Venous Thromboembolism in Pregnancy

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Abstract—The purpose of this review is to summarize the epidemiology of venous thromboembolism (VTE) in pregnancy and describe strategies used to prevent and treat it. The main reason for the increased risk of VTE in pregnancy is hypercoagulability. The hypercoagulability of pregnancy, which has likely evolved to protect women from the bleeding challenges of miscarriage and childbirth, is present as early as the first trimester and so is the increased risk of VTE. Other risk factors include a history of thrombosis, inherited and acquired thrombophilia, certain medical conditions, and complications of pregnancy and childbirth. Candidates for anticoagulation are women with a current thrombosis, a history of thrombosis, thrombophilia, and a history of poor pregnancy outcome, or postpartum risk factors for VTE. For fetal reasons, the preferred agents for anticoagulation in pregnancy are heparins. There are no large trials of anticoagulants in pregnancy and recommendations are based on case series and the opinion of experts. Nonetheless, anticoagulants are believed to improve the outcome of pregnancy for women who have or have had VTE. (*Arterioscler Thromb Vasc Biol*. 2009;29:326-331.)

Key Words: venous thromboembolism ■ arterial thromboembolism ■ deep vein thrombosis ■ pulmonary embolus ■ pregnancy ■ anticoagulation

W omen are at an increased risk of both venous and arterial thromboembolism during pregnancy. Compared to women who are not pregnant, the risk of arterial thromboembolism (strokes and heart attacks) is increased 3- to 4-fold[1,2] and the risk of venous thromboembolism (VTE) is increased 4- to 5-fold.[3] Postpartum, the risk is even higher (20-fold[3]). The overall prevalence of thromboembolic events during pregnancy is approximately 2 per 1000 deliveries.[1,2,4] Approximately 20% of these events are arterial, and the other 80% are venous.[1,2,4] VTE accounts for 1.1 deaths per 100 000 deliveries,[1,2] or 10% of all maternal deaths.

Approximately 80% of venous thromboembolic events during pregnancy are deep vein thrombosis (DVT) and 20% are pulmonary emboli.[4] Approximately one third of pregnancy-related DVT and half of pregnancy-related pulmonary emboli occur after delivery.[5–8] When DVT occurs during pregnancy, it is more likely to be proximal,[9] massive,[9] and in the left lower extremity.[7,8] Distal thromboses are as likely to occur on the right as on the left, but proximal thromboses occurring under the influence of estrogen[10,11] are more likely to be on the left. This left-sided predominance is thought to be attributable to a relative stenosis of the left common iliac vein where it lies between the lumbar vertebral body and the right common iliac artery,[12] but the true mechanism is unknown.[13] Pelvic vein thromboses, which account for less than 1% of all cases of DVT,[14] are rare outside of pregnancy or pelvic surgery yet account for approximately 10% of DVT during pregnancy and the postpartum period.[7]

Pregnant women are probably at an increased risk for VTE as a result of hormonally induced decreased venous capacitance and decreased venous outflow,[15,16] possibly as a result of mechanical obstruction by the uterus,[17] and questionably as a result of decreased mobility.[18–21] These factors, along with vascular injury,[17] are important, especially during the postpartum period, but the risk of VTE is as high during the first trimester[7,8] as it is during the second and third trimesters. Therefore, the risk of VTE increases before many of the anatomic changes of pregnancy take place, suggesting that, overall, the most important reason for the increased risk of VTE during pregnancy is hypercoagulability.

Normal pregnancy is accompanied by increased concentrations of factors VII, VIII, X, and von Willebrand factor and by pronounced increases in fibrinogen.[22] Factors II, V, and IX are relatively unchanged.[22] Free protein S, the active, unbound form, is decreased during pregnancy secondary to increased levels of its binding protein, the complement component C4b.[22] Plasminogen activator inhibitor type 1 (PAI-1) levels increase 5-fold.[22] Levels of PAI-2, produced by the placenta, increase dramatically during the third trimester.[23] Markers of thrombin generation such as prothrombin $F1+2$ and thrombin-antithrombin (TAT) complexes are increased.[24–27] These changes, which may not completely return to baseline until more than 8 weeks postpartum,[22] begin with conception. So does the risk of thrombosis.[7,8]

