

## Anticoagulation in Pregnant Women with Prosthetic Heart Valves

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### Abstract

The combination of heart disease and pregnancy can present a formidable challenge to the clinician entrusted to care for both the mother and fetus. Since most data is retrospective, a definitive prognosis for such a patient may be difficult to obtain. Nevertheless, certain cardiac conditions carry greater risks of maternal mortality than do others. However, even for certain preexisting conditions, a tremendous amount of debate persists with respect to risks during pregnancy and optimal peripartum management.

One such area of controversy concerns anticoagulation in pregnant women with prosthetic heart valves. For patients who require anticoagulation for mechanical valves, the choice of some combination of warfarin, unfractionated heparin, and low-molecular-weight heparin (LMWH) has resulted in many small-scale trials, which have not yet provided definite guidance as to the best course of action. Even more controversial has been the recent labeling change that advises against the use of LMWH in all patients with prosthetic heart valves, as a result of two cases of prosthetic valve thrombosis in women using LMWH while pregnant. Although the latest product labeling, in the summer of 2003, was changed to a less restrictive recommendation, debate persists. A discussion of the available data on anticoagulation in pregnant women with prosthetic heart valves is presented here, to inform the clinician and the patient of the risks and benefits of the options presently available.

**Key Words:** Anticoagulation, pregnancy, prosthetic heart valves.

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### Normal Physiology of Pregnancy

THE NORMAL HEMODYNAMIC CHANGES that occur during pregnancy may exacerbate underlying cardiac disease. Cardiac output increases 30–50% (1–4) early in pregnancy, due largely to an increase in stroke volume (5). By the third trimester, as venous return diminishes secondary to enlargement of the uterus, with concomitant obstruction of the inferior vena cava and an increase in dilatation of the venous beds, it is the 15–25% increase in heart rate that accounts for the increase in the cardiac output (1). A 15–25% fall in systemic vascular resistance results in either a slight decrease or no change

in blood pressure; there is no change in the ejection fraction. A relative anemia results from the 20–30% increase in red blood cell mass that occurs with the 30–50% increase in plasma volume (6). The increased metabolic demands of both the mother and fetus account for the 30% increase in oxygen consumption (1). The increase in arterial and venous capacity may result in an increase in fragility of the vessel wall, which may be partly responsible for the increase in thromboembolic phenomena seen in pregnancy (7–10).

Other hemostatic changes that occur with normal pregnancies involve the coagulation cascade. There is an increase in coagulability of the blood and a decrease in fibrinolytic potential (6). These changes appear to coincide with the development of the uteroplacental circulation. Fibrinogen, factors VII, VIII and X, and von Willebrand factor increase throughout pregnancy. Levels of protein S decrease throughout pregnancy (6). A large study in Sweden found that the incidence of thrombosis was 1.3 per 1000 deliveries; this rate was ten times

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that for nonpregnant women in the same age group (11).

### **Evaluation of the Pregnant Patient**

It is common for a pregnant woman to have some symptoms of cardiac disease, such as fatigue, dyspnea on exertion, palpitations, pedal edema and weakness, all of which may simply result from the normal physiologic changes associated with pregnancy. Common physical findings on examination include a mildly elevated jugular venous pressure, brisk carotid upstrokes, basilar crackles, a laterally displaced point of maximal impulse, a third heart sound, early peaking systolic murmur and peripheral edema. Abnormal findings include cyanosis or clubbing, a loud systolic murmur ( $>3/6$ ), a diastolic murmur and fixed splitting of the second heart sound (12). If imaging studies are needed, electrocardiogram, echocardiogram, and exercise testing to submaximal levels can be done safely (13). X-ray procedures should be avoided, especially during the first trimester. Radionuclide imaging and catheterization under fluoroscopy should be avoided unless urgently needed (8, 14).

### **Anticoagulation in Pregnant Women with Prosthetic Heart Valves**

#### **Complications in Pregnant Women with Mechanical Heart Valves**

Because of the hypercoagulability that results during pregnancy, women with mechanical heart valves are particularly at risk for increased thromboembolic events, with incidence ranging from 7.5–23%. Most such events present as valve thrombosis, with a resultant mortality rate of 40% (11–18). The highest risk of thromboembolism occurs at the mitral position with older mechanical valves (19). Such is the case with the Bjork-Shiley spherical occlude valve, as compared to the Starr-Edwards or St. Jude valves (20). The various methods of anticoagulation will be presented, to determine whether any one method provides superior anticoagulation and/or minimal toxicity to the fetus.

