Endometriosis and Recurrent Pregnancy Loss as New Risk Factors for Venous Thromboembolism during Pregnancy and Post-Partum: The JECS Birth Cohort

Mayumi Sugiura-Ogasawara[1] Takeshi Ebara[2] Taro Matsuki[2] Yasuyuki Yamada[2,3] Toyonori Omori[4,5] Yosuke Matsumoto[1] Sayaka Kato[2,6] Hirohisa Kano[2] Takahiro Kurihara[2] Shinji Saitoh[6] Michihiro Kamijima[2] and the Japan Environment & Children's Study (JECS) Group

[1] Department of Obstetrics and Gynecology, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan
[2] Department of Occupational and Environmental Health, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan
[3] Graduate School of Health and Sports Science, Juntendo University, Chiba, Japan
[4] Department of Health Care Policy and Management, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan
[5] National Center for Child Health and Development, Tokyo, Japan
[6] Department of Pediatrics and Neonatology, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan

Address for correspondence Mayumi Sugiura-Ogasawara, MD, PhD, Department of Obstetrics and Gynecology, Graduate School of Medical Science, Nagoya City University, Mizuho-ku, Nagoya 4678601, Japan (e-mail: og.mym@med.nagoya-cu.ac.jp).

Thromb Haemost 2019;119:606–617.

Abstract

Background Since venous thromboembolism (VTE) is one of the causes of maternal mortality, several guidelines recommend prophylaxis using low molecular weight heparin for women in high-risk groups. The number of large population-based studies examining predictors for VTE has been limited, and there has been no study based on a Japanese population.

Objective Our objective was to examine VTE risk factor during the pregnancy and post-partum period.

Materials and Methods A nationwide birth cohort study known as the 'Japan Environment and Children's Study (JECS)' was conducted by the Ministry of the Environment. The subjects consisted of 103,070 pregnancies recruited by the JECS between January 2011 and March 2014. Pregnant women completed the questionnaires during the first and second/third trimester. Their medical records were transcribed by physicians or research coordinators at registration, just after delivery and at 1 month after delivery.

Results The frequency of VTE was 7.5 per 10,000 pregnancies (77 of 103,070) during the pregnancy and post-partum period. After the adjustment of multiple covariates for each factor, endometriosis and recurrent pregnancy loss (RPL) were identified as novel independent risk factors for VTE. Adjusted odds ratios were as follows: 2.70 (95% confidence interval, 1.21–6.00) for endometriosis and 6.13 (2.48–15.16) for RPL. Threatened abortion, threatened pre-term birth, pre-term birth and caesarean section were ascertained to be risk factors for VTE.

Conclusion Careful attention should be given to novel predictors, such as endometriosis and a history of RPL, to prevent VTE during the pregnancy and post-partum period.

Keywords
- venous thromboembolism
- birth cohort study
- pregnancy
- post-partum
- recurrent pregnancy loss

received
October 11, 2018
accepted after revision
December 17, 2018

DOI https://doi.org/10.1055/s-0039-1677733.
ISSN 0340-6245.

Introduction

It is well known that pregnancy and puerperium is associated with venous thromboembolism (VTE). The frequency of post-partum VTE was reported to be 7.2 per 10,000 deliveries in an English cohort registered between 1997 and 2014 and 7.9 in a Swedish cohort registered between 2005 and 2011.[1] Since VTE is one of the causes of maternal mortality, several guidelines recommend prophylaxis using low molecular weight heparin (LMWH) for women in the high-risk group.[2,3] The strongest risk factor is a previous episode.[2,3] The recurrence rate of withholding heparin was 2.4% in 125 pregnant women with previous VTE, 0% in 44 women without thrombophilia and 5.9% in 51 women with thrombophilia and/or previous episode of idiopathic thrombosis.[4] Pregnant women who have had two or more episodes, one episode plus thrombophilia associated with anti-phospholipid antibodies, protein C (PC), protein S (PS) or an antithrombin (AT) deficiency, and one episode plus a history of VTE in a first-degree relative are all included in the highest risk group.[2,3] The second highest risk group includes women with an isolated episode during bed rest, dehydration and surgery, thrombophilia or with a complication such as heart disease, lung disease, systemic lupus erythematosus (SLE), cancer, inflammatory bowel disease or nephrotic syndrome.[2,3,5] The third highest group includes women with an age $\geqq$ 35 years, a body mass index (BMI) of $>$ 30 kg/m^2, a smoker, parity $\geqq$ 3, a systemic infection, gross varicose veins, paraplegia, pre-eclampsia, hyperemesis, ovarian hyperstimulation syndrome, multiple pregnancies, use of artificial reproductive technology, caesarean section and post-partum haemorrhage.[2,3,5] Accordingly, LMWH is recommended for pregnant women with three or more of these risk factors.

However, both the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines and the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines have recommended that LMWH use should be decided upon after discussion between two or more doctors in the case of the second and third highest risk groups since these guidelines were based on expert opinion due to limited evidence concerning the effect of thromboprophylaxis during pregnancy.[2,3,6]

The Japan Society of Obstetrics and Gynecology (JSOG) drew up guidelines in 2014 that conformed to the RCOG and ACCP guidelines due to a lack of evidence in Japan.[7] Before April 2014, thromboprophylaxis was performed according to the previous guidelines, under which an episode of VTE, thrombophilia, age $\geqq$ 35 years, a caesarean section and obesity were considered to be risk factors for Japanese women.[8] For the highest risk group, low dose unfractionated heparin was recommended for women with a past episode of VTE or thrombophilia who underwent a caesarean section during the post-partum period. Unfractionated heparin or intermittent pneumatic compression was recommended for older obese women after caesarean section or for women with an episode of VTE or thrombophilia after vaginal delivery in the high-risk group. There has been no study of VTE risk factors in Japanese women during the pregnancy and post-partum period. Therefore, it was considered necessary to examine these factors because the frequency of VTE is smaller in Japanese populations than in Caucasian population and the frequency of thrombophilia depends on race.[9]

We have conducted a nationwide population-based birth cohort study known as the 'Japan Environment and Children's Study (JECS)', a project planned by the Ministry of the Environment, Government of Japan.[10–14] The study subjects consisted of 104,102 registered children or foetuses recruited during the first 3 years of the JECS, and the babies are now being followed up for 13 years mainly to examine the influence of the environment on the foetus.

