THE HYPERCOAGULABLE STATE OF PREGNANCY

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.

Mitrail 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.

Disclosures.

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

Because of alterations in hemostasis and coagulability\textsuperscript{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\textsuperscript{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.\textsuperscript{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\textsuperscript{17–23} and, depending on the case series, a 5\% to 30\% risk of congenital anomalies.\textsuperscript{17–19} Placental transfer of warfarin later in pregnancy can result in fetal bleeding or stillbirth\textsuperscript{20–22} and long-term sequelae include an increased risk of adverse neurologic outcome.\textsuperscript{15} Vitale and colleagues\textsuperscript{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\textsuperscript{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\%.\textsuperscript{22}

UFH

UFH has traditionally been considered the drug of choice for the prevention and treatment of thrombotic disorders during pregnancy.\textsuperscript{23} This drug does not cross the placenta and therefore offers little direct risk to the fetus.\textsuperscript{26,27} However, UFH has several disadvantages including heparin-induced thrombocytopenia (HIT) and osteopenia,\textsuperscript{26} and the latter may lead to symptomatic vertebral fracture in approximately 2\% of women.\textsuperscript{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,\textsuperscript{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.\textsuperscript{31} The incidence of HIT is low in pregnancy, but the risk is unknown.\textsuperscript{23} In HIT, fondaparinux, a new selective factor Xa inhibitor, is the anticoagulant of choice, although data on its use in pregnancy are limited.\textsuperscript{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 (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.\textsuperscript{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.\textsuperscript{34} In nonpregnant patients, LMWH has been associated with fewer side effects than UFH.\textsuperscript{23} Potential advantages of LMWH include less bleeding, a more predictable and stable response, and a lower risk of HIT.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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
antithrombotic therapy in pregnant patients with MHVs, because properly designed studies have not been performed. Generally, both the ACC/AHA and the European Society of Cardiology (ESC) guidelines recommend discussing the risks of available anticoagulation regimens with the pregnant patient. Antithrombotic preventive therapy options during pregnancy include continuation of VKAs throughout the second trimester of pregnancy as well as dose-adjusted subcutaneous or intravenous UFH between the sixth and the twelfth week or throughout pregnancy with an activated partial thromboplastin time (aPTT) at least twice the control level. The ACC/AHA guidelines include the option of LMWH instead of UFH with peak anti-Xa factor levels between 0.7 and 1.2 U/mL 4 hours after administration.

The American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy (Box 2) concluded that it is reasonable to use one of the following 3 regimens: (1) either LMWH or UFH between 6 and 12 weeks

<table>
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<th>Box 1</th>
<th>ACC/AHA 2006 recommendation for anticoagulation during pregnancy in patients with mechanical prosthetic valves</th>
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| **Class I** | 1. All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation with frequent monitoring (level of evidence: B).  
2. For women requiring long-term warfarin therapy who are attempting pregnancy, pregnancy tests should be monitored, with discussions about subsequent anticoagulation therapy, so that anticoagulation can be continued uninterrupted when pregnancy is achieved (level of evidence: C).  
3. Pregnant patients with mechanical prosthetic valves who elect to stop warfarin between weeks 6 and 12 of gestation should receive continuous intravenous UFH, dose-adjusted UFH, or dose-adjusted subcutaneous LMWH (level of evidence: C).  
4. For pregnant patients with mechanical prosthetic valves, up to 36 weeks of gestation, the therapeutic choice of continuous intravenous or dose-adjusted subcutaneous UFH, dose-adjusted LMWH, or warfarin should be discussed fully. If continuous intravenous UFH is used, the fetal risk is lower, but the maternal risks of prosthetic valve thrombosis, systemic embolization, infection, osteoporosis, and HIT are higher (level of evidence: C).  
5. In pregnant patients with mechanical prosthetic valves who receive dose-adjusted LMWH, the LMWH should be administered twice daily subcutaneously to maintain the anti-Xa level between 0.7 and 1.2 U per mL 4 hours after administration (level of evidence: C).  
6. In pregnant patients with mechanical prosthetic valves who receive dose-adjusted UFH, the aPTT should be at least twice control (level of evidence: C).  
7. In pregnant patients with mechanical prosthetic valves who receive warfarin, the international normalized ratio (INR) goal should be 3.0 (range 2.5–3.5) (level of evidence: C).  
8. In pregnant patients with mechanical prosthetic valves, warfarin should be discontinued and continuous intravenous UFH given starting 2 to 3 weeks before planned delivery (level of evidence: C). |
| **Class IIa** | 1. In patients with mechanical prosthetic valves, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation because of the high risk of fetal defects (level of evidence: C).  
2. In patients with mechanical prosthetic valves, it is reasonable to resume UFH 4 to 6 hours after delivery and begin oral warfarin in the absence of significant bleeding (level of evidence: C).  
3. In patients with mechanical prosthetic valves, it is reasonable to give low-dose aspirin (75–100 mg per day) in the second and third trimesters of pregnancy in addition to anticoagulation with warfarin or heparin (level of evidence: C). |

