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The association between venous thromboembolism during pregnancy and low birth weight: A retrospective cohort study

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Abstract

Background

Among the causes of maternal morbidity and mortality worldwide, venous thromboembolism (VTE) also impacts long-term effects on some organs beyond physical harm of pregnancy. Evidence on the effect of VTE on neonatal outcomes, especially low birth weight (LBW), is still insufficient and contradicting. The objective of this study was to assess the relationship between maternal VTE during pregnancy and LBW in a large national cohort.

Methods

In a retrospective cohort study, we used data from the Sina Health Information System covering 21094 pregnant women who had received standard prenatal care in Mashhad, Iran from March 2017 to September 2025. The exposed group included 10547 women with VTE confirmed that were each individually matched (1:1) to non exposed pregnant women without a record of VTE. The analysis was performed in Stata version 16. Multivariate logistic regression analysis was used to calculate adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for LBW (< 2500 g) confounders such as mothers education, parity, hypertensive disorders, antepartum haemorrhage and previous miscarriage were considered.

Results

Low birth weight was significantly more frequently recorded in a group of infants whose mothers had VTE compared to a group of infants whose mothers did not have VTE (59% compare to 41%, P < 0.001). Even after the adjustment for confounders, VTE remained a powerful independent factor for LBW (AOR = 2.28, 95% CI: 2.08–2.50, P < 0.001). Besides VTE, maternal hypertension was one of the independent predictors included maternal hypertension (AOR = 1.74, 95% CI: 1.50–2.03), vaginal bleeding during pregnancy (AOR = 1.45, 95% CI: 1.15–1.87) and history of recurrent miscarriage (≥ 3 abortions; AOR = 2.22, 95% CI: 1.72–2.86). Conversely, higher maternal education was associated with a protective effect against LBW.

Conclusion

Maternal VTE during pregnancy is a significant and independent risk factor for low birth weight likely mediated through impaired placental perfusion and inflammatory pathways. These findings underscore the need for early risk assessment, timely diagnosis and optimized management of thromboembolic disorders during pregnancy to improve neonatal outcomes. Further studies are warranted to explore mechanistic pathways and evaluate the impact of preventive anticoagulant interventions.

1. Introduction

Thromboembolism is a clinical condition that usually begins with the formation of a blood clot in a vein. This condition includes deep vein thrombosis and pulmonary embolism. The blood clotting system is more active during pregnancy to protect women from excessive bleeding during childbirth. Some women are at higher risk during pregnancy and around the time of delivery, including women with a history of thrombophilia and following cesarean delivery(1). Deep Vein Thrombosis: Deep vein thrombosis (DVT) occurs when a blood clot blocks blood flow in a vein, which can occur after surgery, after trauma, or when a person has been immobile for a long time. Deep vein thrombosis is a deadly and costly condition and one of the leading causes of death in pregnant mothers (2). In the UK, deep vein thrombosis is the leading direct cause of maternal death and the fifth most common cause of death in pregnancy. The risk of venous thrombosis increases by up to 5-fold during pregnancy; in addition, pregnant women are 6–10 times more likely to develop deep vein thrombosis in the same year than non-pregnant women. The incidence is 1 in 1000 pregnancies (2, 3). On the other hand, pregnancy leads to an increase in the complications of deep vein thrombosis. The higher prevalence of deep vein thrombosis in pregnancy is because the physiological changes in pregnancy affect Virchow's triad. Hormonal changes, increased blood coagulation, decreased anticoagulant and fibrinolytic activity are due to the body's preparation for childbirth to prevent bleeding during birth and the weeks after pregnancy, and the main cause of deep vein thrombosis in pregnant women is hyper coagulopathy (4, 5). Pulmonary embolism: A blood clot that blocks blood flow to part of the lungs. Pregnant women are at high risk of pulmonary embolism, and it is a leading cause of death during pregnancy. According to the World Health Organization, it accounts for up to 3% of maternal deaths worldwide (6, 7). This fatal complication is also a relatively common cause of maternal mortality in Iran(8). Pulmonary embolism occurs when a clot that formed days or weeks earlier in the venous system travels to the heart and enters the pulmonary vascular system through the right ventricle(9). According to various studies, the risk of venous thrombosis, the main cause of pulmonary embolism, can increase up to 5 times during pregnancy and up to 60 times in the first three months after delivery compared to normal people. Symptoms of this disease include: unexplained shortness of breath, rapid breathing, chest pain (which worsens with deep breathing), rapid heartbeat, and a feeling of lightheadedness or fainting (10, 11). In Iran, the annual prevalence of this disease has been reported to be about 130 to 395 cases per 1,000 patients (4, 5). The average annual prevalence of DVT in the general population of Iran is estimated to be between 914 and 2780 cases per 100,000 people(12). Although the prevalence of VTE in obstetrics and gynecology patients is not the highest among different patient groups, given the high number of gynecological surgeries and the high cesarean section rate, which accounts for 35% of all deliveries in Iran, which is twice the maximum rate accepted by the World Health Organization, it seems reasonable to say that Iranian female patients deserve much more attention and even a special guideline for VTE prevention(13, 14). Women are up to 5 times more likely to develop thromboembolism than when they are not pregnant. The hypercoagulable state of pregnancy has probably evolved to protect women from excessive bleeding during abortion and childbirth. In developing countries, hemorrhage is the leading cause of maternal death. However, in the United States and other developed countries, embolic disease is the leading cause of maternal death.