This is the first birth cohort used to examine the frequency of VTE and to determine VTE risk factors during the pregnancy and post-partum period in a Japanese population.

Materials and Methods

Study Design and Participants

Pregnant women were recruited by the JECS between January 2011 and March 2014. Eligibility criteria for expectant mothers were as follows: that they (1) resided at the time of recruitment in any of the study areas selected by 15 regional JECS centres located countrywide; (2) had an expected delivery date after August 1, 2011; and (3) were capable of comprehending the Japanese language and completing the self-administered questionnaire.[10–14] The sample size has been calculated in the JECS protocol by the Ministry of the Environment.[15] In principle, pregnant women completed the questionnaires during the first (MT1) and second/third trimester (MT2). Their medical records were transcribed by physicians or research coordinators at registration (DrT1), just after delivery (Dr0m) and at 1 month after delivery (Dr1m).

This study was based on the jecs-ag-20160424 dataset, which includes 104,102 registered children (foetuses and embryos), and was released restrictively to all concerned in June 2016. The second and third children of multiple pregnancies were excluded and these numbered 1,003 (0.96%). Twenty-nine participants (0.03%) withdrew their consent completely. Finally, 103,070 pregnancies were included in the main analysis. The mean (standard deviation [SD]) age at registration was 30.7 (5.1) years. The mean (SD) gestational weeks at registration was 14.0 (5.7) weeks. The JECS population has been recognized as representative of the pregnant women in Japan.[11]

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions. Written informed consent was obtained from all participating women.

Data Collection

The first questionnaire (MT1) included socio-demographic characteristics, medical histories, the details of all previous pregnancies and exercise habits.

The socio-economic status was assessed by the education level and annual household income in the second questionnaire (MT2). The MT2 included lifestyle details.

The first medical record transcript (DrT1) included maternal age, gestational weeks at registration, maternal body weight, height, conception and details of all previous pregnancies (vaginal delivery/caesarean delivery/miscarriage/induced abortion/stillbirth).

The Dr0m included maternal age, gestational weeks at miscarriage and delivery, single/multiple pregnancies, live birth/stillbirth, miscarriage/induced abortion, male/female, birth weight, vaginal/caesarean delivery, pregnancy complications and perinatal outcome.

VTE was described in the Dr0m and in the third medical record transcription (Dr1m).

Exposures and Covariates

Potential exposures were compiled from medical and obstetrical histories as well as from information on gynaecological diseases, obstetric complications and lifestyle.

Potential covariates were maternal age at registration (categorized as $<$ 20, 20–29, 30–39, $\geqq$ 40 years), BMI (categorized as $<$ 18.5, 18.5–25.0, $\geqq$ 25.0), the presence/absence of in vitro fertilization and embryo transfer (IVF-ET), smoking status and income level (categorize as $<$ 200, 200–$<$ 400, 400–$<$ 600, 600–$<$ 800, 800–$<$ 1,000 JPY $\times$ 10,000 [1 US $ = 114.66 JPY, November 13, 2018]).

Statistical Analysis

Details of potential exposures are listed in ►**Supplementary Table S1** (available in the online version).

Frequencies for discrete data between VTE and each factor were counted with proportion. To compare their respective distributions, a Fisher's exact test was performed. Crude odds ratios (ORs) for all exposures were calculated and multiple logistic regression analyses were further conducted to determine what kind of exposures was predictive of VTE after controlling for maternal age, BMI, the presence/absence of IVF-ET, smoking status and income level. In case the observed number of each factor and VTE was less than 6, adjusted ORs were not calculated because of potential biases depending on the number of cases in the less frequencies.

All calculations were conducted using SPSS version 23 and 24 (IBM Corp., Japan), and a p-value of $<$ 0.05 was regarded as statistically significant.

Results

The frequency of VTE was 7.5 per 10,000 pregnancies (77 of 103,070) during the pregnancy and post-partum period. The presence/absence of VTE according to each factor is shown in ►**Tables 1** and **2**. Age, BMI, the presence of IVF-ET, smoking status and income level were significantly associated with VTE.

After the adjustment of multiple covariates for each factor, endometriosis and recurrent pregnancy loss (RPL) were judged to be novel independent predictors for VTE (►**Table 3**). Adjusted ORs were as follows: 2.70 (95% confidence interval [CI], 1.21–6.00) for endometriosis and 6.13 (2.48–15.16) for RPL. There was no statistically significant risk related to any of the listed medical histories or lifestyle other than those mentioned above.

Regarding pregnancy complications and outcomes, oligohydramnios might be a novel independent predictor for VTE though adjusted ORs were not shown since the number was less than 6 (►**Table 4**). Threatened abortion, threatened pre-term birth, pre-term birth at $<$ 37 weeks and caesarean section remained significantly associated with VTE. Adjusted ORs were as follows: 3.61 (95% CI, 2.16–6.02) for threatened abortion, 2.98 (1.83–4.86) for threatened pre-term birth, 2.64 (1.30–5.36) for pre-term birth both at $<$ 37 weeks and 2.19 (1.32–3.63) for caesarean section.