Table 1.   Medical Conditions and Complications of Pregnancy and Delivery Associated With an Increased Risk of Venous Thromboembolism in Pregnancy

Risk Factor	Odds Ratio	Confidence Interval
Medical conditions		
Heart disease	7.1	6.2, 8.3
Sickle cell disease	6.7	4.4, 10.1
Lupus	8.7	5.8, 13.0
Obesity	4.4	3.4, 5.7
Anemia	2.6	2.2, 2.9
Diabetes	2.0	1.4, 2.7
Hypertension	1.8	1.4, 2.3
Smoking	1.7	1.4, 2.1
Complications of pregnancy and delivery		
Multiple gestation	1.6	1.2, 2.1
Hyperemesis	2.5	2.0, 3.2
Fluid & electrolyte imbalance	4.9	4.1, 5.9
Antepartum hemorrhage	2.3	1.8, 2.8
Cesarean delivery	2.1	1.8, 2.4
Postpartum infection	4.1	2.9, 5.7
Postpartum hemorrhage	1.3	1.1, 1.6
Transfusion	7.6	6.2, 9.4

The hypercoagulability of pregnancy has likely evolved to protect women from hemorrhage at the time of miscarriage or childbirth. Indeed, in the developing world, the leading cause of maternal death is still hemorrhage,[28] but in Western Europe and the United States, where hemorrhage is successfully treated or prevented, the leading cause of maternal death is thromboembolic disease.[29]

Risk Factors for Thrombosis in Pregnancy

The most important risk factor for VTE in pregnancy is a history of thrombosis. Fifteen to 25% of thromboembolic events in pregnancy are recurrent events. The risk of recurrent VTE in pregnancy is also increased 3- to 4-fold (relative risk 3.5 [95% confidence interval 1.6, 7.8]).[30] In recent studies, the rate of recurrent VTE in women who did not receive anticoagulation has been reported to range from 2.4% to 12.2%.[31–33] In women who did receive anticoagulation, the rate of recurrent VTE has been reported to range from 0 to 2.4%.[31,34,35]

Besides a history of thrombosis, the most important risk factor for VTE in pregnancy is thrombophilia.[4,7] Other medical conditions that increase the risk of VTE are heart disease, sickle cell disease, lupus, obesity, anemia, diabetes, hypertension, and smoking. Pregnancy and delivery complications that increase the risk are multiple gestation, hyperemesis, disorders of fluid, electrolyte and acid-base balance, antepartum hemorrhage, cesarean delivery, postpartum infection, postpartum hemorrhage, and transfusion.[4] Odds ratios for these conditions were obtained from an analysis of 14 335 records from the Nationwide Inpatient Sample[4] and are summarized in Table 1. In the same analysis, older age and black race were also found to be risk factors for VTE. The odds ratio (OR) for women age 35 and older was found

Table 2.   Risk of VTE Conferred by Type of Thrombophilia

Thrombophilia	Odds Ratios
Factor V Leiden–homozygosity	34.40 (9.86, 120.05)
Factor V Leiden–heterozygosity	8.32 (5.44, 12.70)
Prothrombin gene mutation–homozygosity	26.36 (1.24, 559.29)
Prothrombin gene mutation–heterozygosity	6.80 (2.46, 18.77)
Protein C deficiency	4.76 (2.15, 10.57)
Protein S deficiency	2.19 (1.48, 6.00)
Antithrombin deficiency	4.76 (2.15, 10.57)

to be 2.1 (2.0, 2.3).[4] After controlling for age, the OR for black women was still found to be 1.4 (1.2, 1.6).[4]

Thrombophilia is present in 20% to 50%[33,36,37] of women who experience VTE during pregnancy and the postpartum period. Both acquired and inherited thrombophilia increase the risk. The absolute risk of VTE conferred by type of thrombophilia was systematically reviewed by Robertson et al[38] and is summarized in Table 2.

