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 as well as patients with pregnancy-induced hypertension. Since antithrombotic agents have the potential to produce complications in both the mother and fetus, their use during pregnancy raises concerns. Definitive guidelines are difficult to establish because the evidence on which recommendations can be based is derived primarily from level V studies in pregnant patients. This article reviews the fetal and maternal effects of antithrombotic agents, including oral anticoagulants, unfractionated heparin, low molecular weight heparins (LMWHs), and aspirin, and provides recommendations for their use during pregnancy.

Since our last review, new information has appeared on the epidemiology of venous thrombosis that has the potential to influence the approach to pregnant women with venous thrombosis, on the incidence of osteoporosis during long-term heparin therapy, on the use of LMWHs during pregnancy, on the safety and efficacy of anticoagulants in pregnant women with prosthetic heart valves, and on the role of aspirin therapy in reducing fetal morbidity and mortality in high-risk pregnancies.

Epidemiology of Venous Thromboembolism

Pregnancy and the postpartum state are considered to be risk factors for venous thromboembolism (VTE), but the absolute risks are likely to be small. There are two recent findings that have the potential to affect the treatment of pregnant women with venous thrombosis: (1) the observation that patients who present with idiopathic deep vein thrombosis (DVT) have a much higher recurrence rate than patients who develop DVT in association with a transient risk factor, and (2) the recent discovery of hereditary resistance to activated protein C, which predisposes affected individuals to VTE.

The results of two randomized trials and a cohort study have shown that patients who develop “secondary” DVT in the presence of a transient risk factor, such as major orthopedic or abdominal surgery, have a much lower incidence of recurrent VTE than patients who develop “idiopathic” DVT (DVT occurring in the absence of a clinical risk factor) or DVT in association with an ongoing risk factor (eg, patients with metastatic cancer). This observation on the prognosis of DVT has the potential to influence the risk of recurrent venous thrombosis in pregnant women with previous VTE. Although accurate estimates of the true incidence of recurrent VTE are not available in such women, it is reasonable to assume that women whose original DVT occurred secondary to a transient risk factor have a lower risk of recurrent VTE in association with pregnancy than women whose original DVT was idiopathic or associated with an ongoing risk factor. Based on these observations in nonpregnant patients, it would be reasonable to follow up low-risk women by surveillance and to use active prophylaxis in high-risk women.

Activated protein C resistance is caused by a mutation in the factor V gene that alters a binding site of factor V for activated protein C. The abnormality can be detected using an activated partial thromboplastin time (APT T)-based assay, or by identification of the specific genetic mutation. Activated protein C resistance has been reported to occur in approximately 5% of the “normal” population and in 20 to 40% of unselected patients with DVT and, therefore, might be the most common hereditary cause of VTE. To date and to our knowledge, there are no published studies on the incidence of activated protein C resistance in pregnant women with previous VTE, but until further information becomes available, women with activated protein C resistance (both with and without a history of previous VTE) should be considered to be at increased risk for VTE.

As in the general population, it is likely that women with congenital deficiencies of antithrombin III, protein C, or protein S, or the persistent presence of antiphospholipid antibodies have an increased risk of VTE during pregnancy and the puerperium. Women with previous VTE might also have an increased risk of recurrent VTE during pregnancy and the puerperium, but the results are conflicting. Thus, retrospective studies have reported the incidence of recurrent VTE to be as high as 15% during pregnancy in women with previous DVT. In contrast, the results of one randomized trial reported that 1 of 20 untreated patients (5%) with previous VTE developed recurrent antepartum VTE and a cohort study (published in letter form) reported that none of 59 pregnant patients with previous VTE developed antepartum recurrence. It is likely that the risks of both initial and recurrent DVT are higher postpartum than antepartum. Conclusions from these studies are limited by the relatively small numbers and lack of description of the inception cohorts. Controlled clinical trials are required to establish the true incidence of recurrent VTE in pregnant women and the safety and efficacy of anticoagulant therapy in preventing recurrent VTE.

Anticoagulant Therapy During Pregnancy

The agents currently available for the prevention and treatment of VTE include heparin and heparin-like compounds (unfractionated heparin, LMWH, and heparinoids) and coumarin derivatives.