The incidence of thrombosis is similar in all three trimesters of pregnancy and also increases in the first 6 weeks postpartum. In addition to mortality and immediate complications, there are long-term complications associated with post-thrombotic syndrome. Most women who suffer from DVT during pregnancy have sequelae ranging from edema and skin changes to recurrent thrombosis and ulcers (11, 15, 16). Pregnancy is one of the most important periods of time that is closely related to the health of the pregnant mother and the baby and requires special care(17). Also, considering the different clinical conditions in pregnancy, as well as the risks of thromboembolism and anticoagulant treatments for the fetus and mother, necessary investigations in this field are important (18). A baby's birth weight is associated with many factors and specific medical conditions that exist or develop during pregnancy(19). According to the World Health Organization definition, babies weighing less than 2500 grams are considered low birth weight(20). This index can be used to interpret past health status and future trajectory. Various genetic and environmental factors can influence this index, which can have different consequences for the child (21, 22). Low birth weight has been consistently reported as one of the most important risk factors for neonatal mortality and one of the leading causes of developmental disorders and neonatal complications (20–24). Given the significant health and economic burden associated with low birth weight, the World Health Organization has prioritized reducing the prevalence of low birth weight as a major public health objective, with a goal of reducing the prevalence of low birth weight by 30% worldwide between 2012 and 2025(25). Identifying and controlling the aforementioned factors in the mother can help reduce the birth of low birth weight infants in subsequent pregnancies. Given the lack of a study investigating the effect of thromboembolism and its treatment in pregnant mothers on low birth weight, we decided to conduct a study aimed at determining the relationship between thromboembolism in pregnant mothers and low birth weight infants.

2. Methods

2.1 Participants and Study Design:

Pregnant women receiving routine prenatal care at health centers affiliated with Mashhad University of Medical Sciences were included in this population-based cohort study. Data were obtained from the Sina Health Information System(26). The study covered the period from March 1, 2017 to September 20 2025. The exposed group in this study were pregnant women with venous thromboembolism who met the inclusion criteria, and pregnant women who were not in terms of venous thromboembolism and were considered as the nonexposed group. Participants in the exposed group were those who were screened using the Thromboembolism Risk Assessment Checklist in an outpatient setting and the disease was not diagnosed by a physician.

2.2 Study variables:

1. Outcome variable: According to the World Health Organization definition, infants weighing less than 2500 grams are considered low birth weight. In the present study, the same amount was considered for low birth weight.

