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Original Article

Incidence of and risk factors for thromboembolism during pregnancy and postpartum: A 10-year nationwide population-based study

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ABSTRACT

Objective: Knowledge of the incidence of pregnancy-related thromboembolism and its risk factors is clinically important because thromboembolism is the leading cause of maternal death. However, there are insufficient large population-based studies on this topic. The purpose of this study was to estimate the incidence of and identify the risk factors for thromboembolism during pregnancy and puerperium.
Materials and methods: We analyzed data from 2007 to 2016 using the Health Insurance Review and Assessment Service (HIRA) database. Women who gave birth in the Republic of Korea were identified. Thromboembolism was defined as the simultaneous presence of both the diagnostic and test codes. Risk factors for thromboembolism were identified using logistic regression.
Results: A total of 1,188 delivery episodes with thromboembolism were extracted from 4,243,393 delivery episodes. The incidence of thromboembolism was 0.28 per 1,000 deliveries, and it increased over the 10-year period. The incidence of antepartum thromboembolism was 0.1 per 1,000 deliveries (418 cases), and the incidence of postpartum thromboembolism was 0.18 per 1,000 deliveries (770 cases). Thromboembolism was associated with ovarian hyperstimulation syndrome, low socioeconomic status, multiple birth, cesarean birth, preeclampsia, postpartum hemorrhage, placenta previa, advanced maternal age, hyperemesis and primiparity. The factors associated with mortality from thromboembolism were cesarean birth and preterm premature rupture of membranes.
Conclusion: The incidence of pregnancy-related thromboembolism increased over the 10-year study period. Low socioeconomic status, ovarian hyperstimulation syndrome, cesarean delivery and premature rupture of membranes were high-risk factors. This study provides an important reference for thromboprophylaxis for pregnancy-related thromboembolism.

Introduction

Thromboembolism, including venous thromboembolism (VTE), deep vein thrombosis (DVT) of the leg or pelvis and its complication, pulmonary embolism (PE), and arterial thromboembolism, can develop into a life-threatening state. It is reasonable to expect that VTE is the leading cause of maternal mortality; death from VTE accounts for 9.2% of all maternal deaths in the United States [1] because VTE is 4- to 5-fold more common in pregnant women than in nonpregnant women [2]. Virchow's triad of factors underlying venous thrombosis—hypercoagulability, venous stasis, and vascular damage—all occur during pregnancy and continue into the postpartum period [3]. In addition to mortality, VTE can cause chronic morbidity. Long-term morbidity, called postthrombotic syndrome, manifests as various degrees of edema, pain and eczema, reduces quality of life and is associated with substantial health care costs [4]. There are reported associations between thrombotic risk factors and poor pregnancy outcomes, such as preeclampsia, intrauterine growth retardation, fetal death and recurrent miscarriage, in addition to the health consequences of these outcomes [5].

As the proportion of high-risk pregnancies increases due to increases in advanced maternal age and obesity, the morbidity and

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mortality of pregnancy-related thromboembolism is expected to increase accordingly. The incidence of pregnancy-related VTE is reported to be 0.08 to 1.76 per 1000 deliveries [6–9]. Possible reasons for the wide range include differences in study design and the methods used to validate the diagnosis.

Arterial thromboembolism usually occurs via platelet-mediated thrombosis after the erosion or rupture of atherosclerotic plaque [10]. The most severe clinical manifestations are stroke and cardiac ischemia. Although studies of pregnancy-related arterial thromboembolism are very limited, the risk of stroke and cardiac ischemia has been reported to be 3- to 4-fold higher among pregnant women than in the nonpregnant population [7,11].

Recently, guidelines for recommending thromboprophylaxis when there are a certain number of risk factors related to thromboembolism have been presented [12,13]. However, because the absolute incidence of pregnancy-related thromboembolism is low, a large population-based study with the power to identify the prevalence of and risk factors for pregnancy-related thromboembolism is needed. In addition, population-based studies, particularly in Asian populations, are insufficient to identify the exact risks and predictors of pregnancy-related thromboembolism.

The aim of our study was to estimate the incidence of and risk factors for thromboembolism during pregnancy and postpartum from 2007 to 2016 using Korean National Health Insurance Data with sufficient power to properly assess this rare event.

Materials and methods

Sample

The Republic of Korea implements compulsory national health insurance by law. Therefore, approximately 98% of Koreans are covered by national health insurance [14]. The Health Insurance Review & Assessment Service (HIRA) is a national institute that reviews and assesses the medical expenses charged by medical institutions and orders the National Health Insurance Corporation (NHIC) to pay medical expenses to medical institutions. Therefore, the HIRA contains most of the medical information (sex, age, diagnosis code, operation code, drug code, admission and discharge date, diagnostic test code, type of medical insurance, size of medical institution, treatment fee and death in hospital) for health insurance subscribers [14]. This study was conducted using HIRA data from 2007 to 2016.

