Use of Antithrombotic Agents During Pregnancy

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Antithrombotic therapy during pregnancy is used for the treatment and prophylaxis of venous thromboembolic disease, for the prevention and treatment of systemic embolism associated with valvular heart disease and/or prosthetic heart valves, and for the prevention of fetal growth retardation and pregnancy loss in patients with antiphospholipid antibodies and pregnancy-induced hypertension. However, all three antithrombotic agents, namely heparin, coumarins, and aspirin, have potential complications in the mother and fetus so that their use during pregnancy could present problems. Furthermore, the literature supporting the use of these antithrombotic agents during pregnancy is difficult to evaluate because most of the reports are level V studies. This article reviews the fetal and maternal effects of anticoagulants and acetylsalicylic acid (ASA) and gives recommendations for their use during pregnancy.

Since our last review, new information has appeared on the anatomic localization and timing of venous thrombosis during pregnancy, on possible changes in heparin clearance at the time of delivery, on the incidence of osteoporosis during long-term heparin treatment, and on a potential role for aspirin therapy during pregnancy in reducing fetal morbidity and mortality.

ANATOMIC LOCALIZATION AND TIMING OF VENOUS THROMBOSIS DURING PREGNANCY

Several studies have reported a striking propensity for venous thrombi during pregnancy to occur in the left leg. The reason for this is not entirely clear, although compression of the left iliac vein by the right iliac artery as they cross may be a contributing factor. Although symptoms of leg swelling and pain occur most commonly in the third trimester, evidence from a recent prospective study indicates that venous thrombosis documented by objective testing occurs with equal frequency in all three trimesters. This apparent discrepancy between subjective and objective evidence of venous thrombosis can probably be explained by compression of the common iliac veins by the enlarged uterus during the third trimester of pregnancy which can produce clinical features that mimic venous thrombosis. The practical implications of these clinical observations are first, that symptoms of pain and swelling in the third trimester are commonly due to extrinsic venous compression, while the appearance of these symptoms in the first two trimesters is more likely to be caused by venous thrombosis; and second, the risk of developing venous thrombosis does not appear to be higher later in pregnancy than during the first two trimesters. This suggests that intensification of surveillance and prophylaxis during the third trimester in pregnant women with previous venous thrombosis (recommended in our previous review) is not indicated.

SIDE EFFECTS OF ANTICOAGULANTS IN PREGNANCY

Fetal Complications

Anticoagulants have the potential to produce adverse effects in mother and fetus, and the safety of their use in pregnancy remains a subject of debate. Heparin does not cross the placenta, and therefore, might not be expected to produce fetal complications, whereas oral anticoagulants cross the placenta, enter the fetal circulation, and have the potential to produce adverse effects in the fetus.

Nevertheless, in a literature review of anticoagulant therapy during pregnancy, it was concluded that the use of anticoagulants was associated with an adverse fetal outcome in approximately one third of pregnancies regardless of whether heparin or coumarin derivatives were used. The implication of the findings of the review is that the use of heparin during pregnancy is not safer for the fetus than oral anticoagulants. However, two recent studies suggest that heparin therapy is relatively safe for the fetus. The first study (level V) reviewed published studies through 1986 and demonstrated that when pregnancies associated with comorbid maternal conditions that could independently cause adverse fetal outcomes and pregnancies associated with uncomplicated prematurity were excluded, the rate of adverse fetal outcomes in heparin-treated patients was similar to a normal population. Thus, the high rate of adverse fetal outcomes associated with heparin is largely due to the practice of treating toxemia, glomerulonephritis, and recurrent abortions (conditions that are independent causes of adverse fetal outcomes) with heparin therapy. The second study (level IV) was a cohort study of 100 consecutive pregnancies associated with heparin therapy and reported that the rate of adverse fetal/neonatal outcomes was comparable to a normal population. Thus, to
summarize, it is likely that heparin therapy is safe for the fetus, whereas oral anticoagulants may not be, particularly during the first trimester.

The reported fetopathic effects of warfarin include the warfarin embryopathy and central nervous system abnormalities. Warfarin embryopathy consists of nasal hypoplasia or stippled epiphyses or both after in utero exposure to oral anticoagulants during the first trimester of pregnancy. Central nervous system abnormalities that have been associated with oral anticoagulant therapy include the following: (1) dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformations, and midline cerebellar atrophy; (2) ventral midline dysplasia characterized by optic atrophy; and (3) hemorrhage.