There was no association with hyperemesis or mild hypertensive disorders of pregnancy (HDP) with VTE. The association with a history of placenta praevia, adenomyosis and PCOS, pre-term birth $<$ 34 weeks' gestation, severe HDP, placenta praevia, abruptio placenta, multiple pregnancy and VTE were unclear in this study because the sample size was relatively small. There were no cases of VTE in patients with a history of stroke, myocardial infarction, congenital heart disease, SLE, Crohn's disease, ulcerative colitis, nephrotic syndrome or various forms of cancer.

Discussion

In the present cohort, we found endometriosis and three or more pregnancy losses as novel risk factors for VTE.

Endometriosis is characterized by endometrial-like tissue outside the uterine and is a major contributor to pelvic pain and infertility.[16] This is the first study that we know of to show that endometriosis is a VTE risk factor. In fact, there was one study in which no episode of deep vein thrombosis and VTE occurred after laparoscopic surgery in a group of 266 patients in which 21% had endometriosis.[17] Lesions and activated macrophages can secrete pro-inflammatory cytokines such as interleukin-1β, interleukin-6, interleukin-8 and tumour necrosis factor α in the peritoneal cavity of patients with endometriosis.[16] These pro-inflammatory cytokines might trigger VTE during pregnancy.

With regard to RPL, to our knowledge, this is the first study to show that a history of RPL has a direct predictive value for assessing VTE risk. Stillbirth was not included in eight women with both a history of RPL and VTE, though stillbirth is well-known to be a strong risk factor for post-partum VTE.[1] RPL and VTE are considered to be associated with acquired and inheritable thrombophilia such as AT deficiency, PC deficiency, PS deficiency and homozygous factor V (FV) Leiden.[18] Clinical criteria for anti-phospholipid syndrome (APS) include thrombosis, recurrent miscarriage, intrauterine foetal death and early-onset pre-term birth following pre-eclampsia or placental insufficiency.[19] Patients with APS received combined therapy of low dose aspirin and heparin, and this applied to 162 women in the present cohort with APS. RPL was an independent predictor when APS was used as a covariate (not shown). Recently, 472 variants in 187 genes have been reported to be associated with RPL.[20] A meta-analysis revealed a significant association between RPL and 21 variants, including loss due to thrombophilia with ORs of 0.51 to 2.37. Thrombophilia related to FV Leiden mutation, pro-thrombin mutation,

Table 1 The presence/absence of venous thromboembolism according to each factor

	Factors	*N*	%		Venous thromboembolism		*p*-Value[a]
		(Missing data)			Absence	Presence	
Medical histories	Atopic dermatitis	98,766	95.8	Absence	83,178	60	0.207
		(4,304)	(4.2)	Presence	15,512	16	
	Asthma	98,766	95.8	Absence	87,905	64	0.194
		(4,304)	(4.2)	Presence	10,785	12	
	Collagen disease	98,766	95.8	Absence	98,560	76	–
		(4,304)	(4.2)	Presence	130	0	
	Autoimmune disease	98,766	95.8	Absence	98,548	76	–
		(4,304)	(4.2)	Presence	142	0	
	SLE	98,766	95.8	Absence	98,618	76	–
		(4,304)	(4.2)	Presence	72	0	
	RA	98,766	95.8	Absence	98,483	76	–
		(4,304)	(4.2)	Presence	207	0	
	IDDM	98,766	95.8	Absence	98,614	76	–
		(4,304)	(4.2)	Presence	76	0	
	NIDDM	98,766	95.8	Absence	98,556	76	–
		(4,304)	(4.2)	Presence	134	0	
	Gestational diabetes	98,766	95.8	Absence	97,950	75	0.436
		(4,304)	(4.2)	Presence	740	1	
	Hyperthyroidism	98,766	95.8	Absence	97,635	76	–
		(4,304)	(4.2)	Presence	1,055	0	
	Hypothyroidism	98,766	95.8	Absence	97,714	75	0.530
		(4,304)	(4.2)	Presence	976	1	
	Anaemia	98,766	95.8	Absence	80,446	60	0.555
		(4,304)	(4.2)	Presence	18,244	16	
	Hypertension	98,766	95.8	Absence	98,220	76	–
		(4,304)	(4.2)	Presence	470	0	
	Hyperlipidaemia	98,766	95.8	Absence	98,206	76	–
		(4,304)	(4.2)	Presence	484	0	
	Stroke	98,766	95.8	Absence	98,579	76	–
		(4,304)	(4.2)	Presence	111	0	
	Myocardial infarction	98,766	95.8	Absence	98,628	76	–
		(4,304)	(4.2)	Presence	62	0	
	Congenital heart disease	98,766	95.8	Absence	98,387	76	–
		(4,304)	(4.2)	Presence	303	0	
	Kawasaki disease	98,766	95.8	Absence	98,271	76	–
		(4,304)	(4.2)	Presence	419	0	
	Depression	98,766	95.8	Absence	95,701	72	0.295
		(4,304)	(4.2)	Presence	2,989	4	
	Dysautonomia	98,766	95.8	Absence	95,044	72	0.366
		(4,304)	(4.2)	Presence	3,646	4	
	Anxiety disorder	98,766	95.8	Absence	95,904	71	0.064
		(4,304)	(4.2)	Presence	2,786	5	
	Gastritis	98,766	95.8	Absence	90,166	65	0.097
		(4,304)	(4.2)	Presence	8,524	11	

(*Continued*)

Table 1 (*Continued*)