Exposure variable: Gender of the baby - Place of residence - Number of pregnancies of the mother - .2 Blood pressure during pregnancy - Nationality - Education level of the mother -thromboembolism - spotting during pregnancy-History of maternal hospitalization during pregnancy- History of Abortion

2.3Measurement tool:

In this study, the Thromboembolic Risk Assessment Checklist (Revised) was used for the initial assessment of venous thromboembolism (VTE) risk in pregnant women in the outpatient setting. This checklist is a clinical screening tool designed to identify pregnant women at moderate to high risk of thromboembolic events and in need of referral for specialist assessment and possibly initiation of anticoagulant prophylaxis. Given the multifactorial etiology of venous thromboembolism, this checklist categorizes risk factors into four main areas: factors related to medical conditions (such as previous history of VTE, thrombophilia, or specific diseases such as cancer or heart failure); factors related to the general condition of the individual (such as body mass index (BMI), age, and smoking) factors related to the current pregnancy or delivery (such as multiple pregnancy or ovarian hyper stimulation syndrome); and transient or reversible factors (such as systemic infection or immobility). This checklist consists of 17 items, each of which is assigned a score between 1 and 4 based on the strength of its association with the risk of venous thromboembolism. The scoring system is such that the scores of all risk factors present for each individual are added together. Based on the checklist protocol, participants who achieved an overall score of 3 or higher were identified as high-risk individuals and were referred to an internist or gynecologist for final evaluation and decision on the need for anticoagulant therapy. After diagnosis and registration in the Sine system, these individuals were included in the study as the exposed group.(27, 28)

.2.4 Sampling technique and procedure:

The number of people in the exposed and non-exposed groups was equal,10547 people, and for each exposed person, one unexposed person was randomly selected.

2.5 Definitions:

Pregnant women who participated in this study and had a screening score of 3 or more were considered to have a positive venous thromboembolism screening. A score of less than 4 indicates that the individual had a negative venous thromboembolism screening. In the present study, participants were referred to a specialist physician after a positive screening and entered the study after diagnosis.

2.6 Statistical Analysis:

After data collection, the information was coded and subsequently entered into Excel software. It was then transferred to Stata version 16 for analysis purposes. Frequencies and percentages were calculated to describe the characteristics of categories and quantitative variables in both case and control groups. Initially, bivariate analysis including chi-square test was performed to assess the unadjusted relationships between each factor and low birth weight. Variables that were statistically significant were

entered into univariate regression model, then if significant, into multivariate regression model. The final model estimated the adjusted odds ratio (OR) and 95% confidence intervals indicating independent relationships. The final model estimated the adjusted odds ratio (AOR) and 95% confidence intervals indicating independent relationships between variables entered into the model. An alpha level of 0.05 determined statistical significance in the regression analysis. Statistical analysis was performed using Stata software version 16.

2.7 Study inclusion criteria:

1. Live birth

2. Venous thromboembolism screening through a checklist

3. Confirmation of the disease by a specialist physician

4. Completeness of the information related to the present study

3. Results

Univariate analysis in Table 1 revealed that several maternal and neonatal factors were significantly associated with the incidence of low birth weight. Low birth weight was observed more in female infants than in male infants. The level of maternal education was also influential, with the highest frequency of low birth weight infants reported among mothers with a diploma. Also, infants born to Iranian mothers were more likely to have low birth weight than non-Iranian mothers. Location also showed a significant association, with rural and suburban residents having more low birth weight infants than mothers living in metropolitan areas and large cities. In terms of the number of pregnancies, the first pregnancy accounted for the largest share of low birth weight infants. In addition, maternal hospitalization during pregnancy, history of miscarriage, hypertension, and spotting during pregnancy were all associated with an increased likelihood of having a low birth weight infant. Importantly, thromboembolism during pregnancy was significantly associated with low birth weight; among mothers with low birth weight infants, the proportion of thromboembolism was significantly higher than in the group of infants with normal birth weight. In univariate analysis, several variables were significantly associated with the likelihood of low birth weight (LBW); specifically, history of venous thromboembolism was associated with OR=1.53 (95% CI: 1.42–1.66, P<0.001), spotting during pregnancy with OR=1.48 (95% CI: 1.18–1.87, P<0.001), and maternal hypertension with OR=1.82 (95% CI: 1.57–2.12, P<0.001). Also, a history of repeated miscarriages, maternal hospitalization, increased number of pregnancies, Iranian nationality, residence in a village/metropolis or suburb, and female gender of the infant were each significantly associated with LBW (four or more miscarriages: OR=2.01, 95% CI: 1.40–2.70, P<0.001; fourth or more pregnancies: OR=1.37, 95% CI: 1.25–1.51, P<0.001). In the multivariate logistic model and after adjustment for these factors, many of these associations were maintained or strengthened; The clinical significance of thromboembolism was prominent (adjusted OR=2.28, 95% CI: 2.08–2.50, P<0.001), blood pressure and spotting remained independent (blood pressure: OR=1.74, 95% CI: 1.50–2.03, P<0.001;

