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Evaluation of early pregnancy risk factors for venous thromboembolism in Turkish pregnant women: a prospective study

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Abstract

Objective: Venous thromboembolism (VTE), a condition during pregnancy that manifests as deep vein thrombosis and pulmonary embolism, is the third most common cause of death in 0.01–0.2% pregnant women worldwide each year. Because this risk has increased in pregnant women and is treatable, early diagnosis and treatment would save lives. The aim of this study was to evaluate the early pregnancy risk factors for VTE in Turkish pregnant women.

Methods: In this prospective study, 480 pregnant women between the ages of 18 and 45 years and who applied to our clinic within their first trimester (4–14 weeks) of pregnancy were enrolled in the study. Because the risk factors of the patients were to be determined, there were no exclusion criteria. The antepartum thromboembolism risk parameters were determined according to Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines.

Results: There were 336 (70%) pregnant women in the low-risk group, 62 (12.9%) in the medium-risk group, and 82 (17.1%) in the high-risk group. The permanent parameters within the groups that determined the risk factors were individually evaluated.

Conclusion: Our results indicated that 30% of the study population needed low-molecular-weight heparin (LMWH) prophylaxis, of whom 12.9% were in the medium-risk group, and 17.1% were in the high-risk group. VTE risk occurs from a combination of minor factors, rather than one high-risk factor. In addition, most of these VTE risk factors can be easily corrected and prevented in the pre-gestational phase or first trimester.

Keywords: Venous thromboembolism, low-molecular-weight heparin, LMWH, pregnancy, first trimester.

Introduction

Venous thromboembolism (VTE), a condition that includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects 0.1–0.2% of pregnant women each year and is the third most common cause of death of these women worldwide.[1,2] The risk factors for VTE are generally classified as patient-related and environment-related or reversible,[3] for which pregnancy is a well-known environmental risk factor. The risk to pregnant women of developing VTE is four to five times greater than that for non-pregnant women. These risk factors include increasing age (>35 years), obesity, hereditary thrombophilia, and grand multiparity; however, the leading causes of VTE in these women are immobility and bed rest caused by preterm birth, premature rupture of membranes, or preeclampsia.[4]

The increased risk of VTE comes from a variety of factors that result from the physiological and anatomical changes that occur during pregnancy. These include blood clotting factors VII, VIII, X, von

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Willebrand disease and fibrinogen increase, and a decrease in free protein S levels with a five-fold increase in the levels of plasminogen activator inhibitor type I. As a result, thrombogenic properties increase because of changes in the balance between procoagulants and anticoagulants.[5] The mainstay of VTE treatment is anticoagulant therapy and the main anticoagulants used are unfractionated heparin and low-molecular-weight heparin (LMWH), with LMWH being the preferred choice.[6] Because the risk in pregnant women increases and it is treatable, early diagnosis and treatment would save lives. The aim of the current study was to evaluate the VTE risk factors early in pregnancy in Turkish pregnant women.

Methods

The current study was conducted at Gynecology and Obstetrics Clinic of Tuzla State Hospital using a cross-sectional design. The Ethics Committee of Faculty of Medicine of Marmara University gave approval for the study (Approval no: 09.2020.1145) which was conducted in accordance with the Declaration of Helsinki.

We evaluated 480 pregnant women who applied to the outpatient clinic between January 1 and October 1, 2021. All pregnant women between the ages of 18 and 45 years and who applied to our clinic within the first trimester (4–14 weeks) were included in the study. Because the risk factors for these women were to be determined, there were no exclusion criteria for the study. The demographic data on the women such as age, height, weight, gravida, parity, abortion, and the number of living children were recorded. In addition, the antepartum thromboembolism risk parameters presented in **Fig. 1** were considered according to Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines[7] as follows: VTE history, presence of thrombophilia, presence of maternal comorbidity, relative history, smoking, presence of large varicose veins, any assisted reproduction technology, presence of a multiple pregnancy, or previous surgery during the current pregnancy. The risk factors of the women were determined by assessing the presence of hyperemesis gravidarum, systemic infection requiring intravenous medication, immobilization status, and any travel history ≥4 h. Scoring was obtained according to VTE risk analyses and classified as follows: low risk, ≤2 points; medium risk, 3 points; and high risk, ≥4 points. Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines uses data from The Royal College of Obstetricians & Gynecologist (RCOG) as a source, and the table in **Fig.1** is a modified version of the RCOG recommendations.[8] Data were analyzed using Minitab®16 (Minitab Inc., State College, PA, USA). The patient analyses based on risk factors for VTE and their parameters were calculated as n%.