and close to term only, with warfarin used at other times; (2) aggressive dose-adjusted UFH throughout pregnancy; or (3) aggressive adjusted-dose LMWH throughout pregnancy aiming to attain a peak anti-Xa level of 0.7 to 1.2 U/mL at 4 to 6 hours after injection. UFH or LMWH throughout pregnancy is not recommended by the recent ESC guidelines, considering continuation of VKAs throughout pregnancy when the warfarin dose is less than 5 mg daily ([Table 1](#)). Discontinuation of VKAs and a switch to UFH or LMWH is recommended between weeks 6 and 12 under strict dose control and supervision. When a higher dose of VKAs is required, discontinuation of VKAs between weeks 6 and 12 and replacement by adjusted-dose UFH (aPTT/C2 ≥2 times the control, in high-risk patients applied as an intravenous fusion) or LMWH twice daily (dose adjusted according to weight) is recommended (the anti-Xa level should be maintained between 0.8 and 1.2 U/mL [4–6 hours after application]) ([Table 2](#)).

**Box 2**

**Recommendations of the 2008 ACCP Consensus Conference on antithrombotic therapy in patients with MHVs**

Adjusted-dose twice a day LMWH throughout pregnancy (grade 1C). We suggest that doses be adjusted to achieve the manufacturer’s peak anti-Xa LMWH 4 hours after subcutaneous injection (grade 2C).

*or*

Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 hours in doses adjusted to keep the midinterval aPTT at least twice control or attain an anti-Xa heparin level of 0.35 to 0.70 U/mL (grade 1C).

*or*

UFH or LMWH (as above) until the thirteenth week with warfarin substitution until close to delivery when UFH or LMWH is resumed (grade 1C).


**REVIEW OF DATA AND RECOMMENDATIONS ON ANTICOAGULATION REGIMENS IN PREGNANT PATIENTS WITH PROSTHETIC HEART VALVES**

In the absence of controlled clinical trials, current recommendations are based on limited, observational data. Only a few and mostly small series comprise the basis from which current guidelines and recommendations are derived. Maternal mortality in patients with MHV remains the most devastating complication, and even contemporary series confirm that mortality and complications may not necessarily be avoided.

In the largest literature review before 1998, which included more than 900 pregnant women with MHV, Chan and colleagues evaluated maternal and fetal outcomes according to the type of anticoagulation used during pregnancy: VKAs alone, VKAs with UFH during the first trimester, UFH throughout pregnancy, and antiplatelet agents alone. Rates of maternal thromboembolic complications in women who received UFH alone, VKAs with heparin substitution during the first trimester, and warfarin alone were 33.3%, 9.2%, and 3.9%, respectively. However, the rates of congenital fetal anomalies were 0%, 3.4%, and 6.4%, respectively. These results suggest that heparin alone is insufficient to prevent thromboembolism among pregnant women with MHV compared with VKA regimens. Compared with regimens using warfarin alone, substitution with UFH during the first trimester was associated with a reduction in embryopathy from 6.4% to 3.4%, but also with an increase in maternal thromboembolic risk from 3.9% to 9.2%.

