The incidence of VTE in London from 1988 and 1997 has been reported to be 85 per 100,000 pregnant women [4]. In the United States, the recent prevalence of VTE is 50–200 per 100,000 pregnant women [8], and the rate of mortality induced by VTE among pregnant women was 9.3% of all maternal deaths. In Japan [3], the incidence of maternal death induced by VTE was 7.1% (24) of all 338 maternal deaths from

2010 to 2016, according to the maternal death registration system established by the Japan Association of Obstetricians and Gynecologists (JAOG) and the Maternal Death Exploratory Committee [3]. The incidence of maternal deaths from VTE was 0.33 deaths per 100,000 live births (7,175,733 women) from 2010 to 2016 in Japan. In the United States, the incidence of VTE was 1.72 per 1000 deliveries, with 1.1 deaths per 100,000 from 2000 to 2001 [9], and the deaths from PTE accounted for 9.2% of all pregnancy-related deaths, or approximately 1.5 deaths per 100,000 live births, from 2004 to 2014 [10].

In the retrospective study from 1991 to 2000 in Japan by the Japan Society of Obstetrical, Gynecological and Neonatal Hematology (JSOGNH) [6], the incidence of VTE before and after delivery was 0.046% (203 of 436,084 women).

In Japan, deliveries by women of older maternal age and by women with overweight or obesity have recently increased; thus, the risk of VTE may have increased. On the other hand, since 2008, the Japan Society of Obstetrics and Gynecology (JSOG) and JAOG have recommended guidelines and practices to prevent the maternal VTE [11, 12], and so the incidence of VTE onset in Japan might have decreased since then.

As members of JSOGNH, we wish to reduce the rate of mortality from VTE among women in Japan.

The primary goal of this study was to clarify the incidence and characteristics of VTE, and to clarify the relationship between the incidence of the VTE and the types of institutions in 2018 in Japan. Furthermore, the secondary goal was to clarify the trend of VTE onset in Japan in comparison with those in previous studies [6, 7].

Methods

Hypotheses

We built the following hypothesis, the frequency of VTE (DVT and PTE) onset and death induced by VTE in the pregnant women would be decrease in 2018 comparison with those of study from 1991 to 2000 in Japan.

Study design

We conducted a cohort study with a surveillance questionnaire. In May 2019, questionnaires were sent to all 2299 hospitals or maternity clinics listed as institutions with obstetric facilities by the JSOG on December 31, 2018. The chairman, chief or substitute of institutions responded by regular mail.

The surveillance questionnaire was designed by JSOGNH, and had four categories of questions: (1) the types and the specialties of institutions, (2) methods used to prevent maternal VTE onset, (3) incidence of maternal VTE (e.g., case numbers, types of VTE, period of VTE onset), and (4) outcomes (mortality

induced by VTE) among pregnant women with VTE onset in 2018. The response from hospitals or maternal clinics that had no deliveries in 2018 was excluded.

The recommendations for thromboprophylaxis in Japan [11] are shown in Table 1. These were determined according to the modified guidelines of the Royal College of Obstetricians and Gynecologists [13] and of the American College of Chest Physicians [14, 15].

Table 1
Recommendations for thromboprophylaxis in Japan

Antepartum thromboprophylaxis					
	Group	Risk of incidence	State during pregnancy	Thromboprophylaxis (heparin administration)	Level of recommendation
1)	1	High	Standard	Perform	B
2)	2	Moderate	Standard	Consider	B
3)	2	Moderate	Operation	Perform	B
4)	3	Low	Standard	Consider	C
Postpartum thromboprophylaxis in Japan					
	Group	Risk of incidence	I. Thromboprophylaxis (heparin administration) II. Intermittent pneumatic compressions		Level of recommendation
1)	1	High	Perform I or I + II		B
2)	2	Moderate	Perform I or II		B
3)	3	Low	Consider I or II		C
<p>Level A and B treatment are regarded as current standard care practices in Japan. Level A recommendations are stronger than level B recommendations. Informed consent is therefore required when maternity service providers do not provide care corresponding to level A or B recommendations.</p> <p>Level C treatment consists of possible options that may favorably affect the outcome but for which it is unclear whether the possible benefits outweigh the possible risks. Thus, care corresponding to level C recommendations is not necessarily provided.</p>					

The criteria of three types of institutions

All institutions were categorized as one of three types. The first type were perinatal medical centers (PMCs), which were defined as hospitals with maternal-fetal intensive care units that had six beds or

more and were always staffed by one or more specified obstetricians and one specified midwife or nursing staff for every three beds over a 24-h period, a neonatal intensive care unit that had nine or more beds and was always staffed by one or more specified pediatricians and one or more specific nurses for every three beds over a 24-h period, a growing care unit that was always staffed by one specific nurse for every six beds over a 24-h period, and a delivery room that was staffed by one or more specific midwives and one or more anesthesiologists. The second type was a general hospital with obstetric facilities (GH), defined as having one or more beds for deliveries by one or more obstetricians supported by one or more pediatricians and one or more anesthesiologists. The third type was a maternal clinic with beds (MC), defined as a hospital with one or more beds for deliveries by one or more obstetricians with possible support by one or more pediatricians but no anesthesiologists.