spotting: OR=1.45, 95% CI: 1.15–1.87, P<0.001), and the dose–response relationship for history of miscarriage and increased parity became more evident in the adjusted model (e.g., triplicate miscarriages: OR=2.22, 95% CI: 1.72–2.86; quadruplet+ pregnancy: OR=3.10, 95% CI: 2.77–3.50; all P<0.001). Instead, higher maternal education appeared to be independently protective (diploma: OR=0.82, higher than diploma: OR=0.86; P<0.001). In summary the results suggest that venous thromboembolism is an independent and strong factor associated with an increased risk of LBW. (Table2)

Table 1: Demographic and risk factors in the two groups of low birth weight and normal weight

Parameter		Normal birth weight	Low birth weight	P-value
Gender	Male	9356 (52)	1481 (48)	<0.001
	Female	8638 (48)	1619 (52)	
Mother's education	Illiterate	4051 (22)	799 (26)	<0.001
	Diploma	10564 (59)	1721 (55)	
	Above the diploma	3379 (19)	580 (19)	
Nationality	Foreign	1715 (10)	241 (8)	<0.001
	Iranian	16279 (90)	2859 (92)	
Place of residence	Village	5013 (28)	900 (29)	<0.001
	Metropolis	4391 (24)	809 (26)	
	Large Cities	3543 (20)	508 (16)	
	Outskirts of the city	5047 (28)	883 (29)	
Number of pregnancies of the mother	First	7499 (42)	1135 (37)	<0.001
	Second	2570 (14)	413 (13)	
	Third	3031 (17)	531 (17)	
	Fourth and more	4894 (27)	1021 (33)	
maternal hospitalization	No	16306 (91)	2728 (88)	<0.001
	Yes	1688 (9)	372 (12)	
History of Abortion	zero	12778 (70)	2113 (68)	<0.001
	First	3509 (20)	630 (20)	
	Second	1206 (7)	218 (7)	
	Third	344 (2)	87 (3)	
	Fourth and more	157 (1)	52 (2)	
Blood pressure	No	17194 (96)	2857 (92)	0.03
	Yes	800 (4)	243 (8)	
spotting during pregnancy	No	17620 (98)	3005 (97)	<0.001
	Yes	374 (2)	95 (3)	
Thromboembolism	No	9279 (52)	1268 (41)	<0.001
	Yes	8715 (48)	1832 (59)	

Table 2. Association between venous thromboembolism and low birth weight

		Univariate regression analysis			Multivariate logistic regression		
Variables	Categories	Odds Ratio	p-value	Confidence Interval	Odds Ratio	p-value	Confidence Interval
Thromboembolism	No	1			1		
	Yes	1.53	<0.001	1.66-1.42	2.28	<0.001	2.5-2.08
spotting during pregnancy	No	1			1		
	Yes	1.48	<0.001	1.87-1.18	1.45	<0.001	1.87-1.15
Blood pressure	No	1			1		
	Yes	1.82	<0.001	1.57-2.12	1.74	<0.001	2.03-1.5
History of Abortion	zero	1			1		
	First	1.08	0.08	1.19-0.98	1.4	<0.001	1.56-1.25
	Second	1.09	0.2	1.27-0.94	1.48	<0.001	1.75-1.25
	Third	1.52	<0.001	1.94-1.20	2.22	<0.001	2.86-1.72
	Fourth and more	2.01	<0.001	2.7-1.4	2.63	<0.001	3.6-1.9
maternal hospitalization	No	1			1		
	Yes	1.31	<0.001	1.48-1.16	1.31	<0.001	1.48-1.16
Number of pregnancies of the mother	First	1			1		
	Second	1.06	0.3	1.19-0.94	1.67	<0.001	1.9-1.4
	Third	1.15	0.01	1.29-1.03	2.13	<0.001	2.4-1.87
	Fourth and more	1.37	<0.001	1.51-1.25	3.1	<0.001	3.5-2.77
Place of residence	Large Cities	1			1		
	Village	1.28	<0.001	1.44-1.14	1.18	<0.001	1.3-1.1
	Metropolis	1.25	<0.001	1.40-1.11	1.34	<0.001	1.51-1.2
	Outskirts of the city	1.22	<0.001	1.37-1.1	1.23	<0.001	1.38-1.1
Nationality	Foreign	1					
	Iranian	1.25	<0.001	1.48-1.1	1.25	<0.001	1.44-1.1