Results

We evaluated 480 pregnant women during their first trimester. The mean maternal age was 29±4.2 years, mean body mass index (BMI) was 27±3.2 kg/m^2, and nulliparity rate was 26.7%. **Fig. 2** illustrates the ratio of patients according to the risk factors for VTE. According to their total scores, there were 336 (70%) pregnant women in the low-risk group, 62 (12.9%) in the medium-risk group, and 82 (17.1%) in the high-risk group (**Fig. 2**).

When the permanent parameters within the groups determining the risk factors in pregnancy were individually evaluated, we found that 5 women had a history of VTE, 12 women had thrombophilia (presence of antithrombin-3 deficiency, protein C and S deficiency, factor V Leiden heterozygous and homozygous mutation, and prothrombin PT G20210A mutation), 22 women had medical comorbidity (heart failure, cancer, active systemic lupus erythematosus, inflammatory polyarthropathy, sickle cell anemia, inflammatory bowel disease, type 1 and 2 diabetes mellitus, nephrotic syndrome, or disease requiring continuous intravenous drug use), 8 women had triggered or estrogen-related VTE, 82 women were >35 years old, 68 women had BMI ≥30 kg/m^2, 6 women had BMI ≥40 kg/m^2, 69 women had parity ≥3, 32 women smoked more than 10 cigarettes per day, 22 women had large varicose veins, and 9 women had a multiple pregnancy (**Fig. 3**).

Considering the distribution of obstetric and transient risk factors within the first trimester, we found that 12 women became pregnant by assisted reproductive technology, 4 women underwent surgical intervention within the first trimester of pregnancy, 28 women had hyperemesis gravidarum, 72 women were immobilized and dehydrated, and 68 women traveled for ≥4 h (**Fig. 4**).

An important prophylaxis analysis to prevent venous thromboembolism in the antepartum period

Patient follow-up form

Name, surname: Identification number: Age: Weight: Height:	Gravida: Parity: Abortion: Living:

RISK FACTORS FOR VTE DURING PREGNANCY

Existing		
Prior VTE (except for a single major surgery event)		4
Previous VTE (triggered by major surgery)		3
Known high-risk thrombophilia		3
Medical comorbidities (e.g., cancer, heart failure; active systemic lupus erythematosus,inflammatory polyarthropathy, inflammatory bowel disease; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease; current IV drug user)		3
History of unprovoked or estrogen-related VTE in a first-degree relative		1
Known low-risk thrombophilia (non-VTE)		1
>35 years of age		1
BMI ≥30		1
BMI ≥40		2
Parity ≥3		1
Smoking		1
Varicose vein		1
Multiple pregnancy		1
Temporary		
Any surgical procedure during pregnancy, except emergency repair of the perineum, (e.g., appendectomy)		3
Hyperemesis		3
OHSS (first trimester only)		4
Systemic infection (requiring hospitalization or antibiotic use) (e.g., pneumonia, pyelonephritis, postpartum wound infection)		1
Immobility and dehydration (long-distance travel >4 h)		1
Total		

VTE: venous thromboembolism; **BMI:** body mass index; **OHSS:** ovarian hyperstimulation syndrome.

If antenatal total score=4, consider thromboprophylaxis from the first trimester.

If antenatal total score=3, consider thromboprophylaxis from 28 weeks.

If postpartum total score=2, consider thromboprophylaxis for at least 10 d.

Consider thromboprophylaxis if hospitalized antenatally.

Thromboprophylaxis is considered in case of prolanged hospitalization (>3 d) or hospital readmission during the puerperal period.

Fig. 1. Patient follow-up form.

Discussion

Pregnancy-related VTE is a leading cause of death in pregnant women at a mortality of 1.1–1.5 deaths per 100,000 deliveries in North America and Europe.[9,10] The risk of VTE also increases during the postpartum period.[11] The reported incidence of VTE ranges from 0.7 to 1.3 per 1000 deliveries, which is four to five times higher than that in non-pregnant women.[9,12] The aim of the current study was to determine the risk of early pregnancy-related VTE in Turkish pregnant women. We first determined that 30% of the study population required LMWH prophylaxis, with 62 (12.9%) in the medium-risk group and 82 (17.1%) in the high-risk group. Second, the risk of VTE occurs from a combination of minor factors such as advanced maternal age, obesity, increased parity, and smoking, rather than one factor alone. Third, we considered the major transient risk factors in pregnancy such as immobilization, dehydration, and traveling for ≥4 h. Fourth, and most impor-