All thromboembolisms were classified as one of four types: (1) DVT, (2) pulmonary thromboembolism (PTE), (3) other vein thrombosis (other VT), and (4) arterial thromboembolism (ATE). The combination of PTE with DVT was classified as PTE. Other VTs were defined as thrombosis of more superficial veins, such as thromboembolisms of veins in the arm, ovary, colon, and brain.

Time of onset was classified as antepartum or postpartum (the latter of which included the period during labor). Operations during pregnancy were defined as invasive procedures in the hospital, e.g., cervical cerclage, laparotomy, or laparoscopic ovarian cystectomy. Delivery mode was classified as vaginal delivery or cesarean section.

Statistical analyses

Data were calculated as frequencies. JMP Pro, version 14.0 (SAS Institute Inc., Cary, NC, USA), was used to perform the statistical analyses. We used Fisher's exact test to compare categorical variables. Pearson's product-moment correlation coefficient was used to measure linear correlations between two variables. In all analyses, a p value of less than 0.05 indicated statistical significance. In linear correlations, statistical significance also required a correlation coefficient (r) of $-0.25 \leq r \leq 0.25$.

Ethical approval

This study was approved by the Institutional Review Board of Hokkaido University Hospital (018-280), Hokkaido, Japan. It was performed in compliance with the Declaration of Helsinki. Consent was not obtained from patients, but the presented data are anonymous, and there is no risk of identification.

Patient and public involvement

No patients were involved in devising the research questions, the outcome measures, or the plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or

writing up of results. There are no plans to disseminate the research study results to study participants or the relevant patient community.

Availability of data

The datasets generated and analyzed during the current study are not publicly available due to taking out to other facilities is restricted by the institutional review board but are available from the corresponding author on reasonable request.

Results

Participants

Of the 2299 institutions sent the surveillance questionnaire, 705 (30.7%) responded to the questionnaires; of those 705, 39 (5.5%) had no deliveries in 2018 and were excluded from the study. The final number of institutions that participated in this study was 666 (29.0%). Of these 666 institutions, 184 (27.6%) were classified as PMCs, 170 (25.5%) as GHs, and 312 (46.8%) as MCs.

At these institutions, 295,961 women delivered after 22 gestational weeks; their infants represented 32.2% of all Japanese births in 2018. Of all these women, 110,865 (37.5%) delivered in PMCs, 63,933 (21.6%) in GHs, and 121,163 (40.9%) in MCs.

Characteristics of institutions

Of the 295,961 births, 110,865 took place at PMCs, 63,933 at GHs, and 121,163 at MCs. Of the 295,961 women, 67,752 (22.9%) delivered by cesarean section.

Routine thromboprophylaxis, both antepartum and postpartum, is described in Table 2. In accordance with the recommendation of thromboprophylaxis in Japan for pregnant women at high risk for VTE [11, 12], unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) was routinely administered by 316 (47.4%) institutions before the women gave birth and by 382 (57.4%) institutions after; compression stockings were routinely applied by 326 (48.9%) institutions before the women gave birth and by 396 (59.5%) institutions after; and intermittent pneumatic compressions were applied by 162 (24.3%) institutions before the women gave birth and by 353 (53.0%) institutions after. The number of institutions in which UFH or LMWH was routinely administered and in which intermittent pneumatic compressions were applied to prevent postpartum VTE was significantly higher than those applying these measures to prevent antepartum VTE ($p < 0.0001$).

The characteristics of pregnant women with venous thromboembolism

The characteristics of pregnant women with VTE were shown in Table 2 and Table 3.

In this study, of the 295,961 women who delivered after 22 gestational weeks, 243 (0.082%) had VTE. Of the 243 women with maternal VTE, 166 (68.3%) gave birth at PMCs, 50 (20.6%) at GHs, and 27 (11.1%) at MCs.

The incidence of VTE onset significantly differed among the three types of institutions (149.7, 78.2, and 22.3 per 100,000 women, respectively). Of the 243 women with VTE, 157 (64.6%) had DVTs, 56 (23.0%) had PTEs, 26 (10.7%) had other VTs, and 4 (1.6%) had ATEs. Among 295,961 women, the incidences of DVT, PTE, other VT, and ATE were 53.0, 18.9, 8.8, and 1.4 per 100,000 women, respectively. The incidence of DVT was significantly higher than those of PTE, other VT, and ATE (all $p < 0.0001$); the incidence of PTE was significantly higher than those of other VT ($p = 0.0009$) and ATE ($p < 0.0001$); and the incidence of other VT was significantly higher than that of ATE ($p < 0.0001$).

