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## Anticoagulation in Pregnant Women With Prosthetic Heart Valves

Uri Elkayam, MD, Harpreet Singh, MD, Adil Irani, MD, and Mohammed W. Akhter, MD

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**Background:** Pregnancy is associated with an increased risk of thrombosis in women with mechanical prosthetic heart valves. Effective anticoagulation is therefore critical in such patients but remains problematic, since oral anticoagulation and both unfractionated and low-molecular-weight heparin may be associated with important fetal and maternal side effects.

**Purpose:** To review information related to the use of anticoagulation with both warfarin and heparin and reassess the safety and efficacy of these therapies in pregnant women with mechanical prosthetic heart valves.

**Data source and selection:** A MEDLINE search from 1966 to October 2003 for English and non-English language articles that reported the use of anticoagulation in pregnancy was conducted. Articles were included if they reported use of anticoagulation in pregnancy with emphasis on those that included women with mechanical prosthetic heart valves.

**Conclusions:** Anticoagulation prophylaxis with both warfarin and heparin (unfractionated heparin and low-molecular-weight heparin) may be associated with important fetal and maternal side effects. Optional regimens for the treatment of low-risk and high-risk patients are proposed to minimize potential complications.

**Key Words:** anticoagulation prophylaxis, pregnancy, mechanical prosthetic heart valves.

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Pregnancy is associated with an increased risk of thrombosis in women with mechanical prosthetic heart valves (1,2). Recent reports have described thromboembolic events in 7% to 23% (average 13%) of such cases; in half of them with valve thrombosis, fatalities were 40% (3-7). Effective anticoagulation is therefore critical in such patients but remains problematic since both oral anticoagulation and unfractionated heparin are associated with important fetal and maternal side effects (1-13). In this article, we review new information related to the use of anticoagulation with both warfarin and heparin and reassess

the safety and efficacy of these therapies in pregnant women with mechanical prosthetic heart valves.

### Unfractionated Heparin

Unfractionated heparin has been traditionally considered the drug of choice for the prevention and treatment of thrombotic disorders during pregnancy (1,11-14). This drug does not cross the placenta and therefore offers little direct risk to the fetus. The use of unfractionated heparin, however, is not without problems and may be associated with adverse effects such as heparin-induced osteopenia (15) that may lead to symptomatic vertebral fracture in approximately 2% of women and thrombocytopenia in a rare minority (14,15).

In addition, two retrospective surveys conducted in Europe and a prospective study performed in Mexico reported a high incidence of valve thrombosis in patients with mechanical prosthetic heart valves who were treated with unfractionated heparin (4,5,7). Although the clinical implications of these data have

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been questioned (11) owing to their retrospective design, the lack of information related to activated partial thromboplastin time levels, and the use of old-generation thrombogenic mechanical valves in most cases (16), these reports influenced guidelines by the European Society of Cardiology (17) and the American Heart Association/American College of Cardiology (18), both of which declared the use of unfractionated heparin less safe and advocated the use of oral anticoagulation during gestation in women with mechanical prosthetic heart valves.

### Warfarin

Exposure to warfarin during the first 8 to 12 weeks of gestation, however, is associated with significant risk to the fetus (19). A recent review of 792 patients with prosthetic heart valves who received warfarin during pregnancy reported a high frequency of spontaneous abortions (25%), warfarin embryopathy (6%), and fetal wastage (34%) (19). These complications were markedly reduced by the initiation of heparin prior to the sixth gestational week.

A recent prospective study by Vitale et al (20) also reported a high frequency (88%) of fetal complications, including spontaneous abortions, congenital heart disease, growth retardation, and warfarin embryopathy, in women with prosthetic heart valves, who were treated with warfarin at a dose exceeding 5 mg/day throughout the pregnancy. Sadler et al (9) reported similar results, regardless of the warfarin dose.

Use of oral anticoagulation during pregnancy may also be associated with fatal hemorrhage in the fetus and central nervous system abnormalities (21). A study of long-term effects of prenatal warfarin exposure in 274 school-age children showed an increase in minor neurologic dysfunction and low intelligence quotients (IQ below 80) (22). Because of these risks, a consideration of pregnancy termination has been recommended by the manufacturer (21) in patients who become pregnant while being treated with warfarin, and both women and physicians have been reluctant to use warfarin during the first gestational trimester (11,18,23).