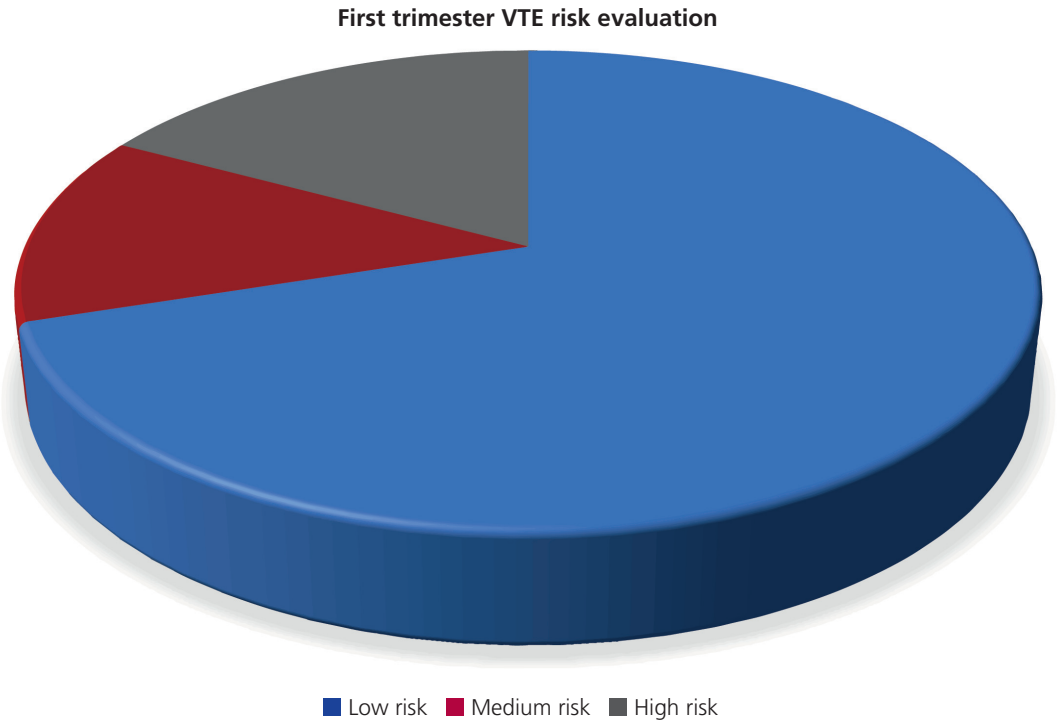

Fig. 2. Ratio of pregnant women according to the risk factors for venous thromboembolism (VTE).

tant, most of these risk factors for VTE are those that can be easily corrected and prevented in the pre-gestational stage or during the first trimester.

We examined the risk factors for VTE in Turkish pregnant women during the first trimester. In the literature, the authors preferred to examine the increased