	Factors	*N*	%		Venous thromboembolism		*p*-Value[a]
		(Missing data)			Absence	Presence	
	Gastric ulcer	98,766	95.8	Absence	96,998	73	0.142
		(4,304)	(4.2)	Presence	1,692	3	
	Irritable colon	98,766	95.8	Absence	97,152	75	1.000
		(4,304)	(4.2)	Presence	1,538	1	
	Crohn's disease	98,766	95.8	Absence	98,655	76	–
		(4,304)	(4.2)	Presence	35	0	
	Ulcerative colitis	98,766	95.8	Absence	98,468	76	–
		(4,304)	(4.2)	Presence	222	0	
	Fatty liver	98,766	95.8	Absence	98,446	76	–
		(4,304)	(4.2)	Presence	244	0	
	Chronic nephritis	98,766	95.8	Absence	98,349	76	–
		(4,304)	(4.2)	Presence	341	0	
	Nephrotic syndrome	98,766	95.8	Absence	98,599	76	–
		(4,304)	(4.2)	Presence	91	0	
	Breast cancer	98,766	95.8	Absence	98,635	76	–
		(4,304)	(4.2)	Presence	55	0	
	Cervical cancer	98,766	95.8	Absence	97,883	75	0.464
		(4,304)	(4.2)	Presence	807	1	
	Endometrial cancer	98,766	95.8	Absence	98,682	76	–
		(4,304)	(4.2)	Presence	8	0	
	Gastric cancer	98,766	95.8	Absence	98,687	76	–
		(4,304)	(4.2)	Presence	3	0	
	Colorectal cancer	98,766	95.8	Absence	98,679	76	–
		(4,304)	(4.2)	Presence	11	0	
	Blood cancer	98,766	95.8	Absence	98,650	76	–
		(4,304)	(4.2)	Presence	40	0	
	Other cancers	98,766	95.8	Absence	98,515	76	–
		(4,304)	(4.2)	Presence	175	0	
Pregnancy histories	Pregnancy loss (total number)	99,687	96.7	Absence	76,885	50	**0.012**
		(3,383)	(3.3)	Presence	22,725	27	
	Pregnancy loss (once)	94,645	91.8	Absence	76,885	50	0.343
		(8,425)	(8.2)	Presence	17,695	15	
	Pregnancy loss (twice)	80,842	78.4	Absence	76,885	50	0.333
		(22,228)	(21.6)	Presence	3,903	4	
	Pregnancy loss (three times or more)	78,070	75.7	Absence	76,885	50	< **0.001**
		(25,000)	(24.3)	Presence	1,127	8	
	Hypertensive disorders of pregnancy	98,766	95.8	Absence	96,791	76	–
		(4,304)	(4.2)	Presence	1,899	0	
	Gestational diabetes	98,766	95.8	Absence	98,223	76	–
		(4,304)	(4.2)	Presence	467	0	
	Abruptio placentae	98,766	95.8	Absence	98,455	75	0.166
		(4,304)	(4.2)	Presence	235	1	
	Ectopic pregnancy	98,766	95.8	Absence	97,742	75	0.520
		(4,304)	(4.2)	Presence	948	1	

Table 1 (*Continued*)

	Factors	*N*	%		Venous thromboembolism		*p*-Value[a]
		(Missing data)			Absence	Presence	
	Placenta praevia	98,766	95.8	Absence	98,216	74	0.052
		(4,304)	(4.2)	Presence	474	2	
	Hydatidiform mole	98,766	95.8	Absence	98,262	76	–
		(4,304)	(4.2)	Presence	428	0	
Gynaecological disease	Menstrual disorder	98,766	95.8	Absence	87,529	68	1.000
		(4,304)	(4.2)	Presence	11,161	8	
	Endometriosis	98,766	95.8	Absence	95,088	69	**0.021**
		(4,304)	(4.2)	Presence	3,602	7	
	Uterine fibroids	98,766	95.8	Absence	92,671	67	**0.049**
		(4,304)	(4.2)	Presence	6,019	9	
	Adenomyosis	98,766	95.8	Absence	98,355	74	**0.028**
		(4,304)	(4.2)	Presence	335	2	
	Uterine anomaly	98,766	95.8	Absence	98,408	76	–
		(4,304)	(4.2)	Presence	282	0	
	Ovarian tumour	98,766	95.8	Absence	95,267	74	1.000
		(4,304)	(4.2)	Presence	3,423	2	
	Polycystic ovarian syndrome	98,766	95.8	Absence	96,477	71	**0.028**
		(4,304)	(4.2)	Presence	2,213	5	
Lifestyle	Strong exercise during pregnancy	96,753	93.9	No	93,448	72	0.325
		(6,317)	(6.1)	Yes	3,229	4	
	Moderate exercise during pregnancy	96,091	93.2	No	72,207	64	**0.049**
		(6,979)	(6.8)	Yes	23,809	11	
	Walking during pregnancy	95,424	92.6	No	27,018	25	0.298
		(7,646)	(7.4)	Yes	68,333	48	
	Night shift work during pregnancy	97,035	94.1	No	88,910	70	1.000
		(6,035)	(5.9)	Yes	8,049	6	
	Breakfast during pregnancy	97,064	94.2	Everyday	69,100	58	0.374
		(6,006)	(5.8)	Not everyday	27,888	18	
	Working h/wk (MT1)	59,428	57.7	0 h	37,614	28	0.995
		(43,642)	(42.3)	0–35 h	21,770	16	
	Working h/wk (MT1)	63,449	61.6	0 h	37,614	28	0.878
		(39,621)	(38.4)	36–45 h	25,789	18	
	Working h/wk (MT1)	49,807	48.3	0 h	37,614	28	0.277
		(53,263)	(51.7)	> 46 h	12,152	13	
	Working h/wk (MT2)	64,615	62.7	0 h	45,672	33	1.000
		(38,455)	(37.3)	0–35 h	18,896	14	
	Working h/wk (MT2)	68,246	66.2	0 h	45,672	33	0.663
		(34,824)	(33.8)	36–45 h	22,522	19	
	Working h/wk (MT2)	55,240	53.6	0 h	45,672	33	0.311
		(47,830)	(46.4)	> 46 h	9,525	10	

Abbreviations: IDDM, insulin-dependent diabetes mellitus; MT1, maternal questionnaires during the first trimester; MT2, maternal questionnaires during the second/third trimester; NIDDM, non-insulin-dependent diabetes mellitus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
[a]The *p*-value was not calculated when expected frequency is less than 1.