Fetal Complications of Anticoagulants During Pregnancy

There are two potential fetal complications of maternal anticoagulant therapy: teratogenicity and bleeding. Heparin does not cross the placenta and, therefore, does not have the potential to cause fetal bleeding or teratogenicity, although bleeding at the uteroplacental junction is possible. Two recent studies strongly suggest that heparin therapy is safe for the fetus.
In contrast to heparin, coumarin derivatives cross the placenta and have the potential for both bleeding in the fetus and teratogenicity.\textsuperscript{15,16} Coumarin derivatives can cause an embryopathy, which consists of nasal hypoplasia and/or stippled epiphyses after in utero exposure to oral anticoagulants during the first trimester of pregnancy, and CNS abnormalities that can occur after exposure to such drugs during any trimester.\textsuperscript{16} It is possible that oral anticoagulants are safe during the first 6 weeks of gestation, but there is a risk of embryopathy if coumarin derivatives are taken between 6 and 12 weeks of gestation.\textsuperscript{17} In addition, these oral anticoagulants cause an anticoagulant effect in the fetus that is a concern, particularly at the time of delivery, when the combination of the anticoagulant effect and trauma of delivery can lead to bleeding in the neonate.

**Maternal Complications of Anticoagulant Therapy During Pregnancy**

In a recent cohort study (level IV), the rate of major bleeding in pregnant patients treated with heparin was 2%,\textsuperscript{14} which is consistent with the reported rates of bleeding associated with heparin therapy in nonpregnant patients\textsuperscript{18} and with warfarin therapy\textsuperscript{19} when used for the treatment of DVT. In addition, adjusted-dose subcutaneous heparin therapy can cause a persistent anticoagulant effect at the time of delivery, which can complicate its use prior to labor.\textsuperscript{20} In a recent study (level IV), an anticoagulant effect persisted for up to 28 h after the last injection of adjusted-dose subcutaneous heparin, frequently resulting in deliveries that were complicated by a prolonged APTT.\textsuperscript{30} The mechanism for this is unclear; however, one way to avoid an unwanted anticoagulant effect during delivery in women receiving adjusted-dose subcutaneous heparin therapy is to discontinue heparin therapy 24 h prior to elective induction of labor. If spontaneous labor occurs in women receiving adjusted-dose subcutaneous heparin therapy, careful monitoring of the APTT is required and, if it is prolonged near delivery, probamine sulfate may be required to reduce the risk of bleeding.

Long-term heparin therapy causes osteoporosis; the mechanism is unknown. Four recent studies provide estimates of the risk of heparin-induced osteoporosis with long-term heparin therapy.\textsuperscript{21-24} The results of these studies show that although the risk of symptomatic fractures is low (\(\leq 2\%\)), a subclinical reduction in bone density, detected radiographically, occurs in up to one third of women receiving long-term (>1 month) heparin therapy. The radiologic effects of heparin are at least partly reversible. It is unknown whether women with reduced bone density due to heparin are predisposed to future fractures. Although none of the four studies showed that the risk of osteoporosis is dependent on the dose of heparin used and the duration of heparin therapy, none was sufficiently large to exclude such relationships.

In some women, there can be considerable discomfort associated with twice-daily self-administered heparin injections. Therefore, the use of an indwelling subcutaneous Teflon catheter (Insuflon), which must be replaced weekly, is a useful approach in pregnant women who require long-term heparin therapy.\textsuperscript{25}

**Use of Anticoagulants in the Nursing Mother**

Heparin is not secreted into breast milk and can be administered safely to nursing mothers.\textsuperscript{26} 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.\textsuperscript{27,28} Therefore, the use of warfarin in women who require anticoagulant therapy postpartum is reasonable; these women should be encouraged to breast feed.

**LMWHs and Heparinoids**

There is accumulating experience with the use of these agents both in pregnant and nonpregnant patients for the prevention and treatment of DVT.\textsuperscript{29-31} Based on the results of large clinical trials in nonpregnant patients, LMWHs and heparinoids are at least as effective and safe as unfractionated heparin for the treatment of patients with acute proximal DVT\textsuperscript{30,31} and for the prevention of DVT in patients who undergo surgery.\textsuperscript{33} They have the advantage of a longer plasma half-life and a more predictable dose response than unfractionated heparin.