### Low-Molecular-Weight Heparin

Because of the concerns related to the use of both warfarin and unfractionated heparin, interest has increased in the use of low-molecular-weight heparin for thromboprophylaxis of patients with mechanical

prosthetic heart valves during pregnancy (8,11,12). Similar to unfractionated heparin, low-molecular-weight heparin does not cross the placental barrier (24–27). In addition, it has several potential advantages, including fewer bleeding complications, a higher resistance to inhibition by activated platelets (25), a lower frequency of heparin-induced thrombocytopenia (28–30), although overall incidence of heparin induced thrombocytopenia was reported to be rare in pregnancy according to one study (31); a lower incidence of osteoporosis (28), superior subcutaneous absorption and bioavailability (14) (90% vs. 10%), and a twofold to fourfold longer half life. Because low-molecular-weight heparin does not bind to plasma proteins, it may be associated with a more predictable dose response (23).

Can low-molecular-weight heparin be used for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves? Substantial evidence shows the efficacy and safety of these drugs in the prevention and treatment of thromboembolism during pregnancy in patients with evidence of deep vein thrombosis and thrombophilia (25). Clinical information is also available on the short-term use of low-molecular-weight heparin for thromboprophylaxis in nonpregnant patients with prosthetic heart valves (32–35). Published data on the use of low-molecular-weight heparin in women with mechanical prosthetic heart valves during pregnancy are presently limited to small groups of patients (8–10,12,36,37) or to isolated reports (38–44), with several of these cases complicated by valve thrombosis (Table 1).

Although this seemingly high incidence of thrombotic complications may raise a concern regarding the safety of low-molecular-weight heparin (46), it probably reflects a biased reporting of cases with complications. In addition, most of these cases have been associated with an inadequate dose, lack of monitoring, or subtherapeutic anti-Xa levels (10,36,38,41–43). For example:

- Lev-Ran et al (41) reported the thrombosis of a Bicarbon (Sorin Biomedica S.p.A., Via Crescentino, Italy) valve in the 35th week of gestation with the use of only 40 mg/day of enoxaparin.
- Berndt et al (38) described thrombosis of a CarboMedics (Austin, Texas) mitral prosthesis during the second month of gestation after 1 month of treatment with enoxaparin at 20 mg/day without the monitoring of anti-factor Xa activity.
- Rowan et al (10) reported on 1 of 14 pregnancies in 11 women with prosthetic heart valves, treated with enoxaparin, who developed a thrombosis of a St. Jude

Medical (St. Paul, Minn) mitral prosthesis at 20 weeks. In spite of a relatively high dose (0.93 mg/kg, twice daily), predose anti-factor Xa level was subtherapeutic at 0.22 U/mL.

- Arnaout et al (36) reported a 20% incidence of valve thrombosis in 10 pregnancies of women with prosthetic heart valves treated with a fixed dose (7500 U, twice daily) of Fraxiparine without the monitoring of anti-Xa levels.

The Heparin In Pregnancy—Cardiac Valve Thromboprophylaxis (HIP-CAT) study was initiated in South Africa in 1999 as a multicenter, randomized (but unblinded) controlled trial designed to compare enoxaparin with standard therapy of warfarin and unfractionated heparin in 110 pregnant women with new-generation prosthetic heart valves from St. Jude Medical, Medical (Minneapolis, Minn), Medtronic-Hall (Minneapolis, Minn) or CarboMedics (45). Enoxaparin (1 mg/kg twice daily) was given subcutaneously and was adjusted to maintain a peak (3 hours postdose) anti-Xa level below 1.2 U/mL. The protocol however did not adjust for subtherapeutic values.

This study was prematurely discontinued after 2 of 7 patients who were treated with enoxaparin developed fatal valve dysfunction. The first patient, who had aortic and mitral Hall-Caster (Medical Inc., Minneapolis, Minn) valves, died of valve dysfunction at 32 weeks after treatment with enoxaparin for 15 weeks. Records of compliance with therapy were not available, and recorded anti-Xa levels ranged between 0.422 and 0.694 U/mL at trough and 0.644 and 1.07 U/mL at peak. The second patient developed a thrombosis of a CarboMedics mitral prosthetic valve at the 14th week after 5 weeks of twice-daily doses of enoxaparin. Two of three measured predose anti-Xa levels were subtherapeutic.

