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Review Article

Pregnancy-related venous thromboembolism: Risk and the effect of thromboprophylaxis

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ABSTRACT

Venous thromboembolism (VTE) is a leading cause of maternal mortality and morbidity during pregnancy in developed countries. The incidence of VTE per pregnancy-year increases about 4-fold during pregnancy and at least 14-fold during the puerperium. Risk factors include a personal history of VTE, presence of inherited or acquired thrombophilia, a family history of VTE and general medical conditions, such as immobilisation, overweight, varicose veins, some haematological diseases and inflammatory disorders. VTE is considered potentially preventable with the prophylactic administration of anticoagulants, but there are no high quality randomized clinical trials that compared different strategies of thromboprophylaxis in pregnant women. Balancing the absolute risk of VTE against the risks of exposure to anticoagulants, this review provides advice regarding which women may benefit from thromboprophylaxis during and after pregnancy.

Contents

Introduction

Venous thromboembolism (VTE) is a leading cause of maternal morbidity and mortality during pregnancy in developed countries [1–3]. A switch in the global haemostatic balance towards a hypercoagulable state, which probably protects the mother from excessive bleeding during delivery, contributes to increasing the risk of VTE. Plasma levels of coagulation factors VII, VIII, IX, X, XII, fibrinogen, Von Willebrand factor, and of markers of thrombin generation, such as the prothrombin fragment F1+2 and thrombin-antithrombin complexes are increased in normal pregnancy [4]. The increase of

Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; FV Leiden, factor V Leiden; APLA, antiphospholipid antibody; APS, antiphospholipid syndrome; HIT, heparin-induced thrombocytopenia; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; VKA, Vitamin K antagonists; ACCP, American College of Chest Physicians; SISET, Italian Society for Haemostasis and Thrombosis; OR, Odds Ratios; CI, Confidence Intervals.

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fibrinogen levels is particularly pronounced during pregnancy [5–7]. Moreover, free protein S levels fall progressively during pregnancy and the anticoagulant response to activated protein C decreases [8–10]. Furthermore, fibrinolytic activity is decreased as plasminogen activator inhibitor −1 increases during pregnancy up to five fold and plasminogen activator inhibitor −2, produced by the placenta, is increased particularly during the third trimester [11–13]. Finally, pregnancy is characterized by an increase in total blood volume and venous stasis occurs as capacitance vessels increase in diameter, while venous return is diminished by the pressure from the gravid uterus on the iliac and inferior caval veins.

Epidemiology of VTE in pregnant women

The risk of VTE in women during pregnancy and puerperium is higher than in non-pregnant women of the same age. In western countries, the overall annual incidence of VTE is 1.2 per 10,000 women of fertile age [14], it increases to about 1 per 1,000 deliveries [3,15,16], accounting for 1.1 deaths in every 100,000 deliveries [1–3,15,17–21]. Globally, the incidence of VTE per pregnancy-year increases about 4-fold during pregnancy and by 14 to 84-fold during the first 6 weeks of puerperium [2,3,22]. Although most studies suggest that the incidence of VTE is similar in the 3 trimesters of pregnancy [20,23,24], a very recent study [25] showed that the risk of VTE increases exponentially through pregnancy. However, these findings should be interpreted with caution because the higher risk during the third trimester might reflect the inclusion of misdiagnoses due to swelling caused by compression of the gravid uterus in this retrospective study. About 80% of pregnancy-associated VTE is deep vein thrombosis (DVT) and 20-25% is pulmonary embolism (PE) [1,20]. Deep vein thrombosis in pregnancy is more likely to be proximal and restricted to the femoral or iliac veins (>60% of cases) [26]; the left leg is more commonly affected by VTE than the right one, probably due to compression of the left iliac vein by the right iliac artery at their crossing [23,24,27]. The incidence of VTE, and especially PE, is higher during the puerperium and is strongly associated with cesarean delivery [23]. Pelvic vein thrombosis, which is rare outside of pregnancy, accounts for approximately 10% of DVT during pregnancy and puerperium [28].

Table 1
Risk factors for pregnancy associated VTE.