Reports by one group suggested that the risk of fetal damage was reduced although not eliminated if the daily warfarin dose was less than 5 mg. However, several reports described the development of warfarin embryopathy and fetal loss with low-dose warfarin. For this reason, pregnancy without fetal complications cannot be guaranteed even to women who are well anticoagulated on less than 5 mg/d of warfarin during pregnancy. The risk of fetal malformation and other effects associated with use of VKAs throughout pregnancy suggests that these drugs should be considered only in women with a high risk of thrombosis, such as highly thrombogenic MHVs or a history of thromboembolic complications on a therapeutic dose of heparin.

Supporting the published review by Chan and colleagues, Silissen and colleagues recently described 79 women who had 155 pregnancies after valve replacement. Two women died during pregnancy: one from heart failure and one from postpartum bleeding. There were 4 thromboembolic episodes in the early study period in women with a mitral prosthesis on UFH. Detailed information on the UFH regimen and monitoring results at the time of the episodes were not available. Because of a lack of information related to the level of anticoagulation and its monitoring, these reports
might suggest resistance to moderate doses of UFH in high-risk women with old-generation prosthetic heart valves. For this reason, if the decision is to use UFH, it should preferably be used as an intravenous continuous infusion and at high dose\textsuperscript{16,39} and adjusted to achieve an aPTT ratio of greater than 2.5 times control value with careful maintenance of the central line to prevent infection and a risk of endocarditis. Because of high risk of valve thrombosis, subcutaneous administration of UFH should be avoided if all possible. If no other choice is available in a woman who prefers not to use warfarin, a high dose (7500 to 20,000 U every 12 hours) should be used, aiming to achieve a mid-level (6 hours) of aPTT ratio of more than 2.5 control value.

Therapy with LMWH in pregnancy is an attractive and convenient alternative to VKAs and UFH. Substantial evidence shows the efficacy and safety of LMWH in prevention and treatment of
thromboembolism during pregnancy in patients with evidence of deep vein thrombosis and thrombophilia,\textsuperscript{38} and there is an increased experience with the use of this therapy in women with MHVs. Earlier published data on the use of LMWH in women with MHV during pregnancy were described by Elkayam and colleagues\textsuperscript{47} and were limited to small groups of patients or to isolated reports; several of these cases were complicated by valve thrombosis and even death. However, a careful review of the reported cases indicated that most, if not all, were associated with an inadequate dose, lack of monitoring, or subtherapeutic anti-Xa levels.\textsuperscript{23,48–54}