Prevention of Thrombosis in Pregnancy

Despite the increased risk of VTE during pregnancy and the postpartum period, most women do not require anticoagulation. In most cases, the risks of anticoagulation outweigh its benefits. Women who would benefit from anticoagulation for prevention of thrombosis in pregnancy are those whose risk of VTE is greater than the risk of bleeding complications from heparin or low-molecular-weight heparin, which has been reported to be as high as 2%.[34,35,39,40] Women who would benefit are those with a history of thrombosis.

Other women who may benefit from anticoagulation in pregnancy are women with inherited or acquired thrombophilia and a history of poor pregnancy outcome. In the antiphospholipid syndrome, several studies have demonstrated that anticoagulation improves the outcome of pregnancy[41] and in inherited thrombophilia, case reports, case series, and one small randomized trial[42] have also suggested that anticoagulation can improve the outcome of pregnancy.

Ideally, evaluation of the woman who may require anticoagulation during pregnancy should occur before conception, or at least early in pregnancy. Women with conditions that place them at a high risk of maternal mortality because of thrombosis may best be counseled against pregnancy. These conditions include mechanical heart valves,[43] chronic thromboembolic pulmonary hypertension, a history of recurrent thrombosis while fully anticoagulated, and a history of myocardial infarction. Most women with a history of VTE, however, can be counseled that their risks are manageable and are probably reduced with anticoagulation.

Women who are already on full anticoagulation will likely need to continue. They should be counseled about the harmful effects of warfarin on the fetus and offered the opportunity to be converted to low-molecular-weight heparin before conception.

Women who have not had a complete thrombophilia work-up may be tested. Although the results of thrombophilia testing will not alter the general recommendation for anticoagulation in pregnancy, the results may alter the intensity

from low or "prophylactic" to full adjusted-dose or "therapeutic." Although some experts would recommend thromboprophylaxis for all pregnant women with inherited thrombophilia, anticoagulation is probably not necessary if there is no personal history of thromboembolism or poor pregnancy outcome.[44] The exceptions, because of their especially high risk of thrombosis, are women with antithrombin deficiency, homozygosity for the factor V Leiden mutation or the prothrombin gene G20210A mutation, or heterozygosity for both mutations (compound heterozygosity).[44]

Anticoagulation and Pregnancy

Unique aspects of anticoagulation in pregnancy include both maternal and fetal issues. Warfarin, the preferred agent for long-term anticoagulation outside of pregnancy, has harmful fetal effects. Warfarin taken during the critical period for organogenesis, the 4th to the 8th week after conception,[45] is associated with a 14.6% to 56% reported risk of miscarriage[49–55] and, depending on the case series, carries up to a 30% risk of congenital anomalies.[46–52] Placental transfer of warfarin later in pregnancy can result in fetal bleeding[52,53] or stillbirth.[47,49,50,54] Long-term sequelae include a 14% reported risk of adverse neurological outcome[55] and a 4% reported risk of low intelligence quotient (IQ).[55]

The preferred agents for anticoagulation in pregnancy are heparin compounds.[44] Neither heparin[56–58] nor low-molecular-weight heparin[57,58] cross the placenta, and both are considered safe in pregnancy.[35,39] Unique aspects of anticoagulation in pregnancy include an increase in maternal blood volume of 40% to 50%[15] and an increase in the volume of distribution. An increase in glomerular filtration[15] results in increased renal excretion of heparin compounds, which are eliminated by this route. Additionally, there is an increase in protein binding of heparin. During pregnancy, both unfractionated heparin[59] and low-molecular-weight heparins[60–64] have shorter half-lives and lower peak plasma concentrations, usually necessitating higher doses and more frequent administration.