Subject selection

To extract patient data, we used the Korean Standard Classification of Diseases (KCD) 6th edition (diagnostic code), which is a modification of the International Classification of Diseases (ICD) 10th edition, and the Health Care Medical Care Costs 2017 (codes for procedures such as surgery, clinical procedures, and diagnostic tests), which was produced by the Ministry of Health and Welfare.

Women who gave birth were identified by the simultaneous presence of both a delivery diagnostic code [O80 (single spontaneous delivery), O81 (single delivery by forceps and vacuum extractor), O82 (single delivery by cesarean section), O83 (other assisted single delivery) or O84 (multiple delivery)] as the primary or secondary diagnosis and a delivery procedure code [normal delivery (R4351, R4353, R4356, R4358), induction delivery (R3131, R3133, R3136, R3138), forceps delivery (R3141, R3143, R3146, R3148), vaginal birth after cesarean section (R4380), breech delivery (R4361, R4362) or cesarean section (R4517, R4514, R4519, R4508, R4520, R4502)].

We defined thromboembolism as the presence of a thromboembolism diagnostic code [G08 (intracranial and intraspinal phlebitis and thrombophlebitis), I26 (pulmonary embolism), I63 (cerebral infarction), I74 (arterial embolism and thrombosis), I80 (phlebitis and thrombophlebitis), I82 (other venous embolism and thrombosis), O22 (venous complications in pregnancy), O87 (venous complications in the puerperium), O88.2 (obstetric blood-clot embolism)] and a thromboembolism test code [D-dimer (B1721, B1722), computed tomography (HA8xx, HA4xx), magnetic resonance imaging (HE1xx, HE2xx, HE3xx, HE4xx, HF1xx, HF2xx, HF2xx, HF2xx, HAxx) or primary angiography (HAxx)]. Arterial thromboembolic events were defined as I63 (cerebral infarction) or I74 (arterial embolism and thrombosis), and VTE was defined using other diagnostic codes.

The pregnancy period was defined as 280 days before delivery to 1 day before delivery, and the postpartum period was defined as the delivery day to 56 days after the delivery day. The pregnancy and postpartum period was defined as 280 days before the delivery day to 56 days after the delivery day.

Cases with a thromboembolism diagnostic code before the pregnancy period were excluded from the group of pregnancy or postpartum thromboembolism cases.

If the same woman had thromboembolism diagnostic codes in each of two separate pregnancies, two thromboembolism cases were counted.

To perform the logistic regression and analyze the risk factors for thromboembolism, we extracted cases with more than one specific diagnostic code [preeclampsia (O14.x), gestational diabetes mellitus (O24.4), hydramnios (O40.x), premature rupture of membranes (O42.x), placenta previa (O44.x), placenta abruptio (O45.x), postpartum bleeding (O72.x), hyperemesis gravidarum (O21.x), ovarian hyperstimulation syndrome (N98.1)] during the pregnancy or postpartum period (from 280 days before the delivery day to 56 days after the delivery day).

Low socioeconomic status (SES) was defined as receiving government support.

A woman with a “death code in the hospital” was defined as dead.

Statistics

All statistical analyses for our study were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). A P-value less than 0.05 was considered significant, and all statistical tests were two-sided. The t-test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical variables. Logistic regression analysis was used to compare the risk of multiple variables. The mean imputation method was utilized for missing values.

Ethics statement

The researcher could not identify individuals by their data because all personal identification numbers were deidentified. Therefore, inclusion in the study could not cause any harm to the insured person. Because this study uses anonymized data by third party, informed consent was not mandatory according to the South Korea's Bioethics and Safety Act. The study protocol and the waiver of informed consent waiver were approved by the Institutional Review Board (IRB) (serial number: GNUCH 2018-11-006) of Gyeongsang National University Changwon Hospital. All methods were performed in accordance with the relevant guidelines and regulations of the institution.

Results

A total of 2,988,651 women who had delivered at least once were extracted from approximately 50 million patients (47~51

million patients from 2007 to 2016) in the HIRA data for 2007–2016 [15]. A total of 4,243,393 delivery episodes were extracted for these women (Fig. 1). During this period, there were 4,242,205 delivery episodes with no thromboembolism and 1,188 delivery episodes with thromboembolism. The mean ages of the two groups were 30.9 ± 0.0 and 32.4 ± 0.1 years, respectively (p-value <0.001) (Table 1). Table 1 shows the characteristics of the delivery cases during this period. The incidence of thromboembolism per 1,000 deliveries was 0.28 (arterial thrombosis: 0.08 per 1,000 deliveries, VTE: 0.2 per 1,000 deliveries). The incidence of thromboembolism during pregnancy was 0.1 per 1,000 deliveries (418 cases), and the incidence of thromboembolism after delivery was 0.18 per 1,000 deliveries (770 cases).