A review of anti-Xa levels in all seven patients treated with enoxaparin in the HIP-CAT study demonstrated occasional subtherapeutic trough and peak values in most of the patients. These findings support reports of lower anti-factor Xa levels during pregnancy (47,48), possibly owing to the normal increase in plasma volume and glomerular filtration rate, as well as increased production of placental heparinase during pregnancy (47–49) and suggest a need for higher doses of low-molecular-weight heparin for adequate treatment. Because of safety concerns, a warning was issued by the manufacturer of enoxaparin (Aventis Pharmaceuticals Inc. Bridgewater, New Jersey) against its use for thromboprophylaxis in both pregnant and nonpregnant patients with mechanical prosthetic heart valves (50).

A recent detailed review of all three anticoagulation options for pregnant patients who have prosthetic heart valves (ie, unfractionated heparin, low-molecular-weight heparin, and oral anticoagulants) has, however, concluded that all three regimens were understudied and that low-molecular-weight heparin could in fact be the best available option (51). More recently, the initial warning by the manufacturer has been rephrased to the “use of Lovenox for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied,” and recommendations for dose adjustment guided by a frequent monitoring of peak and trough anti-factor Xa levels have been added (52).

### Monitoring of Anticoagulation During Pregnancy

The anticoagulant effect of unfractionated heparin is most commonly monitored by the activated partial

**Table 1. Cases of Valve Thrombosis in Pregnant Patients with Mechanical Prosthetic Heart Valves Treated with Low-Molecular-Weight Heparin**

Author	Drug	Dose	Anti-Xa Activity		Type of Valve	Position
			Predose	Peak Level		
1. Lev-Ran (41)	Enoxaparin	40 mg/QD	NM	NM	Sorin Bicarbon	Mitral
2. Berndt (38)	Enoxaparin	20 mg/QD	NM	NM	Carbon-Medics	Mitral
3. Oles (42)	Enoxaparin	1 mg/Kg BID	NM	NM	St. Jude	Mitral
4. Rowan (10)	Enoxaparin	0.93 mg/KG	0.22 U/mL	NA	St. Jude	Mitral
5. Arnaout (36)	Fraxiparine	7500 U/BID	NM	NM	St. Jude	Mitral
6. Arnaout (36)	Fraxiparine	7500 U/BID	NM	NM	NA	NA
7. HIP-CAT (45)	Enoxaparin	80 mg/BID	0.4-0.7 U/mL	0.6-1.1 U/mL	Hall-Caster	Aortic & Mitral
8. HIP-CAT (45)	Enoxaparin	80 mg/BID	0.26-0.67 U/mL	0.47-1.2 U/mL	Carbo-Medics	Mitral

NM = not measured.

thromboplastin time, which is a measure of thrombin, factor Xa, and factor IXa inhibition (53). The therapeutic range for activated partial thromboplastin time value has been traditionally considered to be 1.5 to 2.5 times the control value. However, the different commercial activated partial thromboplastin time reagents vary in their sensitivity to heparin, and any fixed activated partial thromboplastin time is unreliable. For this reason it has been recommended that each institution establish a therapeutic activated partial thromboplastin time range by calibrating it against the heparin concentration from blood samples of patients who are receiving heparin (53,54).

It should also be noted that the activated partial thromboplastin time becomes short (to a variable degree) during pregnancy as a result of the elevation of procoagulant clotting factors (1). The reported activated partial thromboplastin time ratio may therefore be misleading and needs to be validated periodically by the use of specific heparin assays such as anti-Xa levels (1).

Low-molecular-weight heparin has an excellent bioavailability when it is administered subcutaneously and therefore, laboratory monitoring is not required when it is used for prophylaxis or the treatment of venous thromboembolisms. However, in patients at high risk of thrombotic events who are receiving low-molecular-weight heparin for prolonged periods of time, monitoring of anticoagulation level using an anti-Xa activity has been recommended (55,56).

Although the antithrombotic effect of low-molecular-weight heparin includes inhibition of thrombin generation (anti-IIa activity) and platelet aggregation,

as well as release of tissue factor pathway inhibitor, its primary therapeutic effect is through the inhibition of coagulation factor Xa. For this reason measurement of anti-Xa concentration has been the method currently recommended (53–56) and most widely used for the assessment of therapeutic anticoagulation with low-molecular-weight heparin. This assay has been shown to correlate with other blood tests that evaluate overall anticoagulation, such as HEPTEST and thromboelastography (57,58), and has been helpful in determining the level of anticoagulation with low-molecular-weight heparin during high-risk pregnancies (59) and in nonpregnant patients with cardiovascular conditions that increase their risk for thromboembolic complications (34,60,61).

