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Thromboembolism in Pregnancy: Recurrence and Its Prevention

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Fifteen to 25% of thromboembolic events in pregnancy are recurrent events. Women with a history of thrombosis have a three- to fourfold increased risk of recurrence when they are pregnant compared with when they are not. The risks are even higher postpartum. The rate of recurrent venous thromboembolic events without anticoagulation is 2.4% to 12.2%, whereas the rate with anticoagulation is 0% to 2.4%. Because the rates of recurrent thromboembolism can be reduced with anticoagulation, women with a history of thrombosis who are not on lifelong anticoagulation will likely require anticoagulation during pregnancy, or at least during the postpartum period. Women who are already on lifelong warfarin for the prevention of recurrent venous thromboembolism should be counseled about the teratogenic effects of warfarin and offered the opportunity to be converted to heparin before conception. During pregnancy, low-molecular-weight heparin, with fewer side effects and a longer half-life, is generally preferred over unfractionated heparin. Unfractionated heparin with its shorter half-life is generally preferred around the time of delivery. Women on antiplatelet medication for prevention of arterial thromboembolism may be converted to low-dose aspirin after conception and supplemented with low-dose heparin or low-molecular-weight heparin during pregnancy. Because current recommendations rely on case series and expert opinion, additional studies including randomized trials might enhance our ability to prevent recurrent thromboembolism in pregnancy.
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Normal pregnancy is accompanied by an increase in clotting factors.[1,2] The resulting hypercoagulable state has likely evolved to protect women from hemorrhage at the time of miscarriage and childbirth. Indeed, in the developing world, the leading cause of maternal death is still hemorrhage.[3] In Western Europe and the United States, where hemorrhage is successfully treated or prevented, the leading cause of maternal death is thromboembolic disease.[4] During pregnancy, the risk of venous thromboembolism is increased 4-fold,[5] and the risk of arterial thromboembolism, myocardial infarction, and stroke is also increased 3- to 4-fold.[6,7] Postpartum, the risk of venous thromboembolism is 20-fold higher,[5] and the risk of arterial thromboembolism (stroke) is similarly elevated.[8]

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The overall number of maternal deaths from thromboembolism in pregnancy is approximately 3 per 1000 deliveries. Two per 100,000 are due to arterial thrombosis and 1 per 100,000 are due to venous thrombosis.[6,7,9] Although arterial events account for more deaths, venous events are more common, accounting for 4 out of 5 thromboembolic events during pregnancy.[6,7,9] Eighty percent of these events are deep vein thrombosis,[9] and 20% are pulmonary emboli.[9] The most important risk factor for thrombosis during pregnancy is a history of thrombosis.[6,7,9,10]

Epidemiology of Recurrent Thrombosis

During pregnancy, the risk of thromboembolism is increased. This is especially true for women with a history of thrombosis. The risk of recurrent venous thromboembolism in pregnancy is three- to fourfold higher compared with women not pregnant (RR 3.5; 95% CI 1.6, 7.8),[11] and the risk of a recurrent arterial

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Table 1 Rates of Recurrent Venous Thromboembolism (VTE) during Pregnancy and the Postpartum period with and without Anticoagulation*

Study	Rate of Recurrent VTE with Anticoagulation	Rate of Recurrent VTE without Anticoagulation
Badaracco and Vessey, 1974[91]	6/30 (20%)†	-
Tengborn et al., 1989[92]		
Pregnancy	3/20 (15%)	8/67 (12%)
Delivery and puerperium	2/57 (5%)	3/34 (11%)
Sanson et al., 1999[16]	3/149 (1.5%)‡	-
Brill-Edwards et al., 2000[13]		
Pregnancy	-	3/125 (2.4%)
Postpartum		(95% CI: 0.2%, 6.9%)
Lepercq et al., 2001[17]	3/125 (2.4%)§	-
Pabinger et al., 2005[14]	7/574 (1.2%)¶	8/197 (6.9%) (95% CI: 1.6%, 10.6%)
De Stefano et al., 2006[15]	0/87 (0%)#	19/155 pregnancies (12.2%) (95% CI: 7.9%, 18.3%)