Thromboembolism before and after pregnancy occurred in 51.7% within 3 weeks after delivery and was especially common (32.9%) within a week after delivery (Fig. 2). The incidence of thromboembolism before and after pregnancy tended to increase over the years (p-value 0.072) and was significantly increased during pregnancy (p-value 0.049) (Fig. 3).

Pulmonary embolism accounted for the largest portion of total thromboembolism (31%) and thromboembolism in puerperium (41%). However, in cases of thromboembolism in pregnancy, phlebitis and thrombophlebitis accounted for the largest portion (33.5%) (Table 2). In the logistic regression analysis after adjustment for age group (in 5-year intervals), SES and other variables, age group {odds ratio, 1.41; 95% confidence interval, 1.31–1.5; P < 0.001) and low SES (OR, 3.01; CI, 2.07–4.38; P < 0.001) increased the incidence of thromboembolism (Table 3). This tendency was the same in pregnancy and puerperium. Multiple birth also increased the incidence of thromboembolism before and after delivery (OR, 2.29; CI, 1.79–2.93; P < 0.001). Cesarean section increased the incidence of thromboembolism after delivery (OR, 2.68; CI, 2.29–3.12; P < 0.001). Ovarian hyperstimulation syndrome (OHSS) did not affect the incidence of thromboembolism in puerperium (OR, 1.54; CI, 0.68–3.51; P = 0.304); however, it significantly increased the incidence of thromboembolism in pregnancy (OR, 16.07; CI, 10.17–25.41; P < 0.001). In contrast, preeclampsia increased the incidence of thromboembolism in puerperium (OR, 2.32; CI, 1.47–3.66; P < 0.001) but did not affect the incidence of thromboembolism in pregnancy (OR, 1.86; CI, 0.88–3.94; P = 0.104). Postpartum hemorrhage (PPH) increased the incidence of thromboembolism in puerperium (OR, 2.58; CI, 2.03–3.29; P < 0.001). However, gestational diabetes mellitus (GDM), hydramnios, preterm premature rupture of membranes (PPROM), and placenta abruptio were not associated with thromboembolism.

In the logistic regression analysis of death from thromboembolism after adjustment for age group and SES, cesarean section (OR, 15.29; CI, 4.51–51.89; P < 0.001) and PPROM (OR, 2.75; CI, 1.01–7.44; P = 0.047) were associated with an increased risk of death (Table 4).

Discussion

In our study, the incidence of pregnancy-related thromboembolism was 0.28 per 1000 deliveries. Our study included arterial thromboembolic events, which consist of cerebral infarction and arterial embolism and thrombosis. To the best of our knowledge, studies of pregnancy-related arterial thromboembolism have investigated only data from the United States in 2000–2001 [7,11]. These studies included stroke and myocardial infarction in pregnancy-related arterial thromboembolism, which had a reported incidence of 0.4 per 1,000 deliveries; however, VTE was four times more common than arterial thromboembolism [7]. In our study, arterial thromboembolism accounted for 27.9% of all thromboembolisms. Compared with previous studies, the proportion of arterial thromboembolism was high, but the incidence was low, with 0.08 per 1000 deliveries.

Previously published studies of the incidence of pregnancy-related VTE have reported a wide variation in incidence (0.08–1.76 per 1000 deliveries), possibly due to the differences in the study populations investigated, study design, study size and validity of the data [6–9]. For instance, James et al. reported a pregnancy-related VTE incidence of 1.72 per 1000 deliveries, and our results (0.2 per 1000 deliveries) were much lower than this [6]. Possible reasons for this difference are that Asians have a lower