### Published Guidelines

The American College of Cardiology/American Heart Association Task Force report published guidelines for the *Management of Patients with Valvular Heart Disease* in 1998 and included recommendations for anticoagulation during pregnancy in patients with mechanical prosthetic valves (18) (Table 2). These recommendations preferred the use of warfarin, especially in high-risk women (a history of thromboembolism or an older-generation mechanical prosthesis in the mitral position) through week 35, when it should be substituted with unfractionated heparin in anticipation of labor.

These recommendations also recognized that for many women, the risk of warfarin embryopathy (4%

**Table 2. ACC/AHA Recommendation for Anticoagulation During Pregnancy in Patients with Mechanical Prosthetic Valves\***

1. The decision whether to use heparin during the first trimester or to continue oral anticoagulation throughout pregnancy should be made after full discussion with the patient and her partner; if she chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her, with a higher risk of both thrombosis and bleeding, and that any risk to the mother also jeopardizes the baby.
2. High-risk women (a history of thromboembolism or an older-generation mechanical prosthesis in the mitral position) who choose not to take warfarin during the first trimester should receive continuous unfractionated heparin intravenously in a dose to prolong the midinterval (6 hours after dosing) activated partial thromboplastin time to 2 to 3 times control. Transition to warfarin can occur thereafter.
3. In patients receiving warfarin, international normalized ratio should be maintained between 2.0 and 3.0 with the lowest possible dose of warfarin, and low-dose aspirin should be added.
4. Women at low risk (no history of thromboembolism, newer low-profile prosthesis) may be managed with adjusted-dose subcutaneous heparin (17,500 to 20,000 U twice daily to prolong the midinterval (6 hours after dosing) activated partial thromboplastin time to 2 to 3 times control.
5. Warfarin should be stopped no later than week 36 and heparin substituted in anticipation of labor.
6. If labor begins during treatment with warfarin, a caesarian section should be performed.
7. In the absence of significant bleeding, heparin can be resumed 4 to 6 hours after delivery and warfarin begun orally.

\*See reference 17.

to 10%) was unacceptable and recommended continuous unfractionated heparin intravenously during the first trimester to women who chose not to take warfarin. The report recognized the potential advantages of low-molecular-weight heparin over unfractionated heparin, but stated that there were no data to guide their use in pregnant women with mechanical prosthetic heart valves.

More recent recommendations published in 2001 as part of the Sixth American College of Chest Physician (ACCP) Consensus on antithrombotic therapy are shown in Table 3 (62). These recommendations do not differentiate between low-risk and high-risk patients and include the option of the use of adjusted dose low-molecular-weight heparin either throughout pregnancy or during the first trimester and second part of the third trimester.

### Summary and Recommendations

Pregnancy in patients with mechanical prosthetic heart valves is associated with an increased risk of thromboembolic complications that requires effective anticoagulation (Fig. 1) Because of the lack of controlled trials, present recommendations have to rely on available—albeit incomplete—information. Decisions on the choice of therapy should be made both by physicians and patients, who should be fully informed of the potential risks that are associated with various therapeutic options.

Thromboembolic prophylaxis in high-risk patients (older-generation prosthetic heart valves in the mitral position, atrial fibrillation, and history of thromboembolic events) seems to be best achieved with oral anticoagulation for the first 35 weeks. One study showed that warfarin at a daily dose of 5 mg or less was asso-

ciated with a lower incidence of adverse effects (20); however, this result could not be confirmed in others studies (8,9).

The recent ACCP consensus conference on antithrombotic therapy recommended a target international normalized ratio of 3.0 (2.5 to 3.5) in nonpregnant patients with mechanical prosthetic heart valves and additional risk factors (63). These recommendations should also be applied to pregnancy, since it is associated with increased risk. Because of the high incidence of premature labor in women with prosthetic heart valves (7,11), warfarin should be substituted with heparin at the 35th gestational week to avoid onset of labor while the patient on warfarin therapy. Delivery, even by cesarean section, places a fully anticoagulated, preterm infant (< 32 weeks) at high risk for intracranial hemorrhage (64,65); therefore, earlier substitution with heparin should be considered in women with a higher likelihood for a premature delivery (history of previous preterm delivery, shortened and dilated cervix, cardiac surgery during pregnancy, and multiple gestations).

Heparin (either unfractionated heparin or low-molecular-weight heparin) is an alternative therapy for women who elect to avoid warfarin during the first trimester and should also be used in the last 5 weeks of pregnancy. To assure adequacy of anticoagulation during the change from warfarin to heparin, it should preferably be done in the hospital with close monitoring.