Risk factors	Adjusted OR and 95% CI
Pregnancy (antepartum and postpartum combined)	
• Age >35	1.3 (1.0-1.7)
• Sickle cell disease	6.7 (4.4-10.1)
• Heart disease	7.1 (6.2-8.3)
• Varicose vein	2.4 (1.04-5.4)
• Systemic lupus erythematosus	8.7 (5.8-13)
Antepartum	
• Smoking (>10 cigarettes/day)	2.1 (1.3-3.4)
• Slight weight gain (<7 kg)	1.7 (1.1-2.6)
• BMI ≥25 kg/m^2	1.8 (1.3-2.4)
• Immobility	7.7 (3.2-19.0)
• Twins	2.6 (1.1-6.2)
• Assisted reproduction technique	4.3 (2.0-9.4)
Postpartum	
• Smoking (>10 cigarettes/day)	3.4 (2.0-5.5)
• Weight gain (>21 kg)	1.6 (1.1-2.6)
• BMI ≥25 kg/m^2	2.4 (1.7-3.3)
• Immobility	10.8 (4.0-28.8)
• Pre-term delivery	2.4 (1.6-3.5)
• Preeclampsia	3.1 (1.8-5.3)
• IUGR	3.8 (1.4-10.2)
• Acute cesarean section	2.7 (1.8-4.1)
• Postpartum infection	20.2 (6.4- 63.5)
• Cesarean section + postpartum infection	6.2 (2.4-16.2)
• Postpartum bleeding ≥1000 mL	4.1 (2.3-7.3)
• Cesarean section + postpartum bleeding ≥1000 mL	12.0 (3.9-36.9)

Information retrieved from references [29,30];
OR = odds ratios; CI = confidence intervals; IUGR = intrauterine fetal growth restriction.

Risk factors for VTE in pregnancy

General characteristics of women

Several studies have evaluated patient characteristics and medical conditions associated with an increased VTE risk during pregnancy. Known risk factors for VTE in the general population, such as immobilisation, overweight, varicose veins, sickle cell disease, myeloproliferative neoplasia, and inflammatory disorders, are likely also risk factors for pregnancy associated VTE. A comprehensive exploration of risk factors involved in pregnancy associated VTE is provided by a large case–control study from Norway [29], in which 559 women with pregnancy-associated VTE (268 with antenatal VTE and 291 with postnatal VTE) were compared with 1,229 control women. A detailed list of risk factors for VTE in pregnancy and puerperium is also provided by the evidence-based guidelines of the Royal College of Obstetricians and Gynaecologists [30], in which the results from a large number of case–control studies on this topic are summarized, including those from the abovementioned study [29]. Table 1 denotes the most important risk factors for women at increased risk of pregnancy associated VTE.

History of VTE

Women with a personal history of thrombosis are at high risk for recurrence. The largest prospective study assessed the risk of recurrence in 125 pregnant women with a single previous VTE, in whom antepartum heparin was withheld and postpartum anticoagulants were given for four to six weeks (usually warfarin targeted at an INR of 2.0 to 3.0 combined with a short initial course of heparin). The incidence of recurrence was 2.4% (95% CI, 0.2-6.9) antepartum, and 2.5% (95% CI 0.5-7.0) postpartum. The advanced median gestational age at enrollment (approximately 15 weeks) and the exclusion of women with known thrombophilia could have resulted in an underestimation of the risk of pregnancy-related recurrent VTE. A sub-analysis of the same study showed that the incidence of VTE recurrences was as high as 6.0% (95% CI, 1.2-16.2) in women in whom the first event was unprovoked and/or women with an abnormal thrombophilia test [31]. In 44 women without thrombophilia who had a transient risk factor (including oral contraceptive therapy or pregnancy) at the time of their prior VTE, no VTE recurrences were observed 0% (0.0-8.0). In the two largest published retrospective studies, the risk of antepartum recurrent VTE was approximately 6%, with a higher risk in women with a previous unprovoked VTE, or with oral contraceptive or pregnancy- related events [32,33]. In contrast with the prospective study [31], these studies suggest that a first VTE associated with oral contraceptive use or pregnancy is associated with a higher risk of recurrences than an unprovoked first VTE event [32,33] and that thrombophilia is not predictive of an increased risk of recurrent VTE. These findings are consistent with the results of a large population-based retrospective cohort study, in which women who had their first VTE associated with pregnancy had a higher risk of recurrence during a subsequent pregnancy [34].

In conclusion, a personal history of VTE is an important risk factor for recurrence in pregnancy, but there is some conflicting data on what circumstances during the prior VTE are associated with the highest risk of recurrence. Women with unprovoked VTE and oral contraceptive or pregnancy associated VTE probably have higher risk of pregnancy associated recurrences than women who had a major provoking risk factor at the time of their previous event [31–34].