The cohort study (level IV) by Iturbe-Alessio et al9 in which warfarin therapy was administered to 72 pregnant patients with prosthetic heart valves is the only prospective study that reported the incidence of congenital malformations following maternal warfarin therapy. Warfarin embryopathy occurred in 10 of 35 (28.5 percent) infants after warfarin exposure between 7 and 12 weeks of gestation and in none of the infants in whom warfarin was discontinued between 6 and 12 weeks of gestation. There were no central nervous system abnormalities reported.

Although the interpretation of the above data is limited by the design of the reported studies, it is very likely that heparin therapy during pregnancy is safe for the fetus. On the other hand, warfarin therapy during pregnancy may be associated with congenital malformations.

Maternal Complications

**Bleeding:** The most common maternal complication is hemorrhage. In a cohort study (level IV),9 the rate of bleeding in pregnant patients treated with heparin therapy was 2 percent. This is consistent with the reported rates of bleeding associated with heparin therapy in nonpregnant patients and with warfarin therapy when used for the treatment of venous thrombosis.10

Since our previous publication, it has been noted that heparin therapy has the potential to cause a persistent anticoagulant effect at the time of delivery, and thus, increase the risk of bleeding. In a recent cohort study (level IV) of 11 pregnancies in 10 different pregnant women receiving adjusted dose subcutaneous heparin therapy at the time of delivery, it was reported that an anticoagulant effect persisted for up to 28 h after the last injection of heparin.11 As a result, in women who were being treated with adjusted dose subcutaneous heparin, the delivery was frequently complicated by a prolonged activated partial thromboplastin time (APTT) which caused an increased risk of bleeding and frequent cancellation of epidural analgesia. The mechanism for this prolonged anticoagulant effect is unclear. However, one way of avoiding an unwanted anticoagulant effect during delivery is to discontinue heparin therapy 24 h prior to elective induction of labor. This should avoid the problem of having an anticoagulant effect at the time of delivery and reduce the risk of bleeding. If an anticoagulant effect occurs at the time of delivery, judicious use of protamine sulfate, to neutralize heparin, should be considered.

**Heparin-Induced Osteoporosis**

Long-term heparin therapy has been reported to cause osteoporosis in both laboratory animals and humans. Up until recently, the true risk of symptomatic osteoporosis to patients treated with heparin therapy was unknown. Two recent studies have provided estimates of the risk of symptomatic fractures in patients treated with long-term heparin therapy.12,13 In the first level III study,12 a cohort of 61 consecutive premenopausal women previously treated with long-term heparin and a group of control subjects matched for age, parity, and duration between the last pregnancy and study entry were evaluated. These patients were questioned to determine the incidence of symptomatic fractures and were evaluated with dual photon absorptiometry of the lumbar spine and single photon absorptiometry of the wrist in order to detect a subclinical reduction of bone density. None of the heparin-treated patients had suffered symptomatic fractures (0 of 61, 95 percent confidence intervals 0.0 to 5.9 percent), but there was a significantly greater proportion of heparin-treated patients than control subjects who had reduced bone density. In the second study (level V),13 70 patients treated with subcutaneous heparin therapy during pregnancy underwent x-ray examination of the spine and hip immediately postpartum and again 6 to 12 months postpartum. There were 12 patients with osteopenia and 2 women with multiple fractures of the spine. Re-examination 6 to 12 months postpartum demonstrated that the changes were reversible in most cases. Based on the results of these two studies, it can be concluded that although the risk of symptomatic fractures is low, a subclinical reduction in bone density is a potential consequence of long-term heparin therapy. It is unknown whether such women are predisposed to fractures in the postmenopausal period.

The mechanism for heparin-induced osteoporosis is not known. It is likely that the risk of osteoporosis is dependent upon the dose of heparin used and the duration of heparin therapy. It is not known whether intervention with agents such as calcium will be successful in preventing the reduction of bone density that occurs with long-term heparin therapy. A report by Zimran et al,14 in which a bone biopsy was
performed in a patient who developed osteoporosis after heparin therapy during pregnancy, suggests that the bone abnormalities seen pathologically may be reversible after discontinuation of heparin.