A more recent review by Oran and colleagues\textsuperscript{52} comprising 81 pregnancies in women with MHV in whom LMWH was used reported 10 thromboembolic events in women with mechanical mitral valves, of which 9 occurred in the 30 pregnancies with a fixed LMWH dose and only 1 in the 51 pregnancies with adjusted LMWH dose. Rowan and colleagues\textsuperscript{50} reported on their experience in 14 pregnancies in women with a mechanical prosthetic valve who were treated with LMWH; valve thrombosis was described in 1 patient, who had a new generation mechanical mitral valve and had stopped warfarin 3 months before conception. She presented at 8 weeks’ gestation, on no anticoagulation treatment, with transient ischemic attacks and suspected thrombus on transesophageal echocardiography (TEE). The patient was started on enoxaparin, with apparent resolution of the thrombus on TEE, but she re-presented at 20 weeks’ gestation after a further transient ischemic attack caused by subtherapeutic level of anticoagulation (peak anti-Xa level was 0.62 U/mL). Yinon and colleagues\textsuperscript{55} recently reported a series of 23 pregnancies in 17 women with MHVs treated with adjusted LMWH. There was a single maternal thromboembolic event in a patient with a new-generation mechanical aortic prosthesis despite peak anti-Xa levels described in the guidelines as therapeutic (ranging from 1.0 and 1.4 U/mL). This patient was treated with warfarin until 5 weeks of gestation and was then switched to LMWH and aspirin. At 24 weeks of gestation she presented with a transient ischemic event (peak anti-Xa level was 0.99 U/mL). Echocardiography showed an increased mean gradient across her aortic valve of 38 mm Hg (compared with her baseline mean gradient of 15 mm Hg). TEE was performed, and no thrombus was seen, but the aortic valve leaflets were not optimally visualized. The LMWH dose was increased, but at 26 weeks of gestation, the patient was admitted with cardiac arrest and died. The autopsy showed aortic valve thrombosis. This case shows the limitations of reliance on peak anti-Xa levels and the need to ensure a therapeutic trough level as well. Furthermore, because TEE may not allow adequate visualization of the aortic leaflets, significant change in gradients across the valve should alert physicians to the possibility of valve thrombosis, even when a thrombus cannot be seen, and patients should be hospitalized for further diagnosis and management. Abildgaard and colleagues\textsuperscript{56} recently reported on 12 pregnancies with MHVs treated with LMWH, in which thromboembolism occurred in 2 women with aortic MHV. Both events were attributed to subtherapeutic doses of LMWH during the initial 3 weeks of pregnancy. Quinn and colleagues\textsuperscript{57} conducted

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<th>Table 2</th>
<th>Recommended approach for anticoagulation in women with MHV during pregnancy</th>
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<tr>
<td></td>
<td>Higher Risk</td>
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<tr>
<td>Definition</td>
<td>First-generation PHV (eg, Starr-Edwards, Bjork-Shiley) in the mitral position, MHV in the tricuspid position, AF, history of TE on anticoagulation</td>
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<td>Treatment</td>
<td>Warfarin (INR 2.5–3.5) for 35–36 wk, followed by UFH\textsuperscript{A} (aPTT ≥2.5) to parturition + ASA 80–100 mg every day or LMWH (trough anti-Xa ≥0.7, peak ≤1.5) or UFH\textsuperscript{A} (aPTT ≥2.5) for 12 wk, followed by warfarin (INR 2.5–3.5) to 35–36 wk, then IV UFH\textsuperscript{A} (aPTT ≥2.5) to parturition + ASA 80–100 mg every day</td>
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Abbreviations: ASA, acetylsalicylic acid; IV, intravenous; SC, subcutaneous; TE, thromboembolism.\textsuperscript{a} IV preferred.
a prospective audit of the use of adjusted-dose LMWH in 12 pregnancies with MHV. LMWH ± low-dose aspirin was started at therapeutic dose with monitoring of anti-Xa levels to achieve a target level of 1.0 to 1.2 U/mL. This strategy necessitated a mean increase in the dose of LMWH of 54.4% over initial dose. One nonfatal valve thrombosis occurred at 26 weeks’ gestation associated with subtherapeutic anti-Xa levels. Three patients experienced major bleeding.

More recently, McIntosh and colleagues reported thromboembolic complications in 7 of 47 pregnancies, of which 5 were believed to be associated with the use of enoxaparin therapy. Similar to other reports by other investigators described earlier, poor compliance with therapy and subtherapeutic peak anti-Xa levels were an issue in all cases. No thromboembolic complications occurred in the 20 pregnancies when enoxaparin was commenced before 6 weeks’ gestation, a group that was compliant with medication and monitoring of peak anti-Xa levels.