Mother's education	Illiterate	1					
	Diploma	0.82	<0.001	0.9-0.75	0.82	<0.001	0.9-0.7
	Above the diploma	0.87	<0.001	0.91-0.77	0.86	<0.001	72-.9
Gender	Male	1					
	Female	1.18	<0.001	1.27-1.1	1.18	<0.001	1.28-1.1

4. DISCUSSION

The results of the study show that female gender maintained its association after controlling for other factors .The finding that female infants are about 18 percent more likely to be underweight, even after adjusting for other factors, is a consistent, biological pattern. From a causal perspective, this association could be due to a growth advantage in male fetuses, who are genetically predisposed to grow faster and have greater body mass and are more resilient to intrauterine stressors. Also, differences in the hormonal environment and placental function based on fetal gender could produce different growth patterns (29, 30). In the study by Amiri et al., this relationship was also seen, indicating that gender is an unmodifiable but important risk factor in assessing the risk of low birth weight and should be properly adjusted in research models (31). Maternal education is a strong and independent protective factor against low birth weight. In the multivariate model, mothers with a high school diploma were 0.82 times less likely to give birth to a low birth weight infant than mothers with no education, and mothers with more than a high school diploma were 0.86 times less likely to give birth to a low birth weight infant than illiterate mothers. This reduction in risk of approximately 15–18% remained significant even after adjusting for confounding factors such as economic status (partially measured by place of residence in this study) or maternal medical problems. Mothers with higher education generally have better access to and understanding of health information. They better understand the importance of prenatal care, proper nutrition, avoiding harmful substances, and warning signs during pregnancy (32, 33). Examining nationality in this study shows that Iranian mothers are about 25% more at risk of giving birth to a low birth weight baby compared to foreign mothers, and this relationship is statistically significant. In explaining this issue, it can be said that the majority of the immigrants in the study are of Afghan nationality, who are healthier than the female population, or it can be said that this community may mainly include immigrants with a specific socioeconomic status or ethnic and cultural backgrounds similar to Iran, which could affect the results. This result is not consistent with the study by Rezaian and colleagues(34). Living in Village, metropolitan, and Outskirts of the city is independently associated with a higher risk of low birth weight compared with living in large cities. The risk is 18% higher for rural residents, 34% higher for metropolitan residents, and 23% higher for suburban residents. In rural areas, the most important factor is limited access to quality health services and prenatal care (35) in metropolitan areas, a combination of severe air pollution, economic pressures, and the stress of urban life play a major role(36) and in the outskirts of cities, a combination of both deprivation of basic amenities and exposure to environmental pollutants increases the risk(35, 37). The risk of having a low