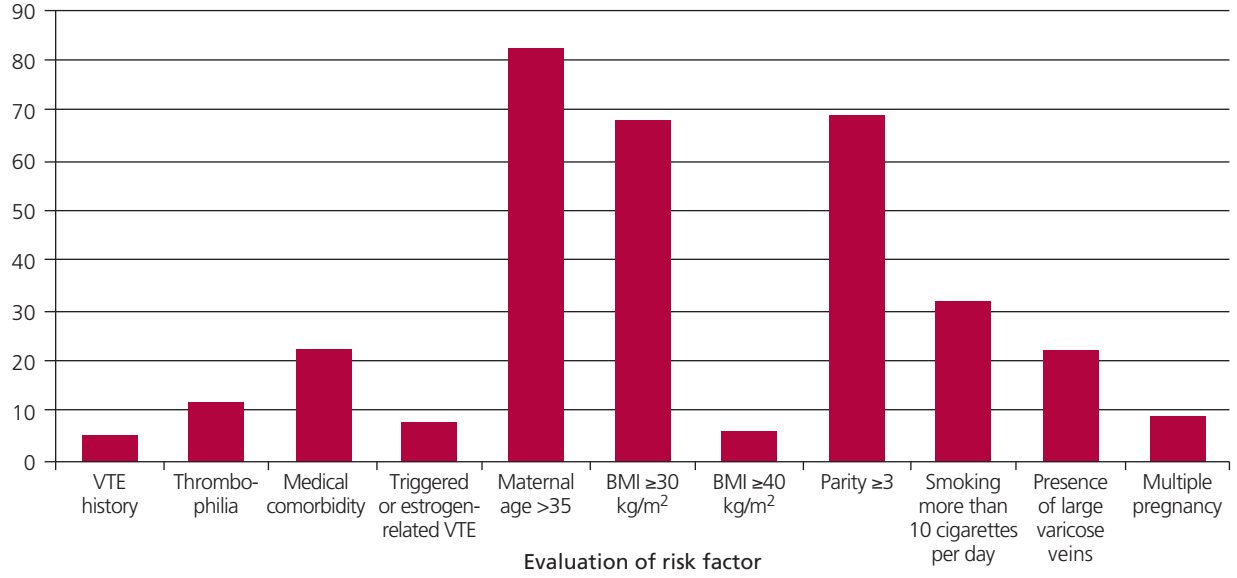

Fig. 3. Ratio of pregnant women with permanent risks for venous thromboembolism (VTE) in the first trimester.

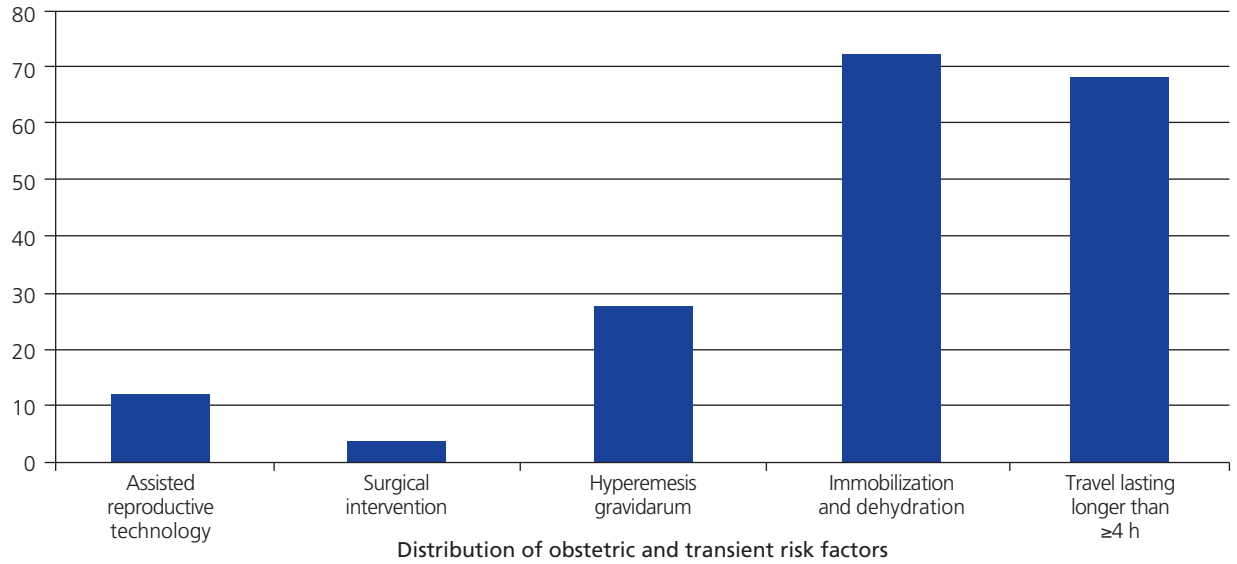

Fig. 4. Ratio of pregnant women obstetric and transient risks for venous thromboembolism (VTE) with in the first trimester.

risk of VTE during the postpartum period;[13] however, many fatal VTE events occur during the first trimester; therefore, prophylaxis for women who had previous VTE should be initiated early in pregnancy. The incidence of VTE in women during their first trimester of pregnancy is higher than that in non-pregnant women and gradually increases thereafter. VTE occurs with increased coagulation factors II, VII, VIII, X, and fibrin, decreased protein S production, and suppression of systemic fibrinolytic activity during the first trimester.[14] In the later weeks of pregnancy, more anatomical factors come into play. As the uterus presses on the inferior vena cava and pelvic veins during pregnancy, venous blood flow slows and venous stasis in the lower extremities increases, which increases the risk of VTE.[15] This becomes even more important in the later stages of pregnancy in cases of complications such as the threat of premature birth, premature rupture of membranes, preeclampsia, and increased inactivity and bed rest. The risk of VTE increases during the postpartum period when a cesarean delivery prevents early mobilization compared to that in normal delivery.[16]