Table 2 The presence/absence of venous thromboembolism according to each factor

Factors	*N*	%		Venous thromboembolism		*p*-Value[d]
	(Missing data)			Absence	Presence	
Threatened abortion	100,818	97.8	Absence	88,624	52	< **0.001**
	(2,252)	(2.2)	Presence	12,117	25	
Threatened pre-term labour	100,818	97.8	Absence	80,909	47	< **0.001**
	(2,252)	(2.2)	Presence	19,832	30	
Hyperemesis	97,070	94.2	Absence	16,745	11	0.648
	(6,000)	(5.8)	Presence	80,249	65	
Early miscarriage (< 12 wk gestation)[a]	99,614	96.6	Absence	99,130	76	–
	(3,456)	(3.4)	Presence	408	0	
Stillbirth (≥ 12 wk gestation)[b]	100,048	97.1	Absence	99,130	76	0.478
	(3,022)	(2.9)	Presence	841	1	
Pre-term birth < 37 wk gestation[c]	99,475	96.5	Absence	94,090	67	**0.020**
	(3,595)	(3.5)	Presence	5,309	9	
Pre-term birth at 34–36 wk gestation[c]	98,196	95.3	Absence	94,090	67	0.539
	(4,874)	(4.7)	Presence	4,035	4	
Pre-term birth < 34 wk gestation[c]	95,436	92.6	Absence	94,090	67	**0.003**
	(7,634)	(7.4)	Presence	1,274	5	
Placenta praevia[c]	99,519	96.6	Absence	98,777	75	0.400
	(3,551)	(3.4)	Presence	666	1	
Abruptio placentae[c]	99,519	96.6	Absence	99,009	75	0.283
	(3,551)	(3.4)	Presence	434	1	
Adherent placenta[c]	99,519	96.6	Absence	99,209	76	–
	(3,551)	(3.4)	Presence	234	0	
Premature rupture[c]	99,519	96.6	Absence	90,648	68	0.545
	(3,551)	(3.4)	Presence	8,795	8	
Oligohydramnios[c]	99,519	96.6	Absence	98,169	72	**0.017**
	(3,551)	(3.4)	Presence	1,274	4	
Mild hypertensive disorders of pregnancy[c]	99,519	96.6	Absence	97,141	74	0.696
	(3,551)	(3.4)	Presence	2,302	2	
Severe hypertensive disorders of pregnancy[c]	99,519	96.6	Absence	98,469	72	**0.007**
	(3,551)	(3.4)	Presence	974	4	
Uterine infection	100,818	97.8	Absence	100,008	75	0.109
	(2,252)	(2.2)	Presence	733	2	
Caesarean section[c]	99,165	96.2	Vaginal	79,785	49	**0.001**
	(3,905)	(3.8)	Caesarean	19,304	27	
SFD (< 10%)[c]	99,360	96.4	Absence	89,385	69	1.000
	(3,710)	(3.6)	Presence	9,899	7	
Multiple pregnancy	100,733	97.7	Single	99,670	74	**0.040**
	(2,337)	(2.3)	Multiple	986	3	

Abbreviation: SFD, small for dates.
[a]Stillbirth (≥ 12 weeks' gestation) and artificial abortion were excluded from analyses.
[b]Early miscarriage (< 12 weeks' gestation) and artificial abortion were excluded from analyses.
[c]Miscarriage and artificial abortion were excluded from analyses.
[d]The *p*-value was not calculated when expected frequency is less than 1.

MTHFR and *ANXA5* single-nucleotide polymorphisms is reported to be associated with RPL.[20,21] Recent large cohort study proved that the rate of VTE within 42 days of an induced abortion was 3.0 per 10,000 women (hazard ratio, 0.16, 95% CI, 0·12–0·22) when compared with women in the live birth cohort, whose VTE rate was 18.5 per 10,000 women.[22] The risk might be due to pathologies common to RPL and VTE.

Table 3 An association of medical histories, gynaecological disease and lifestyle with venous thromboembolism