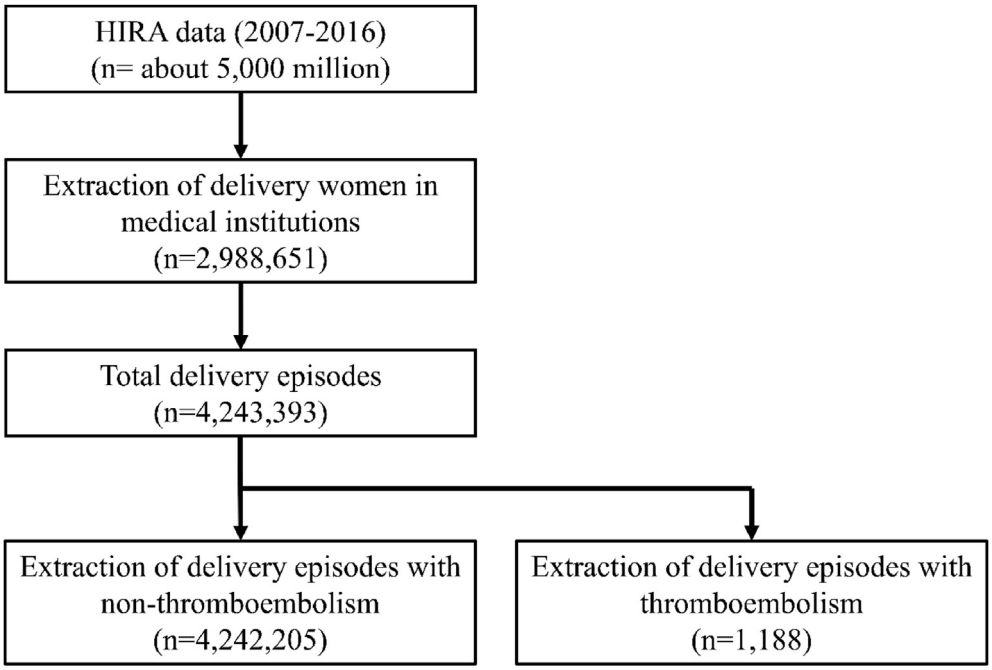

Fig. 1. Flow chart for extracting deliveries and thromboembolisms from HIRA claim data 2007–2016.

Table 1
Characteristics of delivery cases in HIRA claim data 2007–2016.

	No thromboembolism	Thromboembolism	P
Number of women	(N = 2,987,973)	(N = 1,179)	
Number of delivery cases	(N = 4,242,205)	(N = 1,188)	
Age	30.9 ± 0.0	32.4 ± 0.1	<0.001
Age group			<0.001
<25 years	259,697 (6.1%)	54 (4.5%)	
25–35 years	3,217,008 (75.8%)	758 (63.8%)	
≥35 years	765,500 (18.0%)	376 (31.7%)	
Low SES			<0.001
No	4,202,785 (99.1%)	1,160 (97.6%)	
Yes	39,420 (0.9%)	28 (2.4%)	
Normal spontaneous delivery			<0.001
No	2,802,013 (66.1%)	971 (81.7%)	
Yes	1,440,192 (34.0%)	217 (18.3%)	
Forceps or vacuum delivery			0.001
No	3,979,761 (93.8%)	1,114 (96.0%)	
Yes	262,444 (6.2%)	47 (4.0%)	
Cesarean section delivery			<0.001
No	2,693,600 (63.5%)	476 (40.1%)	
Yes	1,548,605 (36.5%)	712 (59.9%)	
Induced labor delivery			<0.001
No	3,266,442 (77.0%)	989 (83.3%)	
Yes	975,763 (23.0%)	199 (16.7%)	
VBAC			0.767
No	4,231,941 (99.8%)	1,185 (99.8%)	
Yes	10,264 (0.2%)	3 (0.2%)	
Breech delivery			0.035
No	4,239,677 (99.9%)	1,185 (99.8%)	
Yes	2,528 (0.1%)	3 (0.2%)	
Cesarean hysterectomy			<0.001
No	4,239,796 (99.9%)	1,181 (99.4%)	
Yes	2,409 (0.1%)	7 (0.6%)	
Primiparous			0.071
No	2,035,713 (48.0%)	539 (45.4%)	
Yes	2,206,492 (52.0%)	649 (54.6%)	
Multiple birth			<0.001
No	4,179,457 (98.5%)	1,104 (92.9%)	
Yes	62,748 (1.5%)	84 (7.1%)	
Preeclampsia			<0.001
No	4,209,554 (99.2%)	1,162 (97.8%)	
Yes	32,651 (0.8%)	26 (2.2%)	
Gestational diabetes mellitus			0.004
No	3,848,603 (90.7%)	1,049 (88.3%)	
Yes	393,602 (9.3%)	139 (11.7%)	
Hydramnios			0.703
No	4,235,759 (99.9%)	1,186 (99.8%)	
Yes	6,446 (0.1%)	2 (0.2%)	
PPROM			0.026
No	3,674,179 (86.6%)	1,055 (88.8%)	
Yes	568,026 (13.4%)	133 (11.2%)	
Placenta previa			<0.001
No	4,197,614 (99.0%)	1,157 (97.4%)	
Yes	44,591 (1.0%)	31 (2.6%)	
Placenta abruptio			0.153
No	4,230,432 (99.7%)	1,182 (99.5%)	
Yes	11,773 (0.3%)	6 (0.5%)	
Postpartum hemorrhage			<0.001
No	4,061,282 (95.7%)	1,103 (92.9%)	
Yes	180,957 (4.3%)	85 (7.1%)	
Hyperemesis			<0.001
No	3,873,806 (91.3%)	1,050 (88.4%)	
Yes	368,399 (8.7%)	138 (11.6%)	
OHSS			<0.001
No	4,233,102 (99.8%)	1,155 (97.2%)	
Yes	9,103 (0.2%)	33 (2.8%)	
Death			<0.001
No	4,241,944 (99.99%)	1,163 (97.7%)	
Yes	278 (0.01%)	27 (2.3%)	