Of the 243 women with maternal VTE, 165 (67.9%) had antepartum VTE and 78 (32.1%) had postpartum VTE. Among 295,961 women, the incidence of antepartum VTE (55.8 per 100,000 women) was significantly higher than that of postpartum VTE (26.4 per 100,000 women; $p < 0.0001$). Of 165 women with maternal antepartum VTE, 18 (10.9%) had perioperative antepartum VTE. Among 78 women with postpartum VTE, the disorder developed in 50 (64.1%) after cesarean section and in 28 (35.9%) after vaginal delivery. The incidence of VTE was significantly higher after cesarean section (73.8 per 100,000 women) than after vaginal delivery (12.3 per 100,000 women; $p < 0.0001$).

Table 2
Characteristic of institutions that participated in this study

Characteristic	Overall	A. PMC	B. GH	C. MC	p < 0.05
No. of institutions	666 (100%)	184 (27.6%)	170 (25.5%)	312 (46.8%)	
Available staff / services					
Overall	243	157	56	26	4
Anesthesiologists ^a	304 (45.6%)	176 (95.7%)	117 (68.8%)	11 (3.5%)	A vs. B / A vs. C / B vs. C
Pediatricians ^a	336 (50.5%)	184 (100%)	132 (77.6%)	20 (6.4%)	A vs. B / A vs. C / B vs. C
MRI, CT, or both	323 (48.5%)	179 (97.3%)	141 (82.9%)	3 (1.0%)	A vs. C / B vs. C
Routine antepartum thromboprophylaxis for women at high risk for thromboembolism	391 (58.7%)	170 (92.4%)	130 (76.5%)	91 (29.2%)	A vs. B / A vs. C / B vs. C
Administration of UFH or LMWH	316 (47.4%)	156 (84.8%)	115 (67.6%)	45 (14.4%)	A vs. B / A vs. C /

					B vs. C
Application of compression stockings	326 (48.9%)	127 (69.0%)	113 (66.5%)	86 (27.6%)	A vs. C
					B vs. C
Application of intermittent pneumatic compressions	162 (24.3%)	55 (29.9%)	61 (35.9%)	46 (14.7%)	A vs. C
					B vs. C
Routine antepartum thromboprophylaxis after surgery	456 (68.5%)	170 (92.4%)	139 (81.8%)	147 (47.1%)	A vs. B / A vs. C /
					B vs. C
Administration of UFH or LMWH	290 (43.5%)	126 (68.5%)	92 (54.1%)	72 (23.1%)	A vs. B / A vs. C /
					B vs. C
Application of compression stockings	416 (62.5%)	153 (83.2%)	128 (75.3%)	135 (43.3%)	A vs. B / A vs. C /
					B vs. C
Application of intermittent pneumatic compressions	332 (49.8%)	128 (69.6%)	107 (62.9%)	97 (31.1%)	A vs. C / B vs. C

Routine postpartum thromboprophylaxis for women at high risk for thromboembolism	444 (66.7%)	177 (96.2%)	137 (80.6%)	130 (41.7%)	A vs. B / A vs. C / B vs. C
Administration of UFH or LMWH	382 (57.4%)	168 (91.3%)	124 (72.9%)	90 (28.8%)	A vs. B / A vs. C / B vs. C
Application of compression stockings	396 (59.5%)	152 (82.6%)	127 (74.7%)	117 (37.5%)	A vs. C / B vs. C
Application of intermittent pneumatic compressions	353 (53.0%)	147 (79.9%)	115 (67.6%)	91 (29.2%)	A vs. B / A vs. C / B vs. C
Outcomes of all deliveries					
Overall	295,961	110,865	63,933	121,163	
Cesarean sections	67,752 (22.9%)	37,567 (33.9%)	13,801 (21.6%)	16,384 (13.5%)	A vs. B / A vs. C / B vs. C
Maternal deaths	20 (0.0068%)	18 (0.016%)	1 (0.0016%)	1 (0.0008%)	A vs. B / A

PMC, perinatal medical centers; GH, general hospitals with obstetrics; MC, maternal clinics with beds; MRI, magnetic resonance imaging; CT, computer tomography; VTE, venous thromboembolism; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin, NS, not significant. ^a Working exclusively at each institution