	Factors	Crude ORs (95% CI)	*p*-Value	Adjusted ORs[a] (95% CI)	*p*-Value
Medical histories	Atopic dermatitis	1.43 (0.82–2.48)	0.204	1.58 (0.89–2.82)	0.119
	Asthma	1.53 (0.83–2.83)	0.178	1.55 (0.81–2.96)	0.188
	Gestational diabetes	1.77 (0.25–12.71)	0.573	–	–
	Hypothyroidism	1.34 (0.19–9.61)	0.774	–	–
	Anaemia	1.18 (0.68–2.04)	0.565	1.22 (0.68–2.21)	0.506
	Depression	1.78 (0.65–4.87)	0.263	–	–
	Dysautonomia	1.45 (0.53–3.97)	0.471	–	–
	Anxiety disorder	2.42 (0.98–6.01)	0.056	–	–
	Gastritis	1.79 (0.94–3.39)	0.074	1.80 (0.92–3.53)	0.089
	Gastric ulcer	2.36 (0.74–7.48)	0.146	–	–
	Irritable colon	0.84 (0.12–6.06)	0.865	–	–
	Cervical cancer	1.62 (0.23–11.65)	0.633	–	–
Pregnancy histories	Pregnancy loss (total number)	**1.83 (1.14–2.92)**	**0.012**	1.42 (0.84–2.39)	0.186
	Pregnancy loss (once)	1.30 (0.73–2.32)	0.368	1.11 (0.59–2.06)	0.755
	Pregnancy loss (twice)	1.58 (0.57–4.37)	0.382	–	–
	Pregnancy loss (three times or more)	**10.92 (5.16–23.08)**	**< 0.001**	**6.13 (2.48–15.16)**	**< 0.001**
	Abruptio placentae	5.59 (0.77–40.34)	0.088	–	–
	Ectopic pregnancy	1.38 (0.19–9.90)	0.752	–	–
	Placenta praevia	**5.60 (1.37–22.88)**	**0.016**	–	–
Gynaecological disease	Menstrual disorder	0.92 (0.44–1.92)	0.829	0.93 (0.42–2.03)	0.851
	Endometriosis	**2.68 (1.23–5.83)**	**0.013**	**2.70 (1.21–6.00)**	**0.015**
	Uterine fibroids	**2.07 (1.03–4.15)**	**0.041**	1.73 (0.84–3.58)	0.139

(*Continued*)

Table 3 (*Continued*)

	Factors	Crude ORs (95% CI)	*p*-Value	Adjusted ORs[a] (95% CI)	*p*-Value
	Adenomyosis	**7.94 (1.94–32.46)**	**< 0.001**	–	–
	Ovarian tumour	0.75 (0.19–3.07)	0.691	–	–
	Polycystic ovarian syndrome	**3.07 (1.24–7.61)**	**0.015**	–	–
Lifestyle	Strong exercise during pregnancy	1.61 (0.59–4.40)	0.356	–	–
	Moderate exercise during pregnancy	**0.52 (0.28–0.99)**	**0.046**	0.62 (0.33–1.19)	0.154
	Walking during pregnancy	0.76 (0.47–1.23)	0.264	0.72 (0.43–1.19)	0.199
	Night shift work during pregnancy	0.95 (0.41–2.18)	0.898	1.03 (0.44–2.39)	0.954
	Breakfast during pregnancy	0.77 (0.45–1.31)	0.330	0.86 (0.48–1.54)	0.607
	Working h/wk (MT1) (0 h vs. 1–35 h)	0.99 (0.53–1.83)	0.968	0.82 (0.42–1.60)	0.562
	Working h/wk (MT1) (0 h vs. 36–45 h)	0.94 (0.52–1.70)	0.831	0.77 (0.40–1.50)	0.443
	Working h/wk (MT1) (0 h vs. 46 h)	1.44 (0.74–2.78)	0.280	1.28 (0.62–2.63)	0.500
	Working h/wk (MT2) (0 h vs. 1–35 h)	1.03 (0.55–1.92)	0.937	0.82 (0.41–1.64)	0.575
	Working h/wk (MT2) (0 h vs. 36–45 h)	1.17 (0.66–2.05)	0.591	0.95 (0.50–1.82)	0.884
	Working h/wk (MT2) (0 h vs. 46 h)	1.45 (0.72–2.95)	0.301	1.53 (0.72–3.25)	0.274

Abbreviations: BMI, body mass index; CI, confidence interval; IVF-ET, in vitro fertilization and embryo transfer; MT1, maternal questionnaires during the first trimester; MT2, maternal questionnaires during the second/third trimester; OR, odds ratio; VTE, venous thromboembolism.
[a]Adjusted for maternal age at registration, BMI, the presence/absence of IVF-ET, smoking and income. Only crude ORs were shown when the number of presence of both factor and VTE was less than 6.

The frequency of VTE was found to be 7.5 per 10,000 pregnancies in the present Japanese population registered between 2011 and 2014. It was similar to that in Caucasian population,[1] but VTE has been speculated to be less frequent in the Japanese population due to the fact that no FV Leiden and pro-thrombin mutations were found in the Japanese population.[9] The frequency of PS deficiency was higher in the Japanese population because of a domestic mutation known as PS-Tokushima (K196E) which has a frequency of 1.8%.[23]

According to the old guidelines, thromboprophylaxis with the use of unfractionated heparin was speculated to be common for post-partum women with a previous episode of VTE or thrombophilia or for older obese women post-partum after a caesarean section that took place between 2011 and 2014.[8] After April 2014, thromboprophylaxis during pregnancy was introduced into the JSOG guidelines.[7] Thus, the effect of thromboprophylaxis during pregnancy might be small in this analysis, but we should consider that some portion of patients with an unexplained RPL may have received a combination of low dose aspirin and unfractionated heparin even though there was no recorded evidence.[24] Actually, 267 and 1,609 women in the two groups above received heparin and low dose aspirin in the present cohort. However, any indication of treatment after VTE, prophylaxis for VTE or prevention of APS or gestational weeks at the start of heparin therapy was not available. This is one of the limitations of this study.