HIRA, Health Insurance Review Agency; SES, socioeconomic status; VBAC, vaginal birth after cesarean section; PPROM, preterm premature rupture of membranes; OHSS, ovarian hyperstimulation syndrome.

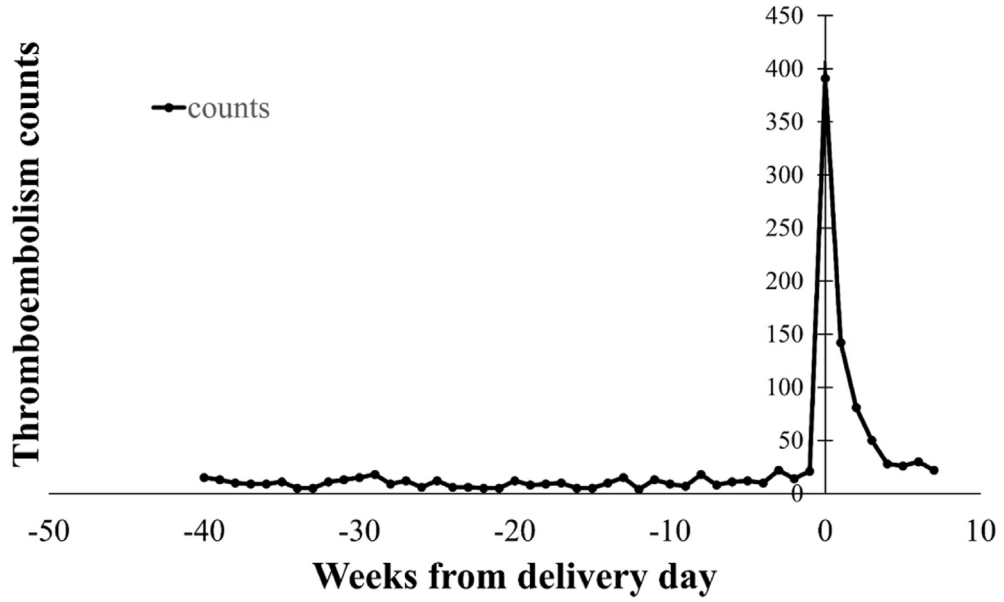

Fig. 2. Number of thromboembolisms by weeks before and after delivery in HIRA claim data 2007–2016.

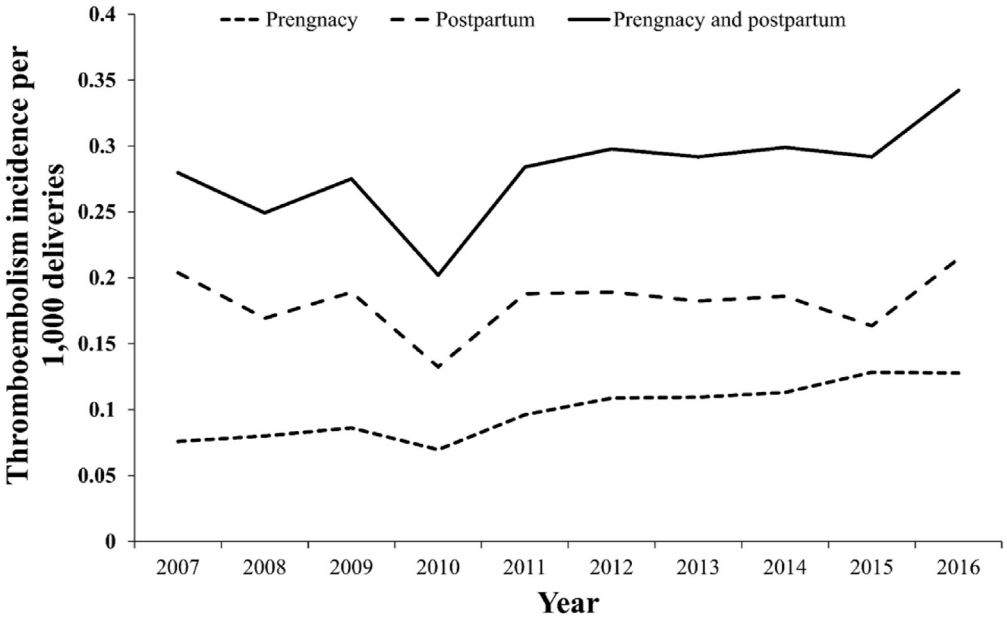

Fig. 3. Number of thromboembolisms by year in HIRA claim data 2007–2016.