#### **Warfarin**

The use of Coumadin (warfarin) in pregnancy is believed to be contraindicated during the first trimester because of the teratogenic effects of the drug, leading to “Coumadin embry-

opathy syndrome” (21–24). The risk of this syndrome has been estimated at 5–25%; toxic effects result in facial abnormalities, optic atrophy, digital abnormalities, epithelial changes and mental impairment of the fetus. As warfarin crosses the placenta, the fetus is exposed to a disproportionately higher dose than the pregnant woman because of the lack of development of the liver enzymes as well as the low levels of the vitamin-K-dependent clotting factors of the fetus (25). After the first trimester, these clotting factors steadily increase until birth (26). Warfarin should be avoided particularly during weeks 7–12 as evidence suggests that the fetus is most vulnerable to the teratogenic effects of the drug during this time (27).

One study (28) suggests that the effects of Coumadin are dose related. A total of 43 women with prosthetic heart valves who continued taking warfarin throughout pregnancy were followed until term. All of these women agreed to have delivery by caesarian section at week 38, with anticoagulation being stopped two days before the scheduled surgery and continued the day after surgery. The international normalized ratio (INR) was kept between 2.5 and 3.5, and the women were divided into two groups, those who required a dose of 5 mg or less and those who required more than 5 mg of warfarin to maintain the desired INR. Out of a total of 58 pregnancies, there were 31 healthy babies born (30 full-term, one pre-term) with 27 fetal complications (22 spontaneous abortions, 2 warfarin embryopathies, one stillbirth, one ventricular septal defect, one growth retardation). Of the 27 fetal complications, 22 occurred in women taking more than 5 mg of warfarin, whereas only 5 occurred in women taking less than 5 mg of warfarin. No fetal or maternal bleeding was observed during caesarian section or premature vaginal delivery. Two women developed valve thrombosis even with desired levels of anticoagulation; both needed surgery. The incidence of embryopathy in this series was 3.4%, while the abortion rate was 37.5%. The results of this study prompted the authors to suggest that anticoagulation with warfarin at doses less than 5 mg to achieve a therapeutic INR may be safe during the first trimester of pregnancy. Women requiring larger doses of warfarin should be informed of the greater risks of teratogenicity and be given the option of continuing warfarin or substituting subcutaneous heparin during the first trimester.

The editorial comment to the study by Vitale et al. (28) was written by Elkayam (19).

Elkayam noted the important findings but cautioned against the use of warfarin at any dose, because of the small number of patients in the study as well as the fact that, when given the choice of using warfarin in the first trimester, most women prefer not to take it. He recommended that women with first generation prosthetic heart valves in the mitral position, should be informed of the higher risk of thromboembolic events with the substitution of subcutaneous heparin for warfarin in the first trimester, and they should be given the option of using warfarin for anticoagulation, especially those women requiring less than 5 mg to achieve a desired INR. Patients need to be informed of the limited data suggesting that lower doses of warfarin may be safer than higher doses. There is also a risk of litigation. Patients at high risk for development of valve thrombosis should be treated with high doses of subcutaneous or intravenous heparin. If heparin is administered, antifactor Xa levels should be monitored in all of these patients. Because of the high incidence of premature labor in patients with prosthetic heart valves, Elkayam recommends that all such patients be hospitalized at 35 or 36 weeks of gestation and warfarin replaced with heparin.

A retrospective study (29) examined maternal and fetal outcomes in patients who used only warfarin throughout pregnancy (group I, n=42 pregnancies) and patients who substituted subcutaneous heparin in the first trimester with continuation of warfarin afterwards (group II, n=21 pregnancies). Although there were no cases of coumarin embryopathy, spontaneous abortion occurred in 11 fetuses (26.2%) in group I and in 3 fetuses (14.3%) in group II. Although there were no maternal deaths, there were two cases of thrombosed mitral valve prosthesis in group II; both occurred at week 14 (two weeks after heparin had been discontinued and Coumadin started), and both required surgery that saved the patients' lives. Both patients' fetuses aborted afterwards. The authors concluded that, although there are no definitive data for use of anticoagulation, warfarin can probably be safely used throughout pregnancy.

### **Use of Unfractionated Heparin During the First Trimester**

Since warfarin use has been discouraged during the first trimester because of possible teratogenic effects, heparin has been recommended during this time period. Unfortunately,

concern over its effectiveness and safety for the mother and fetus remain.