Table 3
Thromboembolism of institutions that participated in this study

Characteristic	Overall	A. PMC	B. GH	C. MC	p < 0.05
All deliveries	295,961	110,865	63,933	121,163	
Thromboembolism onset					
Overall	243 (0.082%)	166 (0.150%)	50 (0.078%)	27 (0.022%)	A vs. B / A vs. C / B vs. C
Time of onset					
Antepartum	165 (0.056%)	118 (0.106%)	33 (0.052%)	14 (0.012%)	A vs. B / A vs. C / B vs. C
Antepartum with operation	18 (0.0061%)	13 (0.012%)	4 (0.0063%)	1 (0.0008%)	A vs. C
Postpartum	78 (0.026%)	48 (0.043%)	17 (0.027%)	13 (0.011%)	A vs. C / B vs. C
Vaginal delivery	28 (0.0095%)	16 (0.0144%)	6 (0.0094%)	6 (0.0050%)	A vs. C
Cesarean section	50 (0.017%)	32 (0.029%)	11 (0.017%)	7 (0.0058%)	A vs. C / B vs. C
Type of thromboembolism					
DVT	157 (0.053%)	108 (0.097%)	32 (0.050%)	12 (0.0099%)	A vs. B / A vs. C / B vs. C
PTE	56 (0.019%)	39 (0.035%)	8 (0.013%)	9 (0.0074%)	A vs. B / A vs. C /
Other VT	26 (0.0088%)	17 (0.015%)	4 (0.0063%)	5 (0.0041%)	A vs. C
ATE	4 (0.0014%)	2 (0.0018%)	1 (0.0016%)	1 (0.0008%)	NS
Maternal deaths from thromboembolism					
Overall	4 (0.0014%)	3 (0.0027%)	0 (0.0000%)	1 (0.0008%)	NS
Time of onset					
Antepartum	1 (0.0003%)	1 (0.0009%)	0 (0.00%)	0 (0.00%)	NS

Antepartum with operation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	NS
Postpartum	3 (0.0010%)	2 (0.0018%)	0 (0.00%)	1 (0.0008%)	NS
Vaginal delivery	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	NS
Cesarean section	3 (0.0010%)	2 (0.0018%)	0 (0.00%)	1 (0.0008%)	NS
Type of thromboembolism					
DVT	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	NS
PTE	4 (0.0014%)	3 (0.0027%)	0 (0.00%)	1 (0.0008%)	NS
Other VT	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	NS
ATE	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	NS
VTE, venous thromboembolism; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; Other VT, other vein thrombosis; ATE, arterial thromboembolism, NS, not significant.					

The relations between types of thromboembolism and onset

The characteristics of the period of VTE onset are summarized in Table 4.

The postpartum incidence of PTE (36/56 [64.3%]) was significantly higher than those of DVT (32/157 [20.4%]; $p < 0.0001$) and other VT (10/26 [38.5%]; $p = 0.0339$). The postpartum incidence of DVT was similar to that of other VT ($p = 0.0745$). In all four women with ATE, the onset was before delivery.

The odds ratio of postpartum PTE was 1.80 (95% CI, 1.04–3.11) in comparison with antepartum PTE ($p = 0.0440$); however, the odds ratio of antepartum DVT was 3.91 (95% CI, 2.65–5.76) in comparison with postpartum DVT ($p < 0.0001$).

Among the 165 women with antepartum VTE, the incidence of perioperative PTE during pregnancy (6/20 [30.0%]) was higher than that of perioperative DVT (11/125 [8.8%]; $p = 0.0150$). The odds ratio of perioperative PTE to perioperative VTE among all women who underwent surgery during pregnancy (6/18 [33.3%]) was 4.75 (95% CI, 1.54–14.6) in comparison with women who did not have perioperative PTE or VTE during pregnancy (14/133 [9.5%]; $p = 0.0108$).

In particular, after cesarean section, the incidence of PTE (26/56 [46.4%]) was significantly higher than that of DVT (17/157 [10.8%]; $p < 0.0001$). The odds ratios of postpartum DVT and PTE after cesarean section were 3.82 (95% CI 1.91–7.65) and 7.86 (95% CI 2.03–30.4), respectively, in comparison with those after vaginal delivery ($p = 0.0002$ and $p = 0.0020$, respectively).