prevalence of VTE than Caucasian populations and that our study strictly defined VTE according to the presence of both a diagnostic code and a test code [8]. However, our results are much higher than the incidences reported in previous Korean studies, which were 0.08 per 1000 deliveries in 2006–2010; this may be because the previous study used a narrower definition of VTE than our study and the because the prevalence rate is increasing every year, which the previous study mentioned and which may be reflected in our study, which included more recent data [8].

Our findings are in line with previous studies of the distribution of thromboembolism during different periods of gestation and puerperium [16,17]. Currently, since hospitalization periods are decreasing, clinicians need to educate and counsel patients regarding the clinical features and symptoms of thromboembolism not only during pregnancy but also after delivery.

Risk factors for thromboembolism in the antepartum and postpartum periods

In our study, we found that OHSS was a stronger risk factor for thromboembolism than other factors in the antepartum period (OR 5.98; CI 4.11–8.71) but not in the postpartum period. This finding is consistent with those of previous studies showing that the incidence of first-trimester thromboembolism related to IVF was 0.2%, and it increased to 1.7% among OHSS inpatients [6,18]. Against the background of these results, OHSS is associated with hemoconcentration and a very high level of estradiol. Ascites are common, and in severe cases, pleural fluid also appears. These clinical features, combined with immobilization and a pregnancy-induced hypercoagulable state, may make women with OHSS more vulnerable to thromboembolism.

Table 2
Thromboembolism cases according to disease subcategory in HIRA claim data 2007–2016.

	Total thromboembolism		Thromboembolism in pregnancy		Thromboembolism in puerperium	
	Count	Incidence per 1,000 deliveries	Count	Incidence per 1,000 deliveries	Count	Incidence per 1,000 deliveries
Intracranial and intraspinal phlebitis and thrombophlebitis	3 (0.3%)	0.0007	1 (0.2%)	0.0002	2 (0.3%)	0.0005
Pulmonary embolism	368 (31.0%)	0.0867	46 (11.0%)	0.0108	322 (41.8%)	0.0759
Cerebral infarction	288 (24.2%)	0.0679	131 (31.3%)	0.0309	157 (20.4%)	0.0370
Arterial embolism and thrombosis	44 (3.7%)	0.0104	4 (1.0%)	0.0009	40 (5.2%)	0.0094
Phlebitis and thrombophlebitis	246 (20.7%)	0.0580	140 (33.5%)	0.0330	106 (13.8%)	0.0250
Other venous embolism and thrombosis	84 (7.1%)	0.0198	38 (9.1%)	0.0090	46 (6.0%)	0.0108
Venous complications in pregnancy	58 (4.9%)	0.0137	58 (13.9%)	0.0137	0 (0.0%)	0.0000
Venous complications in the puerperium	42 (3.5%)	0.0099	0 (0.0%)	0.0000	42 (5.5%)	0.0099
Obstetric blood-clot embolism	55 (4.6%)	0.0130	0 (0.0%)	0.0000	55 (7.1%)	0.0130
Total cases	1,188 (100%)	0.2800	418 (100%)	0.0985	770 (100%)	0.1815

HIRA, Health Insurance Review Agency.

Table 3
Logistic regression analysis of thromboembolism in HIRA claim data 2007–2016.