There is increasing experience with the use of LMWH for anticoagulation in pregnant women with MHV. Most if not all the cases reported to have developed thromboembolic complications were related to poor compliance with therapy, inadequate monitoring, and subtherapeutic levels of anticoagulation. The pharmacokinetics of LMWH have been shown to be altered during pregnancy with lower plasma concentrations, probably related to higher clearance and volume of distribution. Therefore, administration of LMWH by weight alone is inadequate, and peak anti-Xa levels may not reflect adequacy of anticoagulation around the clock. The potential importance of measurement of trough anti-Xa levels was suggested by Barbour and colleagues, who evaluated 138 peak and 112 troughs anti-Xa levels in 13 pregnancies in 12 patients. With peak levels of 0.63, 0.70, and 0.69 U/mL, respectively, at the first, second, and third trimesters, mean trough level were 0.21, 0.30, and 0.40 U/mL, with only 9% of the measurements greater than 0.5 U/mL. Even when peak levels were between 0.75 and 1.0 U/mL, only 15% of trough levels were greater than 0.5 U/mL. Similarly, in a recent series of 15 pregnant women at different gestational ages, a subtherapeutic anti-Xa level was reported in 20% of the peak levels and 73% of the trough levels, despite therapeutic enoxaparin administration 1 mg/kg twice a day.

In our unpublished study of 26 pregnant women who received anticoagulation with LMWH for various indications, including 9 patients with MHV subcutaneously every 12 hours, we analyzed both trough and peak anti-Xa levels throughout pregnancy for a total of 177 determinations. Adjusted-dose LMWH achieving a peak anti-Xa between 0.7 U/mL and 1.2 U/mL, as recommended by guidelines, were associated with subtherapeutic trough anti-Xa levels in about 50% of cases. On the other hand, therapeutic trough anti-Xa levels 0.6 U/mL to 0.8 U/mL were rarely associated with excessive peak anti-Xa levels. These data, in addition to the documented risk of valve thrombosis with subtherapeutic predose anti-Xa levels, suggest the importance of routine measurement and maintenance of trough levels at therapeutic range as recommended by Elkayam and Bitar (anti-Xa ≥0.6 in low-risk patients and ≥0.7 U/mL in high-risk patients) (see Table 2). Because of possible bleeding complications, peak levels should also be monitored to prevent excessive anticoagulation (anti-Xa levels >1.5 U/mL), in which case, an 8-hourly rather than a 12-hourly dosage should be used. To ensure patient compliance and adequate prophylaxis, anti-Xa activity should be measured once weekly for the first 4 weeks and later at least once every 2 weeks. Catheter placement for epidural anesthesia is not advisable within 10 to 12 hours of the last dose, because of the longer half-life of LMWH. For this reason, and to prevent spinal or epidural hematoma, LMWH should be withdrawn 18 to 24 hours before an elective delivery and substituted with intravenous UFH. Because of the potential added benefit, a small dose of aspirin (75–100 mg/d), which is safe during pregnancy, might be added in high-risk patients to further reduce the incidence of thromboembolism.

OTHER CARDIAC DISORDERS REQUIRING ANTICOAGULATION IN PREGNANCY

**Mitrail Stenosis**

Mitrail stenosis (MS) is the most common valvular heart disease in pregnancy, with a significant impact on both maternal and fetal outcome, and it is a disease that carries a significant risk of thromboembolism. Prophylactic anticoagulation is indicated in MS patients who have the highest risk for thromboembolic events (ie, patients with atrial fibrillation [AF] or a previous history of an embolic event). According to the ACC/AHA guidelines, anticoagulation may be considered for asymptomatic patients with severe MS and left atrial dimension greater than or equal to 55 mm by echocardiography. The hypercoagulable state of pregnancy appears as another risk factor for thromboembolism in pregnant patients with MS, and the investigators suggest considering anticoagulation therapy in pregnant patients with MS, even in the absence of AF. These recommendations are supported by a recently
published case series that reported left atrial thrombus formation and ensuing clinical events in 3 pregnant patients with MS in the absence of AF. Strong consideration should therefore be given to prophylactic full-dose anticoagulation in patients with severe MS, especially those with an enlarged left atrium, throughout pregnancy, even in the absence of AF or a history of thromboembolism.