Table 4

Relations between type of thromboembolism and time of thromboembolism onset / maternal deaths from thromboembolism

	Overall	A. DVT	B. PTE	C. Other VT	D. ATE	p < 0.05
	(n = 243, 100%)	(n = 157, 64.6%)	(n = 56, 23.0%)	(n = 26, 10.7%)	(n = 4, 1.6%)	
Thromboembolism onset						
Overall	243 (100%)	157 (100%)	56 (100%)	26 (100%)	4 (100%)	
Antepartum	165 (67.9%)	125 (79.6%)	20 (35.7%)	16 (61.5%)	4 (100%)	A vs. B / B vs. C
Antepartum with operation	18 (7.4%)	11 (7.0%)	6 (10.7%)	0 (0.0%)	1 (20.0%)	NS
Postpartum	79 (32.5%)	32 (20.4%)	36 (64.3%)	10 (38.5%)	0 (0.0%)	A vs. B / B vs. C
Cesarean section	50 (20.6%)	17 (10.8%)	26 (46.4%)	7 (26.9%)	0 (0.0%)	A vs. B
Maternal deaths from thromboembolism						
Overall	4 (1.6%)	0 (0.0%)	4 (7.1%)	0 (0.0%)	0 (0.0%)	A vs. B
Antepartum	1 (0.4%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	NS
Antepartum with operation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
Postpartum	3 (1.2%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	A vs. B
Cesarean section	3 (1.2%)	0 (0.0%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	A vs. B
VTE, venous thromboembolism; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; Other VT, other vein thrombosis; ATE, arterial thromboembolism						

The characteristics of death from venous thromboembolism

The characteristics of deaths from VTE are listed in Table 3 and Table 4.

In this study, of the 295,961 women who delivered after 22 gestational weeks, 20 (0.0068%) died. Of the 20 women who died, 18 (90.0%) died in PMCs.

Of 243 women with thromboembolism, 4 (1.6%) died. The mortality rate among women with maternal thromboembolism was significantly higher than that among women without it (16/295,718 [0.0054%]; $p < 0.0001$). All four women who died of VTE had PTE. Of the 165 women with antepartum VTE, 1 (0.61%) died, and of the 78 women with postpartum VTE, 3 (3.8%) died; in terms of the 243 with thromboembolism, these frequencies were similar ($p = 0.0986$). Of the 18 women (7.4%) with perioperative antepartum VTE, none died. Of the 50 women (20.6%) who had VTE after cesarean section, 3 (6.0%) died. Of the four women who died, three were at a PMC and one at a MC.

Discussion

Our findings emphasized four points: (1) The incidence of VTE in PMCs was higher than GHs or MCs; (2) the incidence of postpartum PTE onset was significantly higher and the incidence of postpartum DVT onset was significantly lower than those during pregnancy; (3) the incidence of PTE in association with cesarean section was significantly higher than that of DVT; and (4) of 243 women with VTE, 4 (1.6%) died, and all 4 had PTE.

To the best of our knowledge, this is the first study to demonstrate that the incidence of VTE onset in perinatal medical centers was higher in spite of their higher incidence of thromboprophylaxis. Many pregnant women who delivered in PMCs were apparently at higher risk of VTE.

This study included data from 295,961 women, who represented 32.2% of the 918,400 women who gave birth in Japan in 2018 reported by the Ministry of Health, Labour and Welfare (Japan). Of the women in our study, 20 women (0.0068%) died; of these 20 women, 18 (90.0%) died in PMCs. The 184 PMCs (27.6% of the 666 institutions surveyed) represented 45.3% of all 406 Japanese PMCs in 2018. According to these data, 47.3 women would have died during the periparturition period in 2018.

The JAOG reported the deaths of 36 women in 2018, in contrast to the 40, 50, 43, and 47 deaths in 2014, 2015, 2016, and 2017, respectively [3]. In our study, as mentioned, of the four women who died of PTE, three (75.0%) died in PMCs. These data indicate that 12.4 women would have died of PTE in 2018. The maternal deaths from PTE in Japan might be more numerous than those in the previous reports [3, 6, 7].

Of 203 women with VTE in the 1991–2000 study in Japan by JSOGNH [6], 127 (62.6%) had DVT and 76 (37.4%) had PTE. In that study and ours, the incidences of PTE in Japan were similar (17.4 to 18.9 per 100,000, $p = 0.6405$); however, the incidence of DVT increased 82% between that study and ours (29.1 to 53.0 per 100,000; $p < 0.0001$).

Comparison with the risks of VTE onset during the first trimester, second trimester, third trimester antepartum, the risk of VTE onset during the first 6 weeks' postpartum are significantly higher [16, 17], and the peak of VTE onset occurred in the first 3 week [17]. While, in the previous report, the frequencies of VTE onset at antepartum and at postpartum were similar (48.9% and 51.1%) among all women with VTE [16]. In our study, among the 243 women with VTE, the frequency of PTE onset at antepartum was low in comparison with at postpartum (35.7% vs. 64.3%), while, the frequency of DVT onset at antepartum was high in comparison with at postpartum (79.6% vs. 20.4%). The women with DVT onset was more than those with VTE. Thus, the ratio of VTE onset at antepartum were high in comparison with at postpartum (67.9% vs. 32.1%; Table 4).