Associations with pre-term birth, HDP, uterine infection, multiple pregnancies and caesarean section with VTE were reported in the previous studies.[2,3,5] A recent risk prediction model showed that emergency caesarean delivery, stillbirth, varicose veins, pre-eclampsia and post-partum infection were the strongest predictors of post-partum VTE.[1] A pre-conceptional history of VTE was reportedly associated with an

Table 4 An association between pregnancy complication and venous thromboembolism

Factors	Crude ORs (95% CI)	*p*-Value	Adjusted ORs[a] (95% CI)	*p*-Value
Threatened abortion	**3.52 (2.18–5.67)**	**< 0.001**	**3.61 (2.16–6.02)**	**< 0.001**
Threatened pre-term labour	**2.60 (1.65–4.12)**	**< 0.001**	**2.98 (1.83–4.85)**	**< 0.001**
Hyperemesis	1.23 (0.65–2.34)	0.521	1.21 (0.62–2.38)	0.573
Stillbirth (≥ 12 wk gestation)	1.55 (0.22–11.17)	0.663	–	–
Pre-term birth < 37 wk gestation[b]	**2.38 (1.19–4.78)**	**0.015**	**2.64 (1.30–5.36)**	**0.007**
Pre-term birth 34–36 wk gestation[b]	1.39 (0.51–3.82)	0.521	–	–
Pre-term birth < 34 wk gestation[b]	**5.51 (2.22–13.70)**	**< 0.001**	–	–
Placenta praevia[b]	1.98 (0.28–14.24)	0.499	–	–
Abruptio placentae[b]	3.04 (0.42–21.93)	0.270	–	–
Premature rupture[b]	1.21 (0.58–2.52)	0.606	1.14 (0.52–2.50)	0.744
Oligohydramnios[b]	**4.28 (1.56–11.73)**	**0.005**	–	–
Mild hypertensive disorders of pregnancy[b]	1.14 (0.28–4.65)	0.854	–	–
Severe hypertensive disorders of pregnancy[b]	**5.62 (2.05–15.40)**	**< 0.001**	–	–
Uterine infection	3.64 (0.89–14.85)	0.072	–	–
Caesarean section[b]	**2.28 (1.42–3.64)**	**< 0.001**	**2.19 (1.32–3.63)**	**< 0.001**
SFD (< 10%)[b]	0.92 (0.42–1.99)	0.825	0.95 (0.41–2.20)	0.899
Multiple pregnancy	**4.10 (1.29–13.02)**	**0.017**	–	–

Abbreviations: BMI, body mass index; CI, confidence interval; IVF-ET, in vitro fertilization and embryo transfer; OR, odds ratio; SFD, small for dates; VTE, venous thromboembolism.

[a]Adjusted for maternal age at registration, BMI, the presence/absence of IVF-ET, smoking and income. Only crude ORs were shown when the number of presence of both factor and VTE was less than 6.

[b]Miscarriage and artificial abortion were excluded from analyses.

increased risk of pre-eclampsia, stillbirth and placental abruption.[25] These might also be induced by common genetic factors.

An association with oligohydramnios was not confirmed by a logistic model because of the small sample size. The major limitation was that there was no distinction made between VTE during pregnancy and that occurring post-partum. Data on gestational weeks at the VTE occurrence were also not available. This might be a reason why hyperemesis were not associated with VTE in this study. Thus, we could not dismiss these associations. The majority of women were recruited at 14 weeks' gestation, therefore, we should keep in mind that we did not cover all early miscarriages or hyperemesis.

Endometriosis and a history of RPL were found to be novel risk factors for VTE. Endometriosis and RPL affect 6 to 10% and 4.2% of women of reproductive age, respectively.[16,26] Consequently, we should pay careful attention to novel predictors, such as endometriosis and RPL, to prevent VTE in pregnant women.

What is known about this topic?

- Venous thromboembolism (VTE) prophylaxis during pregnancy and post-partum is recommended for women in high-risk groups.
- The strongest risk factor is a previous episode. Thrombophilia, an age ≧ 35 years, obesity, a smoker, parity ≧ 3, a systemic infection, gross varicose veins, paraplegia, pre-eclampsia, hyperemesis, multiple pregnancies, caesarean section, stillbirth and post-partum haemorrhage were considered to be risk factors.
- The number of large population-based studies examining predictors for VTE has been limited, and there has been no study based on a Japanese population.

What does this paper add?

- Endometriosis and recurrent pregnancy loss (RPL) were identified as novel independent risk factors for VTE.
- Threatened abortion, threatened pre-term birth, preterm birth and caesarean section were ascertained to be risk factors for VTE.

Authors' Contributions

The JECS group conducted the nationwide study project. M.S.O. designed the present study, analysed the data and wrote the first draft of the manuscript. T.E. organized the study team and was responsible for obtaining and analysing the data. M.K., a member of the JECS Steering Committee, was responsible for data acquisition and supervision of the study. M.K. and T.O. took the initiative in the launch of the Aichi regional sub-cohort of JECS. T.M. analysed the data. Y.Y., T.O., Y.M., S.K. and S.S. were responsible for data acquisition. All authors interpreted the data, contributed to the writing of the manuscript and revised it critically for important intellectual content.

Note

Data sharing is not permitted by the JECS due to a government policy restricting the deposition of data containing personal information. See the reference for more details.[12]

Funding

This study was funded by the Ministry of the Environment, Government of Japan.

Conflict of Interest

M.S.-O. received grants from the Japanese Ministry of Education, Science, and Technology for conducting studies on the topic of RPL in the different patient population, and payment for lectures from Kaken Pharmaceutical Co. Ltd., Kissei Pharmaceutical Co., Aska Pharmaceutical Co. Ltd., Sekisui Medical Co. Ltd. and Siemens Japan. The remaining authors report no conflict of interest.

Acknowledgements

We would like to express our gratitude to all of the JECS participants and all obstetricians in the 15 areas.

The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the Ministry of the Environment.