**USE OF ANTICOAGULANTS IN THE NURSING MOTHER**

Heparin is not secreted into breast milk and can be safely administered to nursing mothers. There have been two convincing reports that warfarin does not induce an anticoagulant effect in the breast-fed infant when the drug is administered to a nursing mother. In the first report, which used a sensitive and specific warfarin assay, warfarin was not detected in the breast milk of 13 nursing mothers. Seven of these mothers were breast-feeding their infants and warfarin was not detected in the plasma of any of the infants. In the second study, detailed investigations were performed on the plasma and breast milk of two nursing mothers who were being treated with warfarin and on the plasma of their breast-fed infants. Coagulation tests in each mother performed over a period of 56 days of warfarin treatment in one and over 132 days of warfarin treatment in the other, revealed that the prothrombin times were between 20 and 30 percent of control and that factor II, factor VII, and factor X levels were approximately 20 percent. No warfarin could be detected in the breast milk. In contrast to the effects seen in the mothers, the prothrombin times of both infants were 100 percent of control activity and factor II, factor VII, and factor X assays were 100 percent. The results of these two studies indicate that treatment of a nursing mother with warfarin does not induce an anticoagulant effect in the breast-fed infant.

**ANTIPHOSPHOLIPID ANTIBODIES**

Antiphospholipid antibodies (APLA) are a heterogenous group of antibodies directed against phospholipids that can be detected using clotting assays (lupus anticoagulant) or immunoassays (anticardiolipin antibodies). These antibodies have been reported to occur in systemic lupus erythematosus, with certain drugs, and in apparently healthy individuals. There is convincing evidence that the presence of APLA is associated with an increased risk of thrombosis. In addition, there is some evidence that the presence of APLA is associated with an increased risk of pregnancy loss. Thus, pregnant individuals with APLA should be considered at risk for both pregnancy loss and thrombosis.

The management of these patients is problematic because no large clinical trials evaluating therapy have been performed. There are descriptive studies (level V) suggesting that heparin alone or the combination of ASA and prednisone are effective at preventing pregnancy loss in individuals with APLA who have a history of multiple pregnancy losses. However, the use of high doses of prednisone is associated with significant side effects. The use of low dose ASA (100 mg) alone has been suggested, but its relative efficacy in preventing pregnancy loss or thrombosis has never been demonstrated by clinical trial. Based on current evidence, any recommendations on management must be very tentative. Women with APLA and a history of multiple pregnancy losses are considered candidates for either heparin or ASA plus prednisone, but the supporting evidence is based on two level V studies. Whether the patient with APLA and either no or one pregnancy loss should be treated with such therapy is unclear. Pregnant women with APLA and previous venous thrombosis should be considered candidates for heparin therapy. Women with APLA and no previous venous thrombosis should receive either with low dose heparin therapy or have surveillance with impedance plethysmography (IPG) or compression ultrasonography throughout pregnancy.

**SAFETY OF ASPIRIN DURING PREGNANCY**

Potential complications of aspirin administration during pregnancy include birth defects and bleeding in the neonate and in the mother. A recent critical review of the literature concerning the safety of aspirin during pregnancy has been published, and several conclusions were reached. Aspirin in any dose produces measurable hemostatic abnormalities in the mother but an increase in maternal bleeding is only seen with ingestion of more than 1 g per day; lesser doses do not appear to cause an increase in maternal bleeding. There may also be an increase in neonatal bleeding with maternal ingestion of one to four aspirin tablets per day close to term. Aspirin is a definite teratogen in animals, but it is not clear if it is teratogenic in humans. There are alleged associations between maternal aspirin use and cardiac abnormalities, problems with cognitive development and subsequent childhood cancer, but the studies are not all positive. The results of a recent meta-analysis (level I) reported that low dose (60 to 150 mg/dl) aspirin therapy administered during the second and third trimesters of pregnancy in women at risk for pregnancy-induced hypertension reduced the incidence of pregnancy-induced hypertension and the risk of severe low birth weight among newborns. The safety of these low dose aspirin regimens was strongly suggested because no maternal or neonatal adverse effects occurred in aspirin-treated individuals. Thus, based on current evidence, low dose (less than 150 mg/dl) aspirin during the second and third trimesters appears to be safe, but the safety of higher doses of aspirin and/or aspirin ingestion during the first trimester remains a subject of debate.