Because of the reports of possible resistance to moderate doses of unfractionated heparin in high-risk women with mechanical prosthetic heart valves, a high heparin dose should be started (starting dose 7500 to 20,000 U, every 12 hours) (66) and adjusted to a midinterval activated partial thromboplastin time ratio of  $\geq 2$  times control in lower and  $> 2.5$  times in

**Table 3. Recommendations of the Sixth ACCP Consensus Conference on Antithrombotic Therapy for Prophylaxis in Patients with Mechanical Heart Valves\***

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1. Aggressive adjusted-dose unfractionated heparins, given every 12h subcutaneously throughout pregnancy; midinterval activated partial thromboplastin time maintained at  $\geq 2$  times control levels, or anti-Xa heparin level maintained at 0.35 to 0.70 IU/mL

or

  2. Low molecular weight heparins throughout pregnancy, in doses adjusted according to weight or as necessary to maintain a 4-h postinjection anti-Xa heparin level of about 1.0 IU/mL.

or

  3. Unfractionated heparins or low molecular weight heparins, as above, until the 13th week; change to warfarin until the middle of the third trimester, then restart unfractionated heparins or low molecular weight heparins therapy until delivery.
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\*See reference 62.

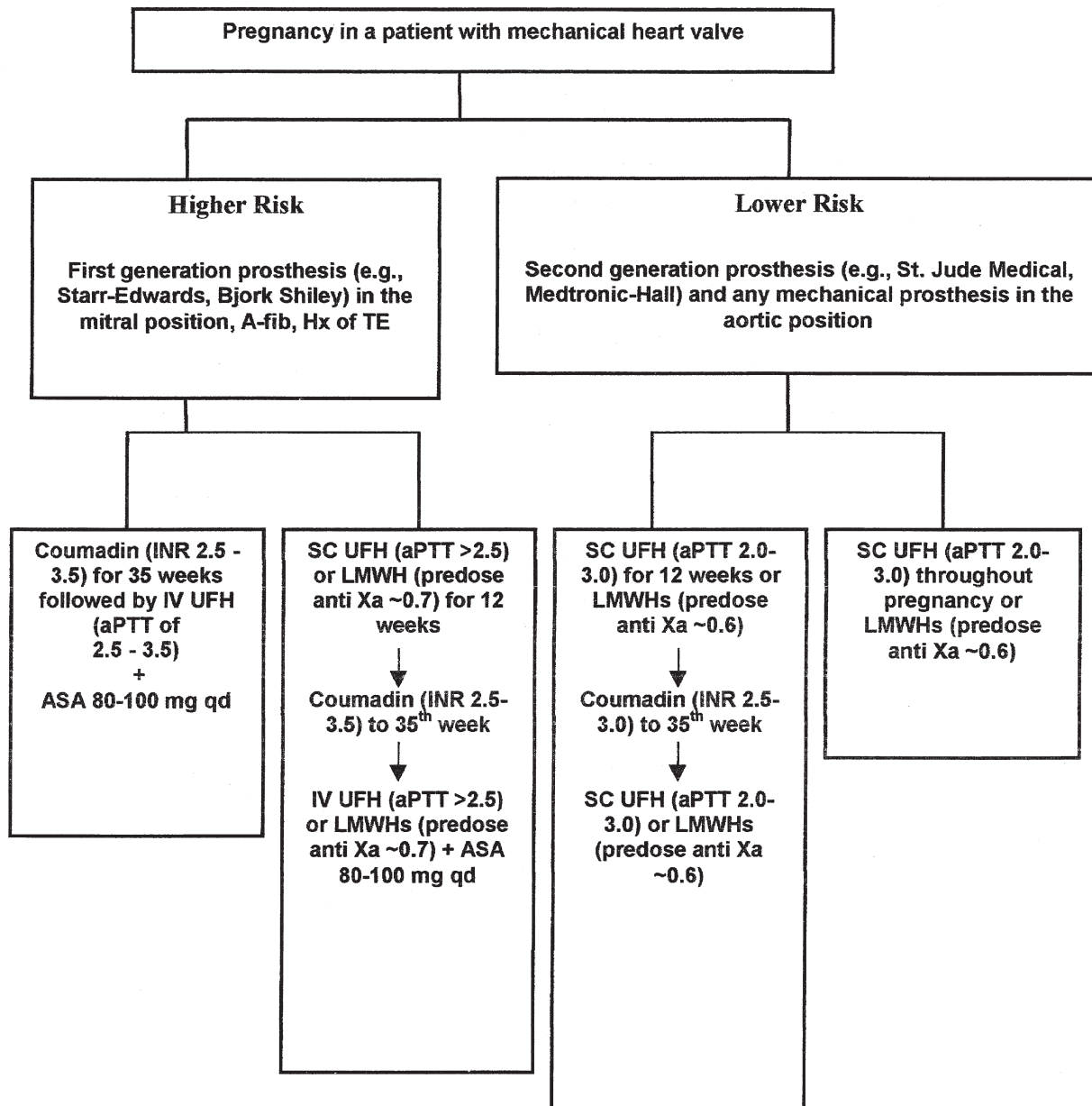


Fig. 1. Recommended approach for anticoagulation prophylaxis in women with mechanical prosthetic heart valves during pregnancy.

higher risk patients, respectively (11,12,63). Unfractionated heparin has a relative short duration of action, therefore, predose activated partial thromboplastin time values should be measured to determine a potential need of dosing every 8 hours. Since there is no evidence for an increased risk of thromboembolism with unfractionated heparin in low-risk patients (prosthetic valve in the aortic position and new gen-

eration prosthetic valves), adjusted-dose heparin throughout pregnancy (midinterval activated partial thromboplastin time 2.0 to 3.0 times control) may be adequate (12).

The use of warfarin during weeks 13 to 35 is an alternative regimen in cases where self-injection of heparin is not desirable. The change of subcutaneous unfractionated heparin to in-hospital intravenous

administration, prior to elective delivery may be advisable, since it allows the discontinuation of therapy 4 hours before the delivery is expected (67).

To detect heparin-induced osteoporosis, bone densitometry has been recommended after delivery in women who have been treated with unfractionated heparin throughout pregnancy, so that dietary, life-style, and therapeutic modifications can be made if needed (14).

Low-molecular-weight heparin has been recommended as an alternative to unfractionated heparin in the recently published Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (63). These recommendations call for the use of adjusted-dose low-molecular-weight heparin given subcutaneously every 12 hours, aiming at peak anti-factor Xa heparin levels of around 1.0 U/mL.