	Thromboembolism		Thromboembolism in pregnancy		Thromboembolism in puerperium	
	Adjusted Model[a]		Adjusted Model[b]		Adjusted Model[a]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age per 5 years	1.41 (1.31,1.50)	<0.001	1.33 (1.18,1.49)	<0.001	1.47 (1.35,1.60)	<0.001
Low SES	3.01 (2.07,4.38)	<0.001	3.55 (1.95,6.47)	<0.001	2.75 (1.70, 4.45)	<0.001
Multiple birth	2.29 (1.79,2.93)	<0.001	2.95 (1.97,4.42)	<0.001	2.26 (1.67,3.07)	<0.001
Cesarean section	2.17 (1.91,2.45)	<0.001			2.68 (2.29,3.12)	<0.001
Primiparous	1.21 (1.07,1.36)	0.002	1.17 (0.95,1.44)	0.139	1.24 (1.07,1.44)	0.005
OHSS	5.98 (4.11,8.71)	<0.001	16.07 (10.17,25.41)	<0.001	1.54 (0.68,3.51)	0.304
Hyperemesis	1.34 (1.12,1.60)	0.001	1.81 (1.38,2.36)	<0.001	1.10 (0.87,1.40)	0.435
Preeclampsia	2.13 (1.44,3.15)	<0.001	1.86 (0.88,3.94)	0.104	2.32 (1.47,3.66)	<0.001
GDM	1.10 (0.92,1.31)	0.299	1.09 (0.80,1.48)	0.596	1.11 (0.89,1.38)	0.345
Hydramnios	0.86 (0.22, 3.45)	0.831	0 (0, 0)	0.953	1.30 (0.33, 5.22)	0.71
PPROM	0.98 (0.81,1.18)	0.817	0.81 (0.60,1.10)	0.183	1.04 (0.83,1.31)	0.71
Placental previa	1.55 (1.08,2.22)	0.017	2.04 (1.12,3.72)	0.021	1.45 (0.93,2.27)	0.102
Placental abruptio	1.25 (0.56,2.79)	0.591			1.51 (0.62, 3.64)	0.361
PPH	1.84 (1.47,2.29)	<0.001			2.58 (2.03,3.29)	<0.001

HIRA, Health Insurance Review Agency; OR, odds ratio; CI, confidence interval; SES, socioeconomic status; OHSS, ovarian hyperstimulation syndrome; GDM, gestational diabetes mellitus; PPROM, preterm premature rupture of membranes; PPH, postpartum hemorrhage.

[a] Thromboembolism = age per 5 years + low SES + multiple birth + cesarean section + primi-parous + OHSS + hyperemesis + preeclampsia + GDM + hydramniosis + PRROM + placental previa + placental abruptio + PPH.

[b] Thromboembolism = age per 5 years + low SES + multiple birth + primiparous + OHSS + hyperemesis + preeclampsia + GDM + hydramniosis + PRROM + placental previa.

Our results are consistent with previously published studies on socioeconomic factors and thromboembolism that suggest that low socioeconomic conditions increase the risk of thromboembolism [19]. Socioeconomic factors can increase the risk of diseases in many ways. However, it is unclear which factors influence the observed differences in the relationship between thromboembolism and socioeconomic status. Our findings should be interpreted with caution because our data could not be related to clinical factors, such as body mass index (BMI).

We found that multiple births increased the risk of thromboembolism more than 2-fold (OR 2.29; CI 1.79–2.93). This result is accordance with a previously published study [6,7,20,21]. The possible reason for these results is that multiple births are more related to gestational hypertension, antenatal hemorrhage and cesarean delivery than singleton pregnancy.

We identified that placenta previa was related to antenatal thromboembolism, and postpartum hemorrhage (PPH) was related to postpartum thromboembolism. Consistent results were obtained in previous studies [6,7,9,21]. In cases of placenta previa or PPH, blood transfusions are common, and the storage and retention of red blood cells can contribute to an increased risk of thrombosis as a result of altered aggregability [22]. In addition, these situations are present in many vascular injuries and imply critical illness.

We have confirmed that preeclampsia is a postpartum but not antenatal risk factor for thromboembolism, which is consistent with previous studies [6,23]. The main causes of this result are vascular endothelial damage and the thrombophilic disorder underlying the pathology of preeclampsia; another possible cause is the limitation of movement during delivery because of the mother's condition during preeclampsia [3].

Risk factors that increase mortality from thromboembolism

In our study, cesarean section not only increased the risk of thromboembolism (OR 2.17, CI 1.91–2.45) but also was, interestingly, identified as a contributing factor that greatly increased the

Table 4
Logistic regression analysis of death from postpartum thromboembolism in HIRA claim data 2007–2016.