**SUMMARY AND CONCLUSIONS**

Anticoagulant therapy is indicated during pregnancy.
for the prevention and treatment of venous thromboembolism and for the prevention and treatment of systemic embolism in patients with prosthetic heart valves and other valvular heart disorders. Aspirin is effective in reducing complications associated with pregnancy-induced hypertensive disease and may be effective in combination with prednisone for the prevention of fetal loss associated with the presence of APLA. Several questions concerning anticoagulant therapy remain unanswered. Although it is highly likely that heparin therapy is safe for the fetus, the true risk of clinically important maternal osteoporosis after long-term heparin is unknown. Oral anticoagulants are fetopathic, but the true risks of the warfarin embryopathy and central nervous system abnormalities are unknown. There is some evidence that warfarin embryopathy occurs only when oral anticoagulants are administered between 6 and 12 weeks of gestation and that oral anticoagulants may not be fetopathic when administrated in the first 6 weeks of gestation. The fetal risks are probably lower after the 12th week of gestation than between the 6th and 12th weeks, but warfarin is probably still fetopathic when administered during the 2nd and 3rd trimesters. Oral anticoagulant therapy should be avoided in the weeks before delivery because of the risk of serious perinatal bleeding caused by the trauma of delivery to the anticoagulated fetus. The safety of aspirin during the first trimester of pregnancy is still a subject of debate. In addition, it is not clear whether aspirin alone is effective for the prevention of fetal loss associated with APLA.

**Recommendations**

Because it is safe for the fetus, heparin is the anticoagulant of choice during pregnancy for situations in which its efficacy is established (Table 1). The evidence for the efficacy of heparin for the prevention and treatment of venous thromboembolic disorders during pregnancy is based on level IV studies. Although it is likely that full doses of heparin are effective for the prevention of systemic embolism in patients with prosthetic heart valves, studies demonstrating the efficacy of heparin in such patients have not been published. Low doses of heparin appear not to be effective in preventing systemic embolism in patients with mechanical prosthetic valves (level IV). Thus, all studies of anticoagulants during pregnancy are level IV and level V studies, so all recommendations must be classed as grade C.

**Previous Venous Thromboembolism (Prophylaxis)**

In pregnant women with a history of previous venous thromboembolic disease, the risk of recurrence in untreated patients has been estimated at 4 to 12 percent. Consequently, some form of prophylaxis or surveillance should be considered. A recent cohort study (level IV) reported that the incidence of symptomatic recurrence in pregnant women with previous thromboembolism who were treated with heparin was very low. In view of the cohort study reporting that the incidence of venous thrombosis is not highest during the third trimester, a reasonable approach to patients with previous venous thromboembolism is to use low dose heparin (5,000 U every 12 h, subcutaneously) throughout pregnancy. This is a change from our previous recommendation (which was to use low dose heparin during the first two trimesters followed by adjusted dose heparin during the third trimester).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
<th>Grading of Recommendation</th>
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<tbody>
<tr>
<td>Previous venous thrombosis or pulmonary embolism prior to current pregnancy</td>
<td>Heparin 5,000 U q12h throughout pregnancy</td>
<td>Grade C</td>
</tr>
<tr>
<td>Venous thrombosis or pulmonary embolism during current pregnancy</td>
<td>Heparin in full intravenous doses for 5-10 days, followed by q12h subcutaneous injections to prolong 6 h postinjection APTT to 1 1/2 times control until delivery. Warfarin can then be used postpartum.</td>
<td>Grade C</td>
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<tr>
<td>Planning pregnancy in patient requiring long-term anticoagulation</td>
<td>Either heparin q12h subcutaneously to prolong 6 h postinjection APTT to 1 1/2 times control, or Frequent pregnancy tests and substitute heparin (as above) for warfarin when pregnancy achieved</td>
<td>Grade C</td>
</tr>
<tr>
<td>Mechanical prosthetic heart valves</td>
<td>Either heparin q12h subcutaneously to prolong 6 h postinjection APTT to 1 1/2 times control, or Adjusted dose subcutaneous heparin until the 13th week, warfarin until the middle of the third trimester, then adjusted dose subcutaneous heparin until delivery</td>
<td>Grade C</td>
</tr>
<tr>
<td>APLA and &gt;1 previous pregnancy loss</td>
<td>Either aspirin plus prednisone, or heparin</td>
<td>Grade C</td>
</tr>
<tr>
<td>APLA and 0 or 1 previous pregnancy loss</td>
<td>Low dose aspirin during the second and third trimester</td>
<td>Grade C</td>
</tr>
<tr>
<td>APLA and previous venous thrombosis</td>
<td>Heparin q12h subcutaneously to prolong 6 h postinjection APTT to 1 1/2 to 2 1/2 times control</td>
<td>Grade C</td>
</tr>
<tr>
<td>APLA without previous venous thrombosis</td>
<td>Either weekly or biweekly 1PC or compression ultrasonography, or heparin 5,000 U q12h throughout pregnancy</td>
<td>Grade C</td>
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since there is now evidence that the risk of venous thromboembolism during pregnancy is equally distributed throughout the three trimesters. Warfarin can then be used postpartum. This is a grade C recommendation.

