

Thrombosis during pregnancy: risk factors, diagnosis and treatment

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Abstract

Venous thromboembolism occurs infrequently but is a leading cause of illness and death during pregnancy and the puerperium and remains a diagnostic and therapeutic challenge. In the general population the incidence of pregnancy associated VTE has been estimated to vary from 1 in 1000 to 1 in 2000 deliveries. The risk of VTE is five times higher in a pregnant woman than in a nonpregnant woman of similar age. Postpartum VTE is more common than antepartum VTE. Women with congenital abnormalities or persistent presence of antiphospholipid antibodies have an increased risk of VTE during pregnancy and the puerperium. In individuals with well defined hereditary thrombosis risk factors, such as the factor V:R506Q mutation, the factor II:G20210A variation, antithrombin-deficiency or protein C-deficiency, a relative risk of pregnancy associated VTE between 3.4 and 15.2 has been found. Women with previous VTE have an approximately 3.5 fold increased risk of recurrent VTE during pregnancy compared to non-pregnant periods.

Our ability to diagnose deep-vein thrombosis clinically is generally poor and is further hampered during pregnancy since dyspnea, tachypnea, swelling and discomfort in the legs are common. Objective diagnosis is essential for treatment decisions. Exposure to radiation

of less than 50,000 μ Gy (5rad) has not been associated with a significant risk of fetal injury. Therefore, besides sonography, routine diagnostic procedures should be performed, if clinically necessary.

Heparin does not cross the placenta and is therefore the anticoagulant treatment of choice during pregnancy. In case of acute new onset of thrombosis during pregnancy, treatment is performed like in non-pregnant patients with acute deep vein thrombosis or pulmonary embolism. There is ongoing debate, whether or not pregnant women with previous venous thrombosis should routinely receive prophylactic anticoagulation. In patients who have hereditary antithrombin deficiency, antiphospholipid antibodies, a combined abnormality or a history of a severe thrombotic event (pulmonary embolism, extended deep vein thrombosis) should be advised to use prophylactic heparin during pregnancy, starting during the first trimester. Post partum prophylaxis should be given in all women with an increased risk for VTE.

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Venous thromboembolism occurs infrequently but is a leading cause of illness and death during pregnancy and the puerperium and remains a diagnostic and therapeutic challenge. In the general population the incidence of pregnancy associated

VTE has been estimated to vary from 1 in 1000 to 1 in 2000 deliveries (1, 2). The risk of VTE is five times higher in a pregnant woman than in a nonpregnant woman of similar age (3). Available evidence suggests that postpartum VTE is more common than antepartum VTE, and it is likely that the risks of both initial and recurrent DVT are higher postpartum than antepartum. In the Leiden Thrombophilia Study (5), pregnancy was associated with a four-fold increased risk of thrombosis, and the puerperium was associated with a 14-fold increased risk.

Women with congenital abnormalities or persistent presence of antiphospholipid antibodies have an increased risk of VTE during pregnancy and the puerperium (4). In individuals with well defined hereditary thrombosis risk factors, such as the factor V:R506Q mutation, the factor II:G20210A variation, antithrombin-deficiency or protein C-deficiency, a relative risk of pregnancy associated VTE between 3.4 and 15.2 has been found (6). For a woman with factor V:R506Q a thrombotic risk of approximately 1 in 400-500 was estimated (7). For the combination of G20210A prothrombin-gene mutation and factor V Leiden the risk is disproportionately higher than that among women with only one mutation.

Women with previous VTE have an approximately 3.5 fold increased risk of recurrent VTE during pregnancy compared to nonpregnant periods (8). In a retrospective evaluation including 72 patients a recurrence rate of 12 % (9) was found. In a recently published prospective study on 125 women who were pregnant after a venous thromboembolic event an antepartum recurrence rate of only 2.4% was found despite thrombosis prophylaxis was withheld in these women (10). In a retrospective cohort study on 159 women (293 pregnancies) a probability of 6.2% (95% confidence interval 1.6 – 10.9) was found (11). Temporary risk factors at first event or the investigation for thrombosis risk factors does not differentiate clearly between women at high or low risk for recurrence.

Our ability to diagnose deep-vein thrombosis clinically is generally poor and is further hampered during pregnancy since dyspnea, tachypnea, swelling and discomfort in the legs are common, particularly at term and must be interpreted with caution during pregnancy. Furthermore, there is concern about performing imaging procedures (such as lung scanning) that expose the fetus to radiation, although the estimated exposure of the fetus to radiation during these examinations is small. The combination of chest roentgenography, ventilation-perfusion scanning, and pulmonary angiography exposes the fetus to less than 5 000 µGy (0.5 rad). Exposure to radiation of less than 50,000 µGy (5rad) has not been associated with a significant risk of fetal injury in most studies (12). Therefore, besides sonography, routine diagnostic procedures should be performed, if clinically necessary.

Treatment and prophylaxis of pregnancy-associated VTE remain a subjects of controversy because of lack of large well designed prospective clinical trials. Antithrombotic agents

might produce complications in both mother and fetus. Coumarin derivatives cross the placenta and have the potential to cause teratogenicity and bleeding in the fetus. Coumarin embryopathy, which consists of nasal hyperplasia and/or stippled epiphyses after in utero exposure to oral anticoagulants during the first trimester of pregnancy. In contrast, heparin does not cross the placenta, and is therefore safe for the fetus. Before licence of low-molecular-weight heparins (LMWH) unfractionated heparin (UFH) was the anticoagulant of choice during pregnancy. Sanson (13) postulated in a systematic review including a total of 486 pregnancies that LMWH are a safe and attractive alternative to UFH. In the 486 pregnancies there was no case of clinically important bleeding or heparin-induced thrombocytopenia, one case of symptomatic osteoporosis, and 3 cases of VTE. Probably LMWH have a lower risk of bleeding, osteoporosis and heparin-induced thrombocytopenia than UFH. In case of acute new onset of thrombosis during pregnancy, treatment is performed like in non-pregnant patients with acute deep vein thrombosis or pulmonary embolism. There is ongoing debate, whether or not pregnant women with previous venous thrombosis should routinely receive prophylactic anticoagulation. Two options have been proposed (14): (1) No routine prophylaxis during pregnancy, but aggressively investigating symptomatic women when they present with a clinical suspicion of VTE or (2) prophylaxis in women who have an increased risk for VTE. In patients who have hereditary antithrombin deficiency, antiphospholipid antibodies, a combined abnormality or a history of a severe thrombotic event (pulmonary embolism, extended deep vein thrombosis) should be advised to use prophylactic heparin during pregnancy, starting during the first trimester. Post partum prophylaxis should be given to all women with an increased risk for VTE.

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