There is also evidence that LMWHs and heparinoids do not cross the placenta.\textsuperscript{35-37} These agents have potential advantages over unfractionated heparin during pregnancy because they cause less heparin-induced thrombocytopenia (HIT),\textsuperscript{38} have the potential for once-daily administration, and may have a lower risk of heparin-induced osteoporosis.\textsuperscript{34,39} In pregnant women who develop HIT and require ongoing anticoagulant therapy, use of the heparinoid danaparoid (Org 10172) ran is recommended because it is an effective antithrombotic agent and has much less cross-reactivity with unfractionated heparin and therefore, less potential to produce recurrent HIT than LMWH.\textsuperscript{40} These agents are more expensive than unfractionated heparin and, therefore, until clinical trials comparing their efficacy and safety with unfractionated heparin are performed, there is insufficient evidence to endorse them for routine clinical use in pregnant patients who require anticoagulant therapy. However, danaparoid is likely to be useful in pregnant patients with HIT, and LMWHs should be considered in patients with intractable painful skin reactions to unfractionated heparin.

**Efficacy of Anticoagulants for the Prevention and Treatment of VTE During Pregnancy**

There is a paucity of data about the efficacy of anticoagulants for the prevention and treatment of VTE during pregnancy. Accordingly, the recommendations about their use during pregnancy are based largely on extrapolations from data in nonpregnant patients and case reports and case series of pregnant patients. Based on the safety data, heparin is the drug of choice for the prevention and treatment of VTE during pregnancy.

The results of a large randomized trial in nonpregnant patients have shown that full-dose IV heparin therapy, followed by 3 months of subcutaneous (SC) heparin every 12 h, in doses adjusted to prolong a midinterval APTT into the therapeutic range (adjusted-dose SC heparin) is safe and effective.\textsuperscript{15} Therefore, it seems reasonable to extrapolate...
these results to pregnant patients with DVT and pulmonary embolism (PE) and use IV heparin therapy followed by at least 3 months of adjusted-dose SC heparin therapy.

Pregnant women with previous VTE are probably at increased risk for recurrent VTE, but the magnitude of the risk is unknown. It is likely that the risk of recurrence is higher in women with previous idiopathic VTE than in women who developed VTE in association with a transient risk factor. It is not clear whether women who developed VTE in association with previous pregnancy are at a relatively higher risk of recurrence. Based on the current state of knowledge, there are two reasonable approaches to pregnant patients with previous VTE: (1) active prophylaxis with heparin, and (2) clinical surveillance with or without regular noninvasive tests such as venous compression ultrasonography (CUS) or impedance plethysmography (IPG). SC heparin, 5,000 U every 12 h, is effective and safe for the prevention of VTE in high-risk nonpregnant patients and its use has been recommended in pregnant patients. However, there is a concern that a dose of heparin, 5,000 U SC every 12 h, may be insufficient in high-risk situations because it does not reliably produce detectable heparin levels. There are also published data (level III) that more intense heparin therapy, in doses that produce plasma heparin levels (measured as antifactor Xa activity) of 0.1 to 0.2 IU/mL, is associated with low recurrence rates. The advantage of this latter approach is that it is more likely to produce a consistent anticoagulant effect throughout pregnancy, but its use is likely to increase the risks of bleeding and osteoporosis and requires laboratory monitoring. Until comparative clinical trials are performed, it is our belief that either approach is reasonable.

In pregnant women with previous VTE who cannot use or refuse to use heparin, an alternative is clinical surveillance with or without regular IPG or CUS. To our knowledge, the safety of this approach has never been demonstrated in a large clinical trial and is dependent on detection and treatment of VTE before the development of major PE. When using this approach, it is important that the clinician recognize the relative insensitivity of IPG and CUS to asymptomatic proximal DVT. This approach is reasonable in women who developed previous VTE in association with a previous risk factor (eg, leg fracture) in whom the risk of recurrence is likely to be low.