Recent work by Barbour et al (68), however, showed that with the use of low-molecular-weight heparin during pregnancy, trough levels were in the therapeutic range of 0.5 U/mL in only 16% of cases at peak levels between 0.75 and 1.0 U/mL. This information, and the evidence of risk of valve thrombosis with subtherapeutic predose anti-Xa levels, suggests the importance of routine measurements of trough levels that should be maintained at the upper therapeutic range (0.6 to 0.7 U/mL).

In addition, peak values should be measured to prevent excessive levels (ie, > 1.5 U/mL), which have been shown to be associated with an increased rate of bleeding in patients with other cardiac conditions (60,61). To assure patient compliance and to maintain therapeutic levels during pregnancy, which requires dose adjustment (68,69), anti-factor Xa activity should be measured at least every 2 weeks. Because of its longer half-life and in order to prevent complications associated with epidural anesthesia, catheter placement within 10 to 12 hours of the last low-molecular-weight heparin dose is not advised (24). For this reason, low-molecular-weight heparin should be withdrawn 18 to 24 hours before an elective delivery and substituted with intravenous unfractionated heparin.

A number of studies have shown a substantial reduction in the incidence of systemic embolization or death when low-dose aspirin is added to warfarin in patients with mechanical prosthetic heart valves (70–72). Since a small dose of aspirin (60 to 150 mg/day) is safe during pregnancy (11,62,63), it may be used in addition to anticoagulation to maximize the antithrombotic effect (Fig. 1).

The need for anticoagulation in pregnant women with mechanical prosthetic heart valves presents a difficult choice for patients and their physicians (58). Data are insufficient to reliably predict efficacy and

safety, and all anticoagulation options are associated with some risks. These risks can be minimized by a strong commitment by both physicians, as well as patients, to a strict compliance with therapy and a close follow-up. It is also recommended that this group of high-risk patients be managed by practitioners at institutions with expertise and experience in this clinical area.

More information will be needed before final recommendations can be made. For this reason, we are presently conducting a national survey of pregnancies in women with mechanical prosthetic heart valves that will possibly provide answers to the existing questions regarding anticoagulation in this patient population. In addition, a strong plea should be made for the design of a large, prospective study, or a registry, to further evaluate the risks that are associated with currently used mechanical prosthetic heart valves during pregnancy and the efficacy, as well as, safety of various anticoagulation regimens and their appropriate monitoring in the thromboprophylaxis of such women.

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