birth weight baby increases exponentially with the number of pregnancies. In the multivariate model, this risk increases 1.67-fold for the second pregnancy, 2.13-fold for the third pregnancy, and 3.1-fold for the fourth and subsequent pregnancies compared to first-time mothers. In analyzing the cause of this association, it can be said that the accumulated complications from previous pregnancies, such as uterine injuries or weakening of the mother's general health, can have an effect on the number of pregnancies(38). On the other hand, in the social dimension, mothers with repeated pregnancies are often in a poor socioeconomic situation and have less access to health care (39). The results of various studies show that the relationship between the number of pregnancies and low birth weight is in the form of a U-curve, meaning that low birth weight is higher in mothers with one pregnancy and in mothers with more than three pregnancies(40). Hospitalization during pregnancy can be stressful for the mother, causing anxiety and depression. Chronic psychological stress is an independent risk factor for preterm birth and low birth weight. Hospitalization usually indicates a serious medical problem during pregnancy(41). These problems can include complications such as bleeding during pregnancy, gestational hypertension, gestational diabetes, or other medical conditions that directly negatively affect fetal development. In the present study, hospitalization was also a significant independent factor for low birth weight during pregnancy(42). The risk of having a low birth weight baby increases exponentially with the number of previous miscarriages. In the multivariate model, the risk increases 1.4-fold for one miscarriage, 1.48-fold for two miscarriages, 2.22-fold for three miscarriages, and 2.63-fold for four miscarriages, compared to mothers with no history of miscarriage. Women who have had a miscarriage are more likely to experience psychological distress, including depression, anxiety, stress, grief, and guilt (43). These psychological challenges may be triggered or exacerbated by subsequent pregnancies. Research shows that women who have had a miscarriage experience higher levels of pregnancy related anxiety and distress in subsequent pregnancies than women who have not (44, 45). Increased miscarriages also cause anatomical and physiological changes in the pregnant mother, which can lead to low birth weight in subsequent pregnancies. This independent association can be seen in other studies, such as the Brown(46) and Monica Rattler(47) study, which reported a strong association between a history of miscarriage and low birth weight, such that in the Brown study, the risk of low birth weight in other infants increased with an increase in the number of miscarriages. Bleeding in early pregnancy may indicate a threatened miscarriage or ectopic pregnancy, while bleeding in the second and third trimesters is often associated with placental problems, such as placental abruption or placenta Previa. These complications can lead to impaired oxygen and nutrient delivery to the fetus, which directly affects fetal development(48). Bleeding can also cause inflammation and uterine contractions, which increase the risk of premature birth and, consequently, low birth weight (49–51). In the present study, bleeding during pregnancy was also a strong independent factor for low birth weight. The study found that venous thromboembolism was the strongest independent predictor of low birth weight. Based on the results of the multivariate model, mothers with venous thromboembolism were 2.28 times more likely to have a low birth weight than mothers without this condition. From a causal perspective, this strong association can be explained by several mechanisms: venous thromboembolism can lead to the formation of clots in the placental vessels, which disrupts uteroplacental blood flow. This reduction in placental perfusion directly affects the delivery of oxygen and nutrients to the fetus and leads to

intrauterine growth restriction. In addition, inflammatory processes associated with thromboembolism can negatively affect placental function. Also, the underlying disease that led to the thromboembolism itself can also make an independent contribution to fetal growth impairment (52, 53).

Conclusions

This large population based study showed a powerful and independent association of maternal venous thromboembolism in pregnancy with the risk of delivering a low birth weight baby. Women with VTE had over a twofold higher odd of having small OVD infants (< 2500 g), even after adjustment for important maternal, pregnancy and social characteristics. These results indicate PROM due to acute thromboembolic disease may injure uteroplacental perfusion and fetal growth by induced the hypercoagulability and inflammatory response. Clinically, the early identification of thromboembolic risk and timely preventive management including risk-based anticoagualnt strategies may become critical for neonatal outcomes. Systematic VTE risk profiling as part of routine prenatal care, in particular for those with a history of obstetric complications or an underlying thrombophilic disorder, could therefore make an important contribution to the low birth weight burden and related perinatal morbidity. More studies need to investigate the pathophysiological link between maternal thrombosis and placental dysfunction due to these combined effects, and potential benefits of targeted prophylactics in prevention of both maternal and neonatal adversities.

Declarations

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Authors' contributions

AM is the principal investigator and research leader. MN and EM designed the Study and drafted the manuscript and analyzed the data. AM contributed to the conception, design, data interpretation, and revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from Mashhad University of Medical Sciences (Approval Code: IR.MUMS.FHMPM.REC. 1403.179). Informed consent to participate was obtained from all of the participants in the study.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number: not applicable

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