Treatment of Pregnant Women With Prosthetic Heart Valves

Women of childbearing potential with valvular heart disease pose problems because of the lack of reliable data on the efficacy and safety of antithrombotic therapy during pregnancy and the concern that bioprosthetic heart valves deteriorate at an accelerated rate during pregnancy. In a recent retrospective survey (level V) describing outcomes in pregnant women with mechanical heart valves, it was concluded that (1) warfarin was safe and not associated with embryopathy, and (2) heparin was associated with more thromboembolic and bleeding complications than warfarin. The reported high rates of thromboembolism might also be explained by inadequate heparin dosing and/or the use of an inappropriate target therapeutic range. Nevertheless, this recent publication does raise the concern that patients with mechanical heart valves are resistant to moderate doses of heparin and draws attention to the need to use adequate heparin doses in these patients. Insufficient heparin dosing is associated with treatment failure, emphasizing the need for adequate initial heparinization and stringent monitoring.

Contemporary APTT reagents are more sensitive to the anticoagulant effect of heparin and, therefore, a minimum target APTT ratio of 1.5 times control is likely to be adequate and a target APTT ratio of at least twice control should be attained. The higher rate of thromboembolic events reported in heparin-treated women compared with warfarin-treated women is based on level V studies and is difficult to interpret because the adequacy of heparin dosing was usually not reported in these studies and a minimum target APTT ratio of 1.5 times control was often used. Long-term 12-hourly SC heparin therapy, in doses adjusted to prolong a midinterval APTT into the therapeutic range, has been shown to be as effective and safe as long-term warfarin therapy (international normalized ratio [INR] equivalent of 2.5 to 4.9) for the treatment of acute venous thrombosis. Such doses of heparin might be less effective than warfarin in preventing arterial thromboembolism in patients with mechanical heart valves but there are no data available (to our knowledge) to support or refute this conclusion.

At present, there are insufficient grounds to make definitive recommendations about optimal antithrombotic therapy in pregnant patients with mechanical heart valves because properly designed studies have not been performed. Substantial concern remains about the fetal safety of warfarin, the efficacy of SC heparin in preventing thromboembolic complications, and the risks of maternal bleeding with various regimens. Extrapolating from the results of a recent level I trial of nonpregnant patients with mechanical prosthetic heart valves or bioprosthetic heart valves and either chronic atrial fibrillation or previous thromboembolic events, it is reasonable to add low-dose (80 to 100 mg/d) aspirin therapy throughout pregnancy to the anticoagulant regimen.46 This recommendation is limited by the lack of safety and efficacy data on the combination of heparin and aspirin. Warfarin therapy should be avoided between 6 and 12 weeks of gestation (to avoid embryopathy) and close to term (to avoid delivery of an anticoagulated fetus) but is reasonable at these times. We believe it is reasonable to use SC heparin either during these periods only, with warfarin, target INR of 2.5 to 3.5, at other times, or to use heparin throughout pregnancy. SC heparin therapy should be initiated in doses of 17,500 to 20,000 U every 12 h and adjusted to prolong a 6-h postinjection APTT into the therapeutic range; strong efforts should be made to ensure an adequate anticoagulant effect since inadequate doses of heparin are ineffective. LMWHs or heparinoids are probably reasonable substitutes for unfractionated heparin because they appear to reduce the risk of bleeding and osteoporosis and do not cross the placenta, but further information is required about dosing and they are relatively expensive.

Antiphospholipid Antibodies

Antiphospholipid antibodies (APLAs) can be detected...
using clotting assays (lupus anticoagulant) or immunoassays (anticardiolipin antibodies)\textsuperscript{47} and 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 APLAs is associated with an increased risk of thrombosis\textsuperscript{47} and pregnancy loss.\textsuperscript{48} Thus, pregnant individuals with APLAs should be considered at risk for both pregnancy loss and thrombosis. The treatment of these patients is problematic because no large clinical trials evaluating therapy have been performed (to our knowledge). Regimens that have been evaluated include acetylsalicylic acid (ASA) alone\textsuperscript{49} or in combination with prednisone or unfractionated heparin,\textsuperscript{50} and IV γ-globulin.\textsuperscript{51} One randomized trial (level II) evaluated 20 pregnant patients with APLAs and histories of multiple prior pregnancy losses.\textsuperscript{50} In this study, patients were randomly allocated to receive ASA plus prednisone or ASA plus heparin. Fetal outcomes were similar in both groups (9 of 12 live births in ASA plus heparin group, 6 of 8 live births in ASA plus prednisone group), but serious maternal morbidity was higher in the prednisone-treated group. The investigators concluded that the regimens were equally effective and that ASA plus heparin was safer for the mother. However, the study was small, and the dose of prednisone was high (40 mg/d). The use of low-dose ASA (81 mg) alone has been shown to be as effective, but safer, than ASA plus prednisone in a small randomized trial (level II).\textsuperscript{49}