The Royal College of Obstetricians & Gynecologist (RCOG) recommends that all women be evaluated either before or early in pregnancy for risk factors for VTE. Risk assessment should be also repeated during delivery or the postpartum period if the woman is hospitalized for any reason or other problems. Based on the risk factors, prophylactic LMWH should be considered during the antenatal period, which requires prophylactic LMWH for 6 weeks postpartum. This protocol is controversial with pregnant women at risk of VTE; therefore, the reasons for individual recommendations should be explained.[8] When the American College of Gynecology (ACOG), Society of Obstetricians and Gynecologists of Canada, and RCOG consider the timeframe of thrombophilia treatment, antepartum care, and VTE-related complications, antiphospholipids, including Factor V Leiden, prothrombin G20210A gene variant, antithrombin III, protein C, and protein S deficiencies recommend screening every pregnant woman with a history of VTE for antibody syndrome and hereditary thrombophilia.[17,18] The risks for VTE are increased by 15 times in pregnant women with hereditary thrombophilia compared to that in normal pregnant women, although even among those without a history of VTE, the magnitude of risk varies with specific thrombophilia and family history of VTE.[9] The risks for VTE also increase with a deficiency of endogenous anticoagulants such as protein C, protein S, and antithrombin III (4.8, 3.2, and 4.7, respectively). A family history of VTE also increases the risk by up to 4 times, even in the absence of thrombophilia.[19] In their studies on in vitro fertilization pregnancies, Sennstrom et al.,[20] have shown that assist-

ed reproduction technology increases the risk of VTE by two to three times during ovarian stimulation compared to that in the general pregnant population. As a result of previous studies, it is believed that estradiol levels that abnormally increase can cause hemoconcentration, activation of coagulation, and fibrinolytic systems.[21] In their study of the risk for VTE in multiple pregnancies, Rova et al.[22] have shown in an antepartum trial that multiple pregnancy increases the risk for VTE by 2.1 to 2.6 times compared to that in normal pregnant women. In another prospective cohort study involving 1.3 million pregnant women in Denmark, the authors[23] have shown that hospitalization for hyperemesis and multiple pregnancy increase the risk for VTE by 2.5 and 2.8 times, respectively. In their study, Saltan et al.[24] have shown that the incidence of VTE within the first trimester is 0.26 per 1000 births. In that study, four (80%) of the five DVTs occurred within the first trimester, and one occurred within the last trimester.[24]

In the risk analyses published in accordance with the Turkish Ministry of Health (**Fig. 1**), it is recommended that those scoring >4 points should begin LMWH prophylaxis, and those with >3 points should begin LMWH at 28 weeks of gestation. As a result of the current study, 62 (12.9%) patients scored >3 points and were in the medium-risk group and LMWH was recommended beginning from the 28th week of gestation, 82 (17.1%) scored >4 and it was recommended beginning LMWH after evaluation.[7] We concluded that approximately one out of every three women should begin LMWH treatment. The clinical significance of this study showed an increase risk for VTE with pregnancy. In line with the current findings, we believe that one out of every three pregnant women is at risk for VTE. This is a key factor for examining risk factors and beginning early prophylaxis to prevent VTE within the first trimester. The risks for VTE increase during both antepartum and postpartum periods with increasing maternal age, obesity, and smoking; therefore, VTE prophylaxis is becoming increasingly important. In addition, at each visit in the presence of increased risk for the development of VTE, the patients should be informed and their awareness should be raised, thereby eliminating the risk factors by providing education before certain conditions occur.

Study limitations

There were some limitations to this study. First, it was a single-center observational study and did not reflect the entire population. As the criteria for the risk for VTE were obtained using the Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines, some undiagnosed conditions such as a mild DVT or PE could have been missed because the diagnoses were made using patient information accompanied by questions and answers. Some factors such as immobilization were observed more frequently because of the increased barrier to mobility within the society from the COVID-19 pandemic. One of the limitations is that the cost of anticoagulant prophylaxis to be used to reduce the risk of VTE during pregnancy and puerperium has not been calculated.

Conclusion

Our results indicated that 30% of the population needed LMWH prophylaxis according to Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines,[7] of whom 12.9% were in the medium-risk group, and 17.1% were in the high-risk group. The risk for VTE occurs from a combination of minor factors such as advanced maternal age, obesity, increased parity, and smoking, rather than only one factor that causes an elevated risk. Immobilization, dehydration, and traveling for ≥4 h were the major transient risk factors for VTE during pregnancy. Additionally, it is noteworthy to mention that many of these factors are those that can be prevented in the pre-pregnancy period.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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