*When available, the rate in pregnancy compared to postpartum is specified.
†Anticoagulation consisted of heparin 5000 units subcutaneously twice daily.
‡Compiled from case series. Anticoagulation consisted of varying doses of varying low-molecular-weight heparins.
§Two of these events occurred in women who were not taking warfarin as prescribed and the third occurred in a woman 2 weeks after anticoagulation was discontinued at 6 weeks postpartum.
¶357/574 (65%) received 20 mg of enoxaparin once daily and 217/574 (35%) received 40 mg of enoxaparin once daily.
#Anticoagulation consisted of heparin 5000 units subcutaneously two or three times daily or low-molecular-weight heparin 4000-5000 anti-factor X units/day.

thromboembolism is probably similarly increased. One study found the relative risk of recurrent stroke to be 2.2 (95% CI 0.5, 17.5) during pregnancy and 9.7 (95% CI 1.2, 78.9) postpartum.[12]

Fifteen to 25% of thromboembolic events in pregnancy are recurrent events. There are few data about the risk of recurrent arterial events in pregnancy, but a study of 115 women with a history of stroke (89 with a history of arterial ischemic stroke and 26 with a history of cerebral vein thrombosis) found the incidence of recurrent stroke during pregnancy to be 1.8% (0.5%, 7.5%) and during the first 6 weeks postpartum to be 4.8% (0.6%, 35.9%). During pregnancy, most of the 115 women with a history of arterial thrombosis received antiplatelet medication, and most of the women with a history of cerebral vein thrombosis received no prophylaxis.[12] Sanson and coworkers found no recurrence of arterial thromboembolic events during pregnancy among 8 women who received anticoagulation with low-molecular-weight heparin.

There are several studies about the risk of recurrent venous events in pregnancy (Table 1). In recent studies, the rate of recurrent venous thromboembolism in women who did not receive anticoagulation has been reported to range from 2.4% to 12.2%.[13-15] In women who did receive anticoagulation, the rate of recurrent venous thromboembolism has been reported to range from 0% to 2.4%.[13,16,17]

Risk Factors for Recurrent Thrombosis in Pregnancy

Although there are no data on the risk factors for recurrent thrombosis in pregnancy, the risk factors are thought to be the same as the overall risk factors for thrombosis. Aside from a history of thrombosis, the most important risk factor for venous thromboembolism is thrombophilia.[9,10] From an analysis of 14,335 records from the Nationwide Inpatient Sample,[9] other medical conditions that were statistically significant risk factors for venous thromboembolism during pregnancy were heart disease, sickle cell disease, lupus, obesity, anemia, diabetes, hypertension, and smoking. Pregnancy and delivery complications that were associated with a significantly increased risk of venous thromboembolism included multiple gestation, hyperemesis, disorders of fluid, electrolyte and acid-base balance, antepartum hemorrhage, cesarean delivery, postpartum infection, postpartum hemorrhage, and transfusion (Table 2). In the same analysis, age and race were also risk factors for venous thromboembolism. The odds ratio (OR) for women age 35 and older was 2.1 (2.0, 2.3).[9] When controlled for age, the OR for black women was still 1.4 (1.2, 1.6).[9] The risk factors for arterial thromboembolism were similar to those for venous thromboembolism, except for stroke, where hypertension OR = 6.1 (4.5, 8.1) and thrombocytopenia OR = 6.0 (1.5, 24.1) were more important risk factors and myocardial infarction, where hypertension OR = 11.7 (6.9, 21.2) and smoking OR = 6.2 (4.1, 9.5) were more important risk factors.

Thrombophilia is present in 20%[18] to 40%[15,19] of women who experience venous thromboembolism during pregnancy and the postpartum period. Both acquired and inherited thrombophilia increase the risk, but it is not clear whether thrombophilia increases the risk of recurrent venous events during pregnancy and the postpartum period. In a systematic review of the risk of recurrent venous thromboembolism in individuals who were not pregnant, factor V Leiden and the prothrombin gene mutation were found to confer a slightly increased risk of recurrence with an OR for factor V Leiden of