Based on current evidence, any recommendations on management must be very tentative. Women with APLAs and a history of multiple pregnancy losses are considered candidates for ASA alone, heparin plus ASA, or alternate-day prednisone plus ASA, but the supporting evidence is based on small studies. Whether the patient with APLAs and either no or one pregnancy loss should be treated with such therapy is unclear. Pregnant women with APLAs and previous venous thrombosis should be considered to be candidates for heparin therapy. Women with APLAs and no previous venous thrombosis should be treated either with low-dose heparin therapy or a combination of clinical surveillance combined with IPG or CUS throughout pregnancy.

Safety of Aspirin During Pregnancy

Potential complications of aspirin during pregnancy include birth defects and bleeding in the neonate and in the mother. The results of a recent meta-analysis\textsuperscript{52} (level I) and a large (>9,000 patients) randomized trial\textsuperscript{53} (level I) reported that low-dose (60 to 150 mg/d) aspirin therapy administered during the second and third trimesters of pregnancy in women at risk for pregnancy-induced hypertension or intrauterine growth retardation was safe for the mother and fetus because no increase in maternal or neonatal adverse effects occurred in aspirin-treated individuals. Thus, based on current evidence, low-dose (≤150 mg/d) aspirin therapy 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.

Conclusions

Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of VTE and for the prevention and treatment of systemic embolism in patients with mechanical heart valves. Aspirin might be effective in conjunction with anticoagulants for the prevention of systemic embolism in patients with mechanical heart valves and might be effective alone or in combination with prednisone or heparin for the prevention of fetal loss associated with the presence of APLAs. Several questions concerning anticoagulant therapy remain unanswered. Oral anticoagulants are fetopathic, but the true risks of the warfarin embryopathy and CNS abnormalities are unknown. There is some evidence that warfarin embryopathy occurs only when oral anticoagulants are administered between the sixth and the 12th weeks of gestation and that oral anticoagulants may not be fetopathic when administered in the first 6 weeks of gestation.\textsuperscript{17} 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. There is a concern about the efficacy of unfractionated heparin in the prevention of arterial embolism in pregnant women with mechanical heart valves. Finally, the role of LMWHs and heparinoids has still to be determined.

Recommendations

The relatively poor quality of evidence from the published studies makes it difficult to provide clear-cut recommendations. Because it is safe for the fetus, heparin is the anticoagulant of choice during pregnancy for situations in which its efficacy is established. The evidence for the efficacy of heparin for the prevention and treatment of VTE 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 mechanical heart valves, to our knowledge, studies demonstrating the efficacy of heparin in such patients have not been published. Low doses of heparin or poorly controlled heparin therapy appears not to be effective in preventing systemic embolism in patients with mechanical heart valves.\textsuperscript{17} Since all studies of anticoagulants during pregnancy are level IV and level V studies, recommendations must be classed as grade C (Table I).

Previous VTE (Prophylaxis)