In the 30 years between 1966 and 1995 in the United States [18], the incidence of VTE was more than five times higher after delivery (511.2 per 100,000) than before delivery (95.8 per 100,000), and the incidence of VTE (151.8 per 100,000) was more than three times higher than that of PTE (47.9 per 100,000). In general, antepartum PTE is less common than postpartum PTE. In the period 1966–1995 in the United States, the incidences of PTE rose from 10.6 to 159.7 per 100,000 [18]. In the 1991–2000 study in Japan [6], of 127 women with DVT, 64 (50.4%) had antepartum onset and 63 (49.6%) had postpartum onset, and of 76 women with PTE, 17 (22.4%) had antepartum onset and 59 (77.6%) had postpartum onset. In comparison with antepartum PTE, the odds ratio of postpartum PTE was 3.47 (95% confidence interval [CI], 2.02–5.95; $p < 0.0001$). In 2018 (our study), those were 1.80 (95% CI, 1.04–3.11) and 3.91 (95% CI, 2.65–5.76), respectively. Thus, obstetricians should be strongly encouraged to administer antepartum thromboprophylaxis to decrease incidence of antepartum DVT in Japan.

Between 1966 and 1995 in the United States [18], the incidence of postpartum PTE decreased by more than 50%. In a 2004–2014 study in the United States [10], the incidence of postpartum DVT decreased by 10% (from 32 to 29 per 100,000), and the incidence of postpartum PTE increased 14% (from 14 to 16 per 100,000). In the 1991–2000 study in Japan [6, 7], 63 women had postpartum DVT and 59 had postpartum PTE. Between the time of that study and ours, the incidence of postpartum DVT in Japan decreased 25% (from 14.4 to 10.8 per 100,000), and that of postpartum PTE decreased 9.6% (13.5 to 12.2 per 100,000; Fig. 1B). However, these trends were not significantly different ($p = 0.1803$ and $p = 0.6147$).

The 2004–2014 study in the United States [10] had no data about the incidence of antepartum VTE (DVT or PTE). In the 1991–2000 study in Japan and our study, the incidences of antepartum PTE were similar (3.9 to 6.8 per 100,000; $p = 0.0962$); however, the incidence of antepartum DVT increased 187% (14.7 to 42.2 per 100,000, $p < 0.0001$) (Fig. 1A).

It is possible that the finding of an increase in antepartum DVT might be attributable to the bias of the surveillance questionnaire. In the 1991–2000 study in Japan, the data were obtained from 102

institutions, which included 68 university hospitals and 34 general hospitals [6, 7]. In our study, the 666 institutions included 63 university hospitals (9.5%). However, we suggest that the incidence of antepartum DVT might have increased for four reasons. First, most obstetricians began to pay more attention to antepartum VTE onset and became more skillful at diagnosing DVT after the 2008 publication of guidelines with the recommendation of thromboprophylaxis in Japan. Thus, the number of diagnoses of antepartum DVT would have increased. Second, of the institutions routinely performing thromboprophylaxis, MCs had the lowest frequencies, especially for antepartum thromboprophylaxis (Table 2). To decrease incidence of antepartum VTE, an extensive and systematic campaign to encourage antepartum thromboprophylaxis according to the recommendations in Japan [11, 12] may be necessary. Third, the numbers of pregnant women at high risk for antepartum DVT (e.g., women older than 35 and those who became pregnant after assisted reproductive technology) in Japan have increased. Hyperemesis, antepartum bed rest, and ovarian hyperstimulation syndrome are risk factors for VTE. Fourth, antepartum laboratory tests of coagulation and fibrinolysis are not performed to screen for thrombophilia in Japan. Thus, thrombophilia in pregnant women is sometimes not diagnosed before the occurrence of antepartum or postpartum VTE.

In many cases of antenatal VTE, onset is during the during the third trimester [16, 17] or during the first trimester [19–21]. Thus, antepartum VTE is a significant concern, and thromboprophylaxis has been recommended [21, 22]. The Royal College of Obstetricians and Gynecologists recommends that women who undergo invasive surgery during pregnancy should be given prophylactic anticoagulation therapy [13]. The 1991–2000 study in Japan had no data about the incidence of perioperative VTE (DVT or PTE) during pregnancy [6, 7]. In our study, among the 165 women with antepartum VTE, the incidence of perioperative PTE during pregnancy was significantly higher than that of perioperative DVT. According to the guidelines about thromboprophylaxis in Japan (Table 1), pregnant women who undergo surgery during pregnancy are at moderate risk for VTE; however, they may have to be considered at high risk to decrease the incidence of perioperative VTE (especially PTE) during pregnancy.