**Peripartum Cardiomyopathy and Pre-existent Dilated Cardiomyopathy**

Peripartum cardiomyopathy (PPCM) is a cardiomyopathy of unknown cause presenting with heart failure secondary to left ventricle (LV) systolic dysfunction toward the end of pregnancy or in the months after delivery. This condition is associated with important and lasting complications, including thromboembolic events, which can lead to severe morbidity and mortality. LV thrombus has been found on initial echocardiography in 10% to 17% of patients, and several reports have described severe thromboembolic events as a result of embolization to the coronary, pulmonary, peripheral, and cerebral arteries. Goland and colleagues recently described 4 patients with severe embolic complications, all of them with left ventricular thrombus: 3 presented as a cerebrovascular accident with residual brain damage (plus pulmonary embolism in one), and 2 with leg ischemia (requiring amputation in one). The increased incidence of thromboembolism in women with PPCM is related to the hypercoagulable state of pregnancy, cardiac dilatation and dysfunction, endothelial injury, venous stasis, and prolonged bed rest. Embolic events usually occur during the period of LV dysfunction until LV function recovers and anticoagulation is therefore strongly advisable. Anticoagulation seems particularly important during pregnancy and the first 6 to 8 weeks post partum because of the persistent hypercoagulable state. As mentioned earlier, because of warfarin-related risk to the fetus, either UFH or LMWH is favored in pregnancy, because (unlike warfarin) they do not cross the placenta. Neither warfarin nor heparin is secreted into breast milk, and both drugs are therefore compatible with breastfeeding.

There is an increased risk of thromboembolism in all types of dilated cardiomyopathy. The risk of thromboembolism in nonpregnant patients may be particularly high in women with concomitant AF, a history of venous thromboembolism, and LV thrombus who require chronic anticoagulation. Because of the increased risk of thromboembolic events during pregnancy, all patients with dilated cardiomyopathies and left ventricular ejection fraction 40% or less should be anticoagulated even in the absence of the other risk factors for TE events mentioned earlier. LMWH are the preferred drugs for this population, and the dose has to be adjusted to achieve therapeutic trough anti-Xa levels (≥0.6 U/mL).

**Pregnant Women with AF**

Increased frequency of arrhythmia has been reported during pregnancy in healthy women or in women with structural heart disease, especially when cardiac output increases 30% to 50%. However, the incidence of AF during pregnancy is low and is usually secondary to congenital or rheumatic valvular disease, hypertrophic cardiomyopathy, thyroid disease, or a pre-excitation syndrome. However, it can represent a benign, episode of lone AF in a pregnant woman with a normal heart. In pregnant women who develop AF, the role of anticoagulation to prevent systemic arterial embolism has not been systematically studied in pregnant patients with nonvalvular AF.

Anticoagulation therapy is not required in pregnant women with a short lone episode of AF. If spontaneous conversion to normal sinus rhythm does not occur, cardioversion should be considered within 48 hours of the onset of AF to avoid the need for anticoagulation. Procainamide or quinidine are recommended for chemical cardioversion, whereas other medications, including flecainide, have also been used successfully in pregnancy. However, some antiarrhythmic drugs such as amiodarone are contraindicated, because of their teratogenic effect. Synchronized cardioversion is safe and can quickly restore hemodynamic stability and perfusion of vital organs of the mother and the fetus, and can be used in the emergency situation or when chemical cardioversion failed. Beta-blockers, calcium channel blockers, and digoxin are recommended for rate control in pregnant women with AF rapid ventricular response. However, precardioversion and postcardioversion anticoagulation with LMWH is recommended. If the arrhythmia or symptom onset began more than 48 hours before presentation in a stable patient, then anticoagulation should be given for 3 to 4 weeks before and after cardioversion. TEE may be performed to rule out thrombus in a pregnant woman in whom cardioversion is considered earlier than 3 to 4 weeks or in those at high risk for bleeding complications with anticoagulation.

Patients with chronic AF, who are considered to be at increased risk for embolic stroke, should be anticoagulated during pregnancy. Although the risk of embolic events in a pregnant patient with lone AF is not clear, we have been anticoagulating...
such women because of the hypercoagulable state of pregnancy.

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