The chief members of the Japan Environment and Children's Study (JECS) as of 2017 are the National Institute for Environmental Studies, Tsukuba (principal investigator, Toshihiro Kawamoto); the National Center for Child Health and Development, Tokyo (Hirohisa Saito); Hokkaido University, Sapporo (Reiko Kishi); Tohoku University, Sendai (Nobuo Yaegashi); Fukushima Medical University, Fukushima (Koichi Hashimoto); Chiba University, Chiba (Chisato Mori); Yokohama City University, Yokohama (Shuichi Ito); University of Yamanashi, Chuo (Zentaro Yamagata); University of Toyama, Toyama (Hidekuni Inadera); Nagoya City University, Nagoya (Michihiro Kamijima); Kyoto University, Kyoto (Takeo Nakayama); Osaka University, Suita (Hiroyasu Iso); Hyogo College of Medicine, Nishinomiya (Masayuki Shima); Tottori University, Yonago (Yasuaki Hirooka); Kochi University, Nankoku (Narufumi Suganuma), University of Occupational and Environmental Health, Kitakyushu (Koichi Kusuhara); and Kumamoto University, Kumamoto (Takahiko Katoh).

References

1 Sultan AA, West J, Grainge MJ, et al. Development and validation of risk prediction model for venous thromboembolism in postpartum women: multinational cohort study. BMJ 2016;355:i6253
2 Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest 2012;141:691–736
3 Royal College of Obstet Gynecol. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. RCOG Green-top Guideline No. 37a;2015
4 Brill-Edwards P, Ginsberg JS, Gent M, et al. Recurrence of Clot in This Pregnancy Study Group. Safety of withholding antepartum heparin in women with a previous episode of venous thromboembolism. N Engl J Med 2000;343:1439–1444
5 Sultan AA, Tata LJ, West J, et al. Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom. Blood 2013;121(19):3953–3961
6 Bain E, Wilson A, Tooher R, Gates S, Davis LJ, Middleton P. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev 2014; 2(02):CD001689
7 Minakami H, Maeda T, Fujii T, et al. Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2014 edition. J Obstet Gynaecol Res 2014;40(06):1469–1499
8 Editorial Committee on Japanese Guidelines for Prevention of Venous Thromboembolism. Japanese guidelines for prevention of venous thromboembolism. Tokyo, Japan: Medical Front International Limited; 2004:47–54
9 James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol 2006;194 (05):1311–1315
10 Kawamoto T, Nitta H, Murata K, et al; Working Group of the Epidemiological Research for Children's Environmental Health.

Rationale and study design of the Japan Environment and Children's Study (JECS). BMC Public Health 2014;14:25
11 Michikawa T, Nitta H, Nakayama SF, et al; Japan Environment and Children's Study Group. Baseline profile of participants in the Japan Environment and Children's Study (JECS). J Epidemiol 2018; 28(02):99–104
12 Suzuki K, Shinohara R, Sato M, Otawa S, Yamagata Z. Association between maternal smoking during pregnancy and birth weight: an appropriately adjusted model from the Japan Environment and Children's Study. J Epidemiol 2016;26(07):371–377
13 Japan Environment and Children's Study. Tokyo: Ministry of the Environment. Available at: http://www.env.go.jp/en/chemi/hs/jecs/ [updated August 12, 2016]. Accessed August 16, 2016
14 Ishitsuka K, Nakayama SF, Kishi R, et al. Japan Environment and Children's Study: backgrounds, activities, and future directions in global perspectives. Environ Health Prev Med 2017;22(01):61
15 National Institute for Environmental Studies/National Centre for Japan Environment and Children's Study, Japan Environment and Children's Study (JECS) Study Protocol (ver. 1.4). Available at: https://www.env.go.jp/chemi/ceh/outline/data/jecs-study_protocol_14_en.pdf. Accessed January 18, 2017
16 Giudice LC. Clinical practice. Endometriosis. N Engl J Med 2010; 362(25):2389–2398
17 Ageno W, Manfredi E, Dentali F, et al. The incidence of venous thromboembolism following gynecologic laparoscopy: a multicenter, prospective cohort study. J Thromb Haemost 2007;5(03): 503–506
18 Croles FN, Nasserinejad K, Duvekot JJ, Kruip MJ, Meijer K, Leebeek FW. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and Bayesian meta-analysis. BMJ 2017;359:j4452
19 Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4 (02):295–306
20 Pereza N, Ostojić S, Kapović M, Peterlin B. Systematic review and meta-analysis of genetic association studies in idiopathic recurrent spontaneous abortion. Fertil Steril 2017;107(01):150–159
21 Hayashi Y, Sasaki H, Suzuki S, et al. Genotyping analyses for polymorphisms of ANXA5 gene in patients with recurrent pregnancy loss. Fertil Steril 2013;100(04):1018–1024
22 Liu N, Vigod SN, Farrugia MM, Urquia ML, Ray JG. Venous thromboembolism after induced abortion: a population-based, propensity-score-matched cohort study in Canada. Lancet Haematol 2018;5(07):e279–e288
23 Kimura R, Honda S, Kawasaki T, et al. Protein S-K196E mutation as a genetic risk factor for deep vein thrombosis in Japanese patients. Blood 2006;107(04):1737–1738
24 Kaandorp SP, Goddijn M, van der Post JAM, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N Engl J Med 2010;362(17):1586–1596
25 Hansen AT, Schmidt M, Horváth-Puhó E, et al. Preconception venous thromboembolism and placenta-mediated pregnancy complications. J Thromb Haemost 2015;13(09):1635–1641
26 Sugiura-Ogasawara M, Suzuki S, Ozaki Y, Katano K, Suzumori N, Kitaori T. Frequency of recurrent spontaneous abortion and its influence on further marital relationship and illness: the Okazaki Cohort Study in Japan. J Obstet Gynaecol Res 2013;39(01):126–131