Cesarean section is a risk factor for postpartum VTE [23]. The unadjusted relative risk of postpartum VTE after cesarean delivery (versus vaginal delivery) was reported to be 2.6 in 1988 and 1997 in London [4]. In the 1991–2000 study in Japan [6], of the 63 women who had DVT and the 59 women who had postpartum PTE, 28 (44.4%) and 9 (15.3%), respectively, experienced onset after vaginal delivery, and 35 (55.6%) and 50 (84.7%), respectively, experienced onset after cesarean section. After vaginal delivery, the incidence of DVT was 0.008% (28/348,702) and the incidence of VTE was 0.003% (9/348,702); after cesarean section, the incidence of DVT was 0.04% (35/87,382) and the incidence of VTE was 0.06% (50/87,382). The odds ratios of postpartum DVT and PTE after cesarean section were 4.99 (95% CI, 3.04–8.20) and 22.2 (95% CI, 10.9–45.1), respectively, in comparison with those after vaginal delivery (both $ps < 0.0001$). The odds ratios were high comparison with those in our study, respectively.

In a 2004–2014 study in the United States [10], the incidence of DVT by cesarean section decreased 40% (from 94 to 56 per 100,000 deliveries); however, the incidence of PTE by cesarean section was not observed to decrease (20, 30, and 23 per 100,000 deliveries in 2012, 2013, and 2014, respectively). In

Japan, the incidences of DVT and PTE after cesarean section in the 1991–2000 study were similar to those in our study; however, the incidence of both DVT and PTE after cesarean section decreased 32.7% (from 97.3 to 65.5 per 100,000; $p = 0.0214$; Fig. 1C). Thus, performing thromboprophylaxis after cesarean section in Japan would be safe and effective.

In the 2004–2014 study in the United States [10], the incidence of neither DVT nor PTE after vaginal deliveries decreased. In Japan, the incidences of DVT and PTE after vaginal delivery in the 1991–2000 study were similar to those in our study (Fig. 1D). Thromboprophylaxis after vaginal delivery by women at high risk for VTE should be promoted more extensively among obstetricians to decrease the incidence of VTE after delivery.

In the 1991–2000 study in Japan [6, 7], none of the 127 pregnant women with DVT died; however, of 76 pregnant women with PTE, 11 (14.5%) died. The rate of mortality from PTE was 0.0025% (11/436,084; Fig. 1E). In our study, the mortality rate among pregnant women with PTE was 7.1% (4/56), and the incidence of maternal death from VTE was 0.0014% (4/295,961; Fig. 1E). The frequencies in the 1991–2000 study in Japan ($p = 0.2688$) and in our study ($p = 0.4307$) were similar.

To our knowledge, this is the first study to demonstrate that the incidences of other VT and ATE onset among pregnant women. In the present study, the frequencies were very low (8.8 and 1.4 per 100,000, respectively). Furthermore, no woman was died from other VT or ATE. Thus, there might be few obstetricians who considered the incidences of other VT and ATE onset among pregnant women. Further studies are required to determine the risk factors of other VT or ATE onset among pregnant women.

Our study had some strength. First, the selection bias of the institutions was low because the surveillance questionnaire was sent to all 2299 hospitals or maternal clinics reported to treat deliveries in Japan. Second, we had access to the data about incidence of perioperative VTE during pregnancy, which was reported by few previous studies. Finally, we were able to describe the relations between VTE onset and the type of institutions.

This study, however, also had some limitations. First, the surveillance questionnaire did create the potential for bias. Second, we had no detailed information about the patients' backgrounds, e.g., age, times of previous deliveries, history of thrombophilia or previous VTE, number of gestational weeks at delivery, number of gestational weeks at onset of antepartum VTE, number of postpartum days at VTE onset, and whether thromboprophylaxis was performed. Finally, the data for only 1 year (in 2018) were available. Thus, our results alone could not describe the trend of incidence and mortality of VTE. However, we compared them with the incidence of VTE found in a previous study in Japan.

Conclusion

Thromboprophylaxis should be promoted more extensively among obstetricians to decrease the incidence of VTE, inasmuch as the incidences of antepartum and postpartum VTE have increased in Japan.

Declarations

Ethics approval and consent to participate

The institutional review board of Hokkaido University Hospital (No. 018-280) approved the present study.

Consent for publication

Not applicable.

Availability of data and materials

To protect the privacy and anonymity of the participants, the data analyzed in the current study are not publicly available.

Competing interests

The authors declare that they have no competing interests.

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Author contributors:

MM wrote the manuscript, researched data, conceived and designed the study.

AI, TA, and TK contributed to the discussion and reviewed/edited the manuscript.

MM conducted the data analysis and drafted the initial version of the manuscript.