	Death from postpartum thrombosis			
	Unadjusted		Adjusted model[a]	
	OR (95% CI)	P	OR (95% CI)	P
Age per 5 years	1.79 (1.16, 2.75)	0.008	1.48 (0.96, 2.29)	0.076
Low SES	4.1 (0.56, 30.21)	0.166	4.219 (0.569, 31.27)	0.159
Multiple birth	0 (0, 0)	0.985	0 (0, 0)	0.988
Cesarean section	13.40 (4.19, 46.13)	<0.001	15.29 (4.51, 51.89)	<0.001
Primiparous	0.86 (0.4, 1.82)	0.688	1.00 (0.45, 2.21)	0.998
OHSS	0 (0, 0)	0.987	0 (0, 0)	0.994
Hyperemesis	0.41 (0.06, 2.98)	0.375	0.42 (0.06, 3.09)	0.393
Preeclampsia	0 (0, 0)	0.984	0 (0, 0)	0.989
GDM	1.70 (0.59, 4.92)	0.327	1.38 (0.47,4.03)	0.555
Hydramnios	0 (0, 0)	0.989	0 (0, 0)	0.995
PPROM	1.47 (0.56, 3.88)	0.437	2.75 (1.01, 7.44)	0.047
Placenta previa	3.62 (0.49, 26.67)	0.207	1.54 (0.21, 11.46)	0.672
Placenta abruptio	0 (0, 0)	0.985	0 (0, 0)	0.994
PPH	1.8 (0.43, 7.58)	0.426	2.34 (0.55, 9.88)	0.249

HIRA, Health Insurance Review Agency; OR, odds ratio; CI, confidence interval; SES, socioeconomic status; OHSS, ovarian hyperstimulation syndrome; GDM, gestational diabetes mellitus; PPROM, preterm premature rupture of membranes; PPH, postpartum hemorrhage.

[a] Death with thromboembolism = age per 5 years + low SES + multiple birth + cesarean section + primiparous + OHSS + hyperemesis + preeclampsia + GDM + hydramniosis + PRROM + placental previa + placental abruptio + PPH.

risk of mortality from thromboembolism (OR 15.29, CI 4.51–51.89). This finding is significant because the cesarean section rate is steadily increasing. Several studies have reported that the incidence of thrombosis is higher in cesarean section than in vaginal delivery, and thromboprophylaxis is recommending following cesarean section in patients with other risk factors [6,7,9,24,25]. Cesarean section increases the risk of thrombosis compared to vaginal delivery because of increased tissue trauma, the additional release of tissue factor and long-term immobilization. In a Scottish study, the risk of thrombosis was greater when emergency cesarean section was performed than in cases of elective cesarean section; additionally, the incidence of postpartum thromboembolism after an emergency cesarean section decreased after the introduction of thromboprophylaxis, whereas there was no difference in the incidence of postpartum thromboembolism after an elective cesarean section [24].

To our knowledge, there is no association between PPROM and the incidence and mortality of pregnancy-related thromboembolism. In our study, PPROM was not associated with the occurrence of thromboembolism but was found to be a risk factor for thrombotic mortality. A possible explanation for this finding is that PPROM increases the risk of infection. This possibility is supported by findings that the incidence of highly suspected and proven sepsis is 7–11% in patients with a prolonged PPROM state [26]. Infection-associated systemic inflammation has been found to be both a cause and a trigger of thromboembolism and to inhibit fibrinolysis [27,28].

Our study has several limitations that should be considered when interpreting the results. First, because we used insurance claims data, we could not rule out the possibility of misclassification, and there was no confirmation of thromboembolism and delivery. However, to overcome this limitation, though not completely, delivery was defined as the simultaneous presence of a diagnostic code and a procedure code, and thromboembolism cases were limited to those with the simultaneous presence of a diagnosis code and a test code. Second, our data do not include patients who died outside the hospital; however, in most cases when a woman of childbearing age dies, she goes to the emergency room, so the influence of deaths outside the hospital seems limited. Third, in this study, only cases that resulted in birth were considered, so we could not confirm whether any of the women died during pregnancy (Table 4 shows the cases of death in puerperium). Fourth, because phlebitis and thrombophlebitis are represented by the common code I80 (phlebitis and thrombophlebitis), phlebitis without thrombosis may be included as venous thromboembolism. However, since the procedure-related phlebitis is represented by T801 (phlebitis following infusion, transfusion and therapeutic injection), the misclassified effect is not significant. It has been reported that thromboembolic events during past pregnancies is a risk factor for the occurrence of thromboembolic events during subsequent pregnancies [29]. However, this study did not consider the occurrence of thromboembolism in previous pregnancies as a risk factor for thromboembolism associated with pregnancy. This is one of the limitations of this study.

In conclusion, using data from a large nationwide database over a 10-year period, we report an incidence of pregnancy-related thromboembolism that demonstrates a significant increase over time. The period of greatest vulnerability to thromboembolism is within 1 week after delivery. Our study identified various risk factors for pregnancy-related thromboembolism, and we confirmed that cesarean section and PPROM were risk factors for death from postpartum thrombosis. We believe this study will provide clinicians with useful information to identify high-risk pregnant and postpartum women who need thromboprophylaxis and will help guide clinical decisions.

Conflicts of interest

The authors report no conflict of interest.

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