Anticoagulation in Pregnancy

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KEYWORDS

• Pregnancy • Anticoagulation • Mechanical prosthetic valves • Thromboembolism
• Antithrombotic therapy

KEY POINTS

- Normal pregnancy is accompanied by changes in hemostasis that produce a hypercoagulable state that helps to prevent possible hemorrhage during delivery or miscarriage. Most clotting factors usually increase in pregnancy, whereas several anticoagulants and fibrinolytic activity decrease.
- In pregnant patients with prosthetic valves, therapy with low-molecular-weight heparin is an attractive alternative to vitamin K antagonists (which can have harmful fetal effects) and unfractionated heparin, which has several disadvantages, including heparin-induced thrombocytopenia and osteopenia.
- Mitral stenosis (MS), the most common valvular heart disease in pregnancy with a significant impact on both maternal and fetal outcome, carries a significant risk of thromboembolism. Prophylactic anticoagulation is indicated in patients with MS with atrial fibrillation or a previous history of an embolic event because these patients have the highest risk for thromboembolic events.
- Anticoagulation therapy is not required in pregnant women with a short episode of lone atrial fibrillation.

THE HYPERCOAGULABLE STATE OF PREGNANCY

Normal pregnancy is accompanied by changes in hemostasis that produce a hypercoagulable state that helps to prevent possible hemorrhage at the time of delivery or miscarriage. Most clotting factors usually increase in pregnancy, together with a decrease in several anticoagulants and fibrinolytic activity. Specifically, there is an increased concentration of factors VII, VIII, X, and von Willebrand factor.[1] Concomitantly, there is a decrease in anticoagulant factors, including free and total protein S, as well as decreased activity during early pregnancy. Although protein C levels remain unchanged,[2,3] there is an increase in activated protein C resistance, partly because of several modifiers such as the presence of factor V Leiden mutation, thrombin generation, and the presence of antiphospholipid antibodies.[4] Fibrinolysis is decreased, predominantly because of diminished tissue plasminogen activator activity. Plasminogen activator inhibitor type 1 (PAI-1) levels are increased as well as levels of PAI-2, produced by the placenta. Other markers of thrombin generation include increased thrombin-antithrombin complexes, prothrombin fragments 1 and 2, peak thrombin generation, and increased D-dimer levels.[2,3,5] All these changes result in a hypercoagulable state of pregnancy and may not return to normal ranges for at least 8 weeks after delivery,[6] and result in a 3-fold to 4-fold and 4-fold to 5-fold increase in arterial thromboembolism (strokes and myocardial infarction) and venous thromboembolism, respectively, during gestation, and a further increased risk (20-fold) post partum[7] compared with that of nonpregnant women.[7–9] The overall prevalence of thromboembolic events during

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pregnancy is approximately 2 per 1000 deliveries[8–10]; most (up to 80%) are venous and the rest of these events are arterial.[9]

Because of alterations in hemostasis and coagulability[11,12] pregnancy in women with mechanical heart valves (MHVs) carries a high rate of thromboembolic complications. Earlier published studies reported thromboembolic events in 7% to 23% of such cases[12–14]; half of them had valve thrombosis, leading to a high mortality of up to 40%. More recent reports, including mostly women with new-generation, less thrombogenic MHVs, have described maternal mortality between 1% and 4%, with most deaths attributable to thrombotic complications.[15,16] Prepregnancy counseling and education of the patient and her family regarding appropriate anticoagulation strategy planning are of paramount importance. However, women receiving suboptimal therapy often come to medical attention already pregnant. Because of the increased risk of severe thromboembolic complications in pregnancy, effective anticoagulation is critical in such patients, but remains problematic because both vitamin K antagonists (VKAs) and unfractionated heparin (UFH) can be associated with important fetal and maternal complications.

ANTICOAGULATION IN PATIENTS WITH PROSTHETIC VALVES

VKAs

VKAs are the preferred agents for long-term anticoagulation in nonpregnant women with MHV, but can have harmful fetal effects. When used during the critical period for organogenesis, the fourth to the eighth week after conception, there is a 15% to 56% reported risk of miscarriage[17–23] and, depending on the case series, a 5% to 30% risk of congenital anomalies.[17–19] Placental transfer of warfarin later in pregnancy can result in fetal bleeding or stillbirth[20–22] and long-term sequelae include an increased risk of adverse neurologic outcome.[15] Vitale and colleagues[24] reported a high frequency of fetal complications (88%), including spontaneous abortions, congenital heart disease, growth retardation, and warfarin embryopathy in women with MHV when treated with warfarin at a dose exceeding 5 mg/d throughout the pregnancy. Sadler and colleagues[25] described similar results, regardless of the warfarin dose. Long-term effects included an adverse neurologic outcome in 14% of cases and low IQ in 4%.[22]

UFH

UFH has traditionally been considered the drug of choice for the prevention and treatment of thrombotic disorders during pregnancy.[23] This drug does not cross the placenta and therefore offers little direct risk to the fetus.[26,27] However, UFH has several disadvantages including heparin-induced thrombocytopenia (HIT) and osteopenia,[26] and the latter may lead to symptomatic vertebral fracture in approximately 2% of women.[28,29] In addition, an increase in the volume of distribution caused by a 40% to 50% increase in maternal blood volume, as well as an increase in glomerular filtration,[12,30] which lead to an increase in renal excretion of heparin compounds, results in a shorter half-life and lower peak plasma concentration of heparin compounds, and the need to use higher doses and more frequent administration.[31] The incidence of HIT is low in pregnancy, but the risk is unknown.[23] In HIT, fondaparinux, a new selective factor Xa inhibitor, is the anticoagulant of choice, although data on its use in pregnancy are limited.[32]

Low-Molecular-Weight Heparin

Therapy with low-molecular-weight heparin (LMWH) in pregnancy is an attractive alternative to VKAs and UFH. LMWH has superior subcutaneous absorption and bioavailability[28] (90% vs 10%), and a 2-fold to 4-fold longer half-life. Because LMWH does not bind to plasma proteins, it may be associated with a more predictable dose response compared with UFH.[33] Similar to UFH and because of accelerated clearance, LMWH has a shorter half-life and lower peak plasma concentration during pregnancy than in nonpregnant women, and therefore requires higher doses and sometimes more frequent administration.[34] In nonpregnant patients, LMWH has been associated with fewer side effects than UFH.[23] Potential advantages of LMWH include less bleeding, a more predictable and stable response, and a lower risk of HIT.[35,36] However, in a randomized trial of low-dose UFH versus LMWH for thromboprophylaxis in pregnancy, there was no difference in the incidence of clinically significant bone loss (2%–2.5%) between women on UFH compared with those on enoxaparin.[37] Disadvantages of LMWH are its longer half-life and the inability to fully reverse its effect, issues that may increase the risk of bleeding at the time of delivery.[38]

GUIDELINES FOR ANTICOAGULATION REGIMENS IN PREGNANT PATIENTS WITH PROSTHETIC HEART VALVES

The 2008 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (**Box 1**) state that there are insufficient grounds to make definitive recommendations about optimal