All authors contributed to data interpretation, critically revised the manuscript, had full access to the data in the study, and take responsibility for the integrity and accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that persons who did not meet the criteria have been omitted from the list of authors. All authors read and approved the final manuscript.

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Patient consent for publication

All the patients provided informed consent to participate in this study.

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Figures

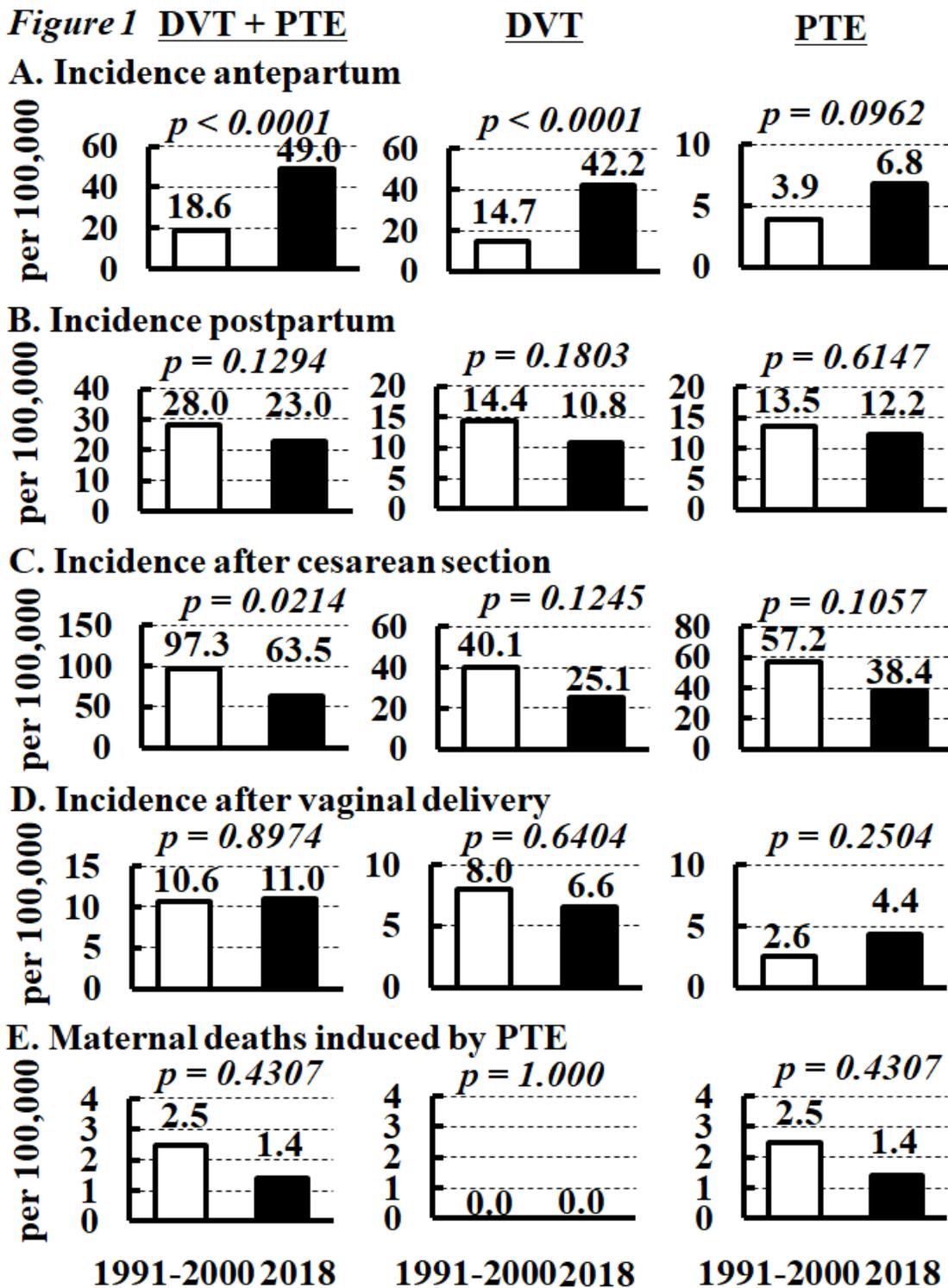


Figure 1

Incidence of deep vein thrombosis (DVT) and/or pulmonary thromboembolism (PTE) in Japan A, Incidence of antepartum DVT or PTE. B, Incidence of postpartum DVT or PTE. C, Incidence of DVT or PTE after cesarean section. D, Incidence of DVT or PTE after vaginal delivery. E, Rates of mortality from PTE. □, The incidence of DVT or PTE in the 1991–2000 study [5]; ■, the incidence of DVT or PTE in this study (2018).