**Treatment of Venous Thromboembolism of Pregnancy**

In patients who develop venous thrombosis during pregnancy, full doses of heparin should be given by intravenous infusion for 5 to 10 days and then by subcutaneous injection, every 12 h in full doses, until term. This recommendation is based on a level I study performed in nonpregnant patients, and a level IV study in pregnant patients that reported the efficacy of heparin for the treatment of acute venous thrombosis. Heparin should be discontinued immediately before delivery, and then both heparin and warfarin can be started postpartum. Once therapeutic prothrombin times are obtained, heparin can be discontinued and warfarin administered for at least a further two weeks.

**Unexpected Pregnancy or Planned Pregnancy During Long-Term Oral Anticoagulant Treatment**

Patients receiving long-term oral anticoagulant therapy for venous thromboembolism or valvular heart disease present problems when planning pregnancy or if pregnancy occurs unexpectedly. It is possible that oral anticoagulants are safe during the first 6 weeks of gestation, but the risk of the warfarin embryopathy may be as high as 25 to 30 percent if warfarin is taken between 6 and 12 weeks of gestation. Ideally, such women should be counselled before pregnancy occurs. If anticoagulant therapy is indicated during pregnancy, the risks should be explained before conception. If pregnancy is still desired, two options can be considered. The first is to perform frequent pregnancy tests and to substitute heparin for warfarin when pregnancy is achieved. The second is to replace warfarin with heparin before conception is attempted. Both approaches have limitations; the first assumes that warfarin is safe during the first 4 to 6 weeks of gestation and the second increases the duration of exposure to heparin, and therefore, there is a higher risk of osteoporosis.

**Prophylaxis in Patients with Prosthetic Heart Valves**

The management of pregnant patients with prosthetic heart valves is problematic because the efficacy of heparin is not established. Nevertheless, it is highly likely that full doses of heparin are effective in preventing systemic embolism. Two approaches have been recommended (both are grade C); the first is to use heparin therapy throughout pregnancy administered every 12 h by subcutaneous injection in doses adjusted to keep the midinterval APTT at 1½ to 2½ times the control value. The second approach is to use heparin until the 13th week, change to warfarin until the middle of the third trimester, and restart heparin therapy until delivery. Although the latter approach might avoid warfarin embryopathy, other fetopathic effects (eg, central nervous system abnormalities) are still possible. Therefore, before this approach is recommended, the potential risks should be explained to the patients. A further potential problem with the use of oral anticoagulants during pregnancy arises from the clear statement in the manufacturer’s package insert that coumarin is contraindicated during pregnancy. This statement carries with it medicolegal implications which would also have to be discussed with the patient if a choice is made to use oral anticoagulants during pregnancy.

**Pregnancy and APLA**

Pregnant patients with APLA and a history of multiple pregnancy losses are candidates for ASA plus prednisone or heparin alone. For pregnant patients with APLA and a history of no or one pregnancy loss, low dose ASA alone during the second and third trimesters seems reasonable since it is relatively safe and may be effective. Patients with APLA and a history of venous thrombosis are candidates for long-term anticoagulant therapy. During pregnancy, adjusted dose subcutaneous heparin therapy seems reasonable. In the absence of previous venous thrombosis, pregnant patients with APLA should be considered to be at risk for the development of venous thrombosis and either surveyed with noninvasive tests (IPG or compression ultrasonography) or treated with low dose subcutaneous heparin.

**References**

Antithrombotic Agents during Pregnancy (Ginsberg, Hirsh)