In pregnant women with a history of previous VTE disease, the true risk of recurrence in untreated patients is unknown and estimates range from 0 to 15%.\textsuperscript{8-12} 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.\textsuperscript{14} Therefore, a reasonable approach to patients with previous VTE is to use low-dose heparin therapy (either 5,000 U every 12 h SC or adjusted to produce a heparin level of 0.1 to 0.2 U/mL) throughout pregnancy. Alternatively, heparin therapy could be withheld antepartum and the patient followed up by clinical surveillance and periodic IPG or CUS. With either option, heparin and warfarin should then be used postpartum for 4 to 6 weeks. This is a grade C recommendation.
Table 1—Recommendations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
<th>Grading of Recommendation</th>
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<tr>
<td>Previous venous thrombosis or PE prior to current pregnancy</td>
<td>Heparin (5,000 U q12h or adjusted to produce a heparin level of 0.1-0.2 U/mL) throughout pregnancy followed by warfarin postpartum for 4 to 6 weeks or Clinical surveillance combined with periodic IPG or CUS followed by warfarin postpartum for 4 to 6 weeks</td>
<td>C</td>
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<tr>
<td>Venous thrombosis or PE during current pregnancy</td>
<td>Heparin in full IV doses for 5-10 days, followed by q12h SC injections to prolong 6-h postinjection APTT into the therapeutic range until delivery; warfarin can then be used postpartum</td>
<td>C</td>
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<tr>
<td>Planning pregnancy in patients who are being treated with long-term oral anticoagulants</td>
<td>Either heparin q12h SC to prolong 6-h postinjection APTT into the therapeutic range or Frequent pregnancy tests and substitute heparin (as above) for warfarin when pregnancy achieved</td>
<td>C</td>
</tr>
<tr>
<td>Mechanical heart valves</td>
<td>Either heparin q12h SC to prolong 6-h postinjection APTT into the therapeutic range or Adjusted-dose SC heparin until the 13th week, warfarin (target INR, 2.5-3.0) until the middle of the third trimester, then adjusted-dose SC heparin until delivery The addition of aspirin 90-100 mg po daily to either regimen should be considered</td>
<td>C</td>
</tr>
<tr>
<td>APLAs and &gt;1 previous pregnancy loss</td>
<td>Either aspirin plus prednisone or Aspirin plus heparin or Aspirin alone</td>
<td>C</td>
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<tr>
<td>APLAs and 0 or 1 previous pregnancy loss</td>
<td>Low-dose aspirin during the second and third trimester</td>
<td>C</td>
</tr>
<tr>
<td>APLAs and previous venous thrombosis</td>
<td>Heparin q12h SC to prolong 6-h postinjection APTT into the therapeutic range</td>
<td>C</td>
</tr>
<tr>
<td>APLAs without previous venous thrombosis</td>
<td>Either clinical surveillance combined with IPG or CUS or Heparin 5,000 U q12h throughout pregnancy</td>
<td>C</td>
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Treatment of VTE of Pregnancy

In patients who develop venous thrombosis during pregnancy, full doses of heparin should be given by IV infusion for 5 to 10 days and then by SC injection every 12 h in full doses, until term. This recommendation is based on a level I study performed in nonpregnant patients\(^{13}\) and a level IV study in pregnant patients\(^ {14}\) that reported the efficacy of heparin for the treatment of acute venous thrombosis. Heparin therapy should be discontinued immediately before delivery and then both heparin and warfarin therapy can be started postpartum. Once a therapeutic INR is obtained, heparin therapy can be discontinued and warfarin administered for a further 4 to 6 weeks.

Unexpected Pregnancy or Planned Pregnancy in Patients Receiving Long-term Anticoagulants

Patients receiving long-term oral anticoagulant therapy for VTE or patients with mechanical heart valves present problems when planning pregnancy if of pregnancy occurs unexpectedly. It is possible that oral anticoagulants are safe during the first 6 weeks of gestation, but there is a risk of warfarin embryopathy if warfarin is taken between 6 and 12 weeks of gestation. Ideally, such women should be counseled 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, to a higher risk of osteoporosis.

Prophylaxis in Patients With Mechanical Heart Valves

The treatment of pregnant patients with mechanical heart

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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 SC injection in doses adjusted to keep the midinterval APTT in the therapeutic range (at least twice control). 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 embroyopathy, other fetpathic effects (eg, CNS 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 manufacturers package insert that coumarin is contraindicated during pregnancy. This statement carries with it medicolegal implications that would also have to be discussed with the patient if a choice is made to use oral anticoagulants during pregnancy. In view of recent concerns about the efficacy of heparin and the recent demonstration that aspirin is useful in combination with warfarin in nonpregnant patients, we believe that low-dose aspirin therapy (50 to 100 mg/d) should be considered in combination with anticoagulants in patients with mechanical heart valves.

**Pregnancy and APLAs**

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

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