Disadvantages of unfractionated heparin include the necessity of parenteral administration, a risk of major bleeding,[39] a risk of reduced bone density,[65–67] a risk of vertebral fracture,[68] and a risk of heparin-induced thrombocytopenia (HIT).[44] Although the risk of HIT is low in pregnancy and may be lower than in nonpregnant patients,[69] the actual risk is unknown.[44]

There are few comparative studies in pregnancy, but in nonpregnant patients, low-molecular-weight heparin has been associated with fewer side effects than unfractionated heparin.[70] Potential advantages of low-molecular-weight heparin are less bleeding, a more predictable response, a lower risk of HIT (no cases were confirmed in two large reviews of the use of low-molecular-weight heparin in pregnancy[34,40]), a longer half-life, and less bone loss.[71] However, in a randomized trial of low-dose unfractionated heparin versus enoxaparin (a low-molecular-weight heparin) for thromboprophylaxis in pregnancy, there was no difference in the incidence of clinically significant bone loss (which was 2 to 2.5%) between women who took unfractionated heparin compared to those who took enoxaparin,[67] and another study found that

bone loss in women who took low-molecular-weight heparin was approximately 4%, the same as in controls.[72] An advantage of enoxaparin, and probably other low-molecular-weight heparins as well, is less bruising at injection sites.[73] A disadvantage of low-molecular-weight heparins, besides their cost, is their longer half-life, which is an issue at the time of delivery.

Fondaparinux is a new selective factor Xa inhibitor used for thromboprophylaxis. Data on its use in pregnancy are limited. Although Lagrange et al[74] observed no transplacental passage of fondaparinux using a perfused cotyledon model, Dempfle et al[75] found transplacental passage of fondaparinux in 5 women who took it for 1 to 101 days because of heparin allergy. Antifactor Xa levels in umbilical cord plasma of newborns were found to be one tenth the concentration of maternal plasma. The clinical significance of this finding is unknown, but no adverse effects were noted in the newborns.[75]

Fondaparinux may not be effective in reducing the risk of pregnancy loss in women for whom it is prescribed for that indication, such as women with the antiphospholipid syndrome. Unlike heparin or low-molecular-weight heparin, fondaparinux does not prevent fetal death in mice with antiphospholipid antibodies.[76] At the present time there are insufficient data to justify the routine use of fondaparinux for prophylaxis of VTE in pregnancy. Nonetheless, fondaparinux is probably the anticoagulant of choice in cases of severe cutaneous allergies or HIT in pregnancy[75,77] where danaparoid (a nonheparin containing heparanoid composed of heparin sulfate, dermatan sulfate and chondroitin sulfate) is unavailable, such as in the United States.

There are no large trials of anticoagulants in pregnancy, and recommendations for their use are based on case series and the opinion of experts. Full-dose (adjusted dose) anticoagulation is recommended[44,78] for women with either a need for life-long anticoagulation or antiphospholipid syndrome with a history of thrombosis. Full-dose (adjusted dose) or an intermediate or moderate dose is recommended[44,78] for women with either antithrombin deficiency or homozygosity for the factor V Leiden mutation, the prothrombin gene G20210A mutation, or compound heterozygosity for both mutations. Low-dose anticoagulation is recommended[44,79] for women with a history of unprovoked thrombosis. In one series, women with a history of thrombosis in the setting of transient risk factors had a rate of recurrence in pregnancy similar to that of other women with a history of thrombosis,[32] but close observation (assessment of signs and symptoms of thrombosis at routine prenatal visits) may be an option for women with a history of thrombosis in the setting of transient risk factors such as injury or immobility.[44] Nonetheless, if these women do not receive anticoagulation during pregnancy, they should be considered for thromboprophylaxis postpartum.

New Onset DVT and Pulmonary Embolism in Pregnancy

The two most common initial symptoms, present in more than 80% of women with pregnancy-related DVT, are pain and swelling in an extremity.[7] When signs or symptoms suggest

new onset DVT, the recommended initial diagnostic test is compression ultrasonography of the proximal veins.[80] When results are equivocal or an iliac vein thrombosis is suspected, magnetic resonance venography (MRV) may be used.[81] The diagnosis of new onset pulmonary embolism (PE) is similar to that in the nonpregnant individual. Ventilation/perfusion (V/Q) scanning gives relatively low radiation exposure to the fetus.[81] With an indeterminate study in a woman without a DVT, a confirmatory test, such as angiography or spiral computed tomography (spiral CT), is necessary to prevent the woman from unnecessary exposure to anticoagulation during the rest of her pregnancy, at delivery, or in future pregnancies.[81]

Management of VTE During Pregnancy

In nonpregnant patients with DVT, hospital admission is frequently not necessary, but pregnant patients, who tend to have large clots, are usually admitted. Although low-molecular-weight heparin is sometimes used for the initial treatment of PE, it has not been as well studied in this situation. An advantage of intravenous unfractionated heparin over low-molecular-weight heparin in the initial treatment of PE is that the infusion can be turned off allowing the heparin to clear in a few hours. This may be important in situations where delivery, surgery, or thrombolysis (indicated for life or limb-threatening thromboembolism) may be necessary. When patients appear to be stable, they are usually switched from intravenous unfractionated heparin to low-molecular-weight heparin and can be discharged from the hospital.

Management of Anticoagulation at the Time of Delivery

Women may be converted from low-molecular-weight heparin to unfractionated heparin in the last month of pregnancy or sooner if delivery appears imminent. The purpose of converting women to unfractionated heparin, which is shorter acting, has less to do with any risk of bleeding at the time of delivery, but rather the rare possibility of an epidural or spinal hematoma with regional anesthesia.[82] Because of this possibility, anesthesiologists are reluctant to place a regional anesthetic if a woman has received low-molecular-weight heparin within the past 12 to 24 hours. Should a woman go into labor while taking unfractionated heparin, the heparin will usually clear within 6 hours. Reversal of heparin is rarely required and is not indicated for low-dose heparin. Although the use of pneumatic compression devices for the prevention of pregnancy-related thrombosis has not been studied, extrapolating from perioperative data,[83] the placement of pneumatic compression devices in labor or before cesarean delivery is recommended for women whose anticoagulation has temporarily been discontinued.

Thromboprophylaxis for Cesarean Delivery

Cesarean delivery at least doubles the risk of VTE,[4,84] but in the otherwise normal patient, the risk remains low (less than 1 per 1000).[84,85] Randomized trials of thromboprophylaxis at the time of cesarean delivery have been small and not adequately powered to assess a decrease in the risk of DVT or PE with anticoagulation and published decision analyses have substantial limitations. Nonetheless, patients with at least one additional risk factor may be candidates for thromboprophylaxis with pneumatic compression devices, unfractionated heparin or low-molecular-weight heparin.[44] Patients with multiple risk factors at high risk of DVT or PE should receive thromboprophylaxis with both pneumatic compression devices and unfractionated heparin or low-molecular-weight heparin.[44] Obviously, any patient receiving thromboprophylaxis during pregnancy will require thromboprophylaxis postpartum.

Postpartum Management of Anticoagulation

To minimize bleeding complications, resumption of anticoagulation should be postponed until 12 hours after vaginal delivery, 12 hours after epidural removal, or 24 hours after cesarean delivery. Pneumatic compression devices should be left in place until the patient is ambulatory and until anticoagulation is restarted. After the risk of postpartum hemorrhage has decreased, which may be 2 or more weeks after delivery, women who require more than 6 weeks of anticoagulation may be bridged to warfarin, which is compatible with breastfeeding.[86–88] Women who have experienced VTE during the current pregnancy should probably remain on warfarin for at least another 3 to 6 months after delivery. Estrogen-containing contraceptives are contraindicated for the woman with thrombophilia or a history of thrombosis who is not on anticoagulation, but progestin-only contraceptives have not been found to increase the risk of thrombosis and are, therefore, generally allowed.[89]

Summary

Women are at an increased risk of both venous and arterial thromboembolism during pregnancy. The main reason is hypercoagulability. Risk factors include a history of thrombosis, thrombophilia, certain medical conditions, and some complications of pregnancy and childbirth. Despite the increased risk of thrombosis during pregnancy and the postpartum period, most women do not require anticoagulation. Exceptions are women with a current thrombosis, women with a history of thrombosis, women with thrombophilia and a history poor pregnancy outcome, and women at high risk for thrombosis postpartum. Unique aspects of anticoagulation in pregnancy include both maternal and fetal issues. For fetal reasons, the preferred agents for anticoagulation in pregnancy are heparin compounds. At the time of delivery, anticoagulation should be manipulated to reduce the risk of bleeding complications while minimizing the risk of thrombosis.

Disclosures

None.

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