Salazar et al. (18) reported on the use of subcutaneous heparin in 37 women with prosthetic heart valves. All the women received subcutaneous heparin from weeks 6–12 and again in the last two weeks of gestation, with a desired goal of partial thromboplastin time (aPTT) at 1.5–2.5 times the control level. Warfarin was used during all other times. Results included 15 spontaneous abortions in the first trimester (37.5%) without any incidence of coumarin-induced embryopathy; one neonatal death occurred due to cerebral hemorrhage during coumarin therapy. Two women died of fatal massive thrombosis of a mitral tilting-disk prosthesis during the heparin therapy, and one woman died of gastrointestinal bleeding while receiving oral anticoagulation. A total of three thromboembolic events occurred in women with Bjork-Shiley mitral prosthesis. In the discussion, the authors commented that the incidence of spontaneous abortions was 8.8–50% in other studies that used heparin for anticoagulation during the first trimester (30, 31), thus offering little advantage to warfarin therapy in terms of protecting the fetus. There were no thromboembolic events while the women were taking warfarin. In addition, other studies suggest that the use of subcutaneous heparin for prevention of thromboembolic events in the pregnant mother is ineffective (32, 33).

The results of the study by Salazar et al. (18) prompted the authors to recommend that, because there were no advantages to the fetus by substituting heparin for warfarin, warfarin should be used until the 38th week of gestation, with the substitution of intravenous heparin at this time to avoid the use of oral anticoagulation during the last two weeks of pregnancy. The accompanying editorial by Elkayam (34) countered that all studies of pregnant women with prosthetic valves and anticoagulation regimens have been small, but the risk of fetal damage due to Coumadin is well established. Definitive recommendations could not be made, but he suggested that women with older generation prosthetic valves in the mitral position should be informed of the risk of valve thrombosis as well as the dangers of Coumadin embryopathy, to help them decide which form of therapy should be given. In women with older generation valves in the aortic position and those with newer valves in the mitral position, subcutaneous heparin during the first trimester and in the last weeks of gestation should still be rec-

ommended. He commented that the aPTT should be kept between 2 and 3 times control value (in a later editorial, he recommends that antifactor Xa levels can also be followed (19)), unlike the minimum of 1.5 times control used by Salazar et al. (18). Finally, it was noted that even the manufacturer of Coumadin has declared the drug to be teratogenic; use by the physician with this knowledge would surely put the practitioner at risk for any ensuing medical legal issues.

The largest review of the use of anticoagulation in pregnant women was reported by Chan et al. (35). The authors included 976 women with 1,234 pregnancies in various studies conducted from 1966–1997. They found that Coumadin embryopathy occurred in 6.4% of live births; if heparin was substituted for warfarin during weeks 6–12 of gestation, this risk could be virtually eliminated. Valve thrombosis occurred in 3.9% of pregnancies when warfarin was used throughout; when heparin was substituted for warfarin in weeks 6–12, valve thrombosis occurred in 9.2% of pregnancies. Maternal risk of death was 1.8% when warfarin was used throughout pregnancy vs. 4.2% when heparin was substituted for warfarin in the first trimester. The authors concluded that the risk of thrombosis was least when warfarin was used, but at the expense of Coumadin embryopathy; use of heparin eliminates this risk, but at the expense of a greater incidence of valve thrombosis and maternal death.

### **Low-Molecular-Weight Heparin in Pregnant Women**

The use of low-molecular-weight heparin (LMWH) as a substitute for warfarin during the first trimester was initially seen as an easy, cost-effective and possibly safer method compared to subcutaneous heparin, given the many reports of thromboembolism with unfractionated heparin. Although there were no randomized, controlled clinical trials to definitively warrant the use of LMWH for this purpose, clinicians seemed to quickly realize the benefits of this alternative. To the surprise of the medical community, however, the pharmaceutical maker of enoxaparin (an LMWH), issued a warning to health care providers discouraging the use of enoxaparin to prevent thromboembolic disease in *any* patient with prosthetic heart valves. Many physicians felt that the real concern of the drug maker was not for pregnant women, given the potential devastating medico-legal consequences for any

adverse outcome to the mother or the fetus with enoxaparin. As cause and effect may be difficult to prove or disprove, no such link would need to be made to proceed with litigation. Shortly afterwards, in the summer of 2003, the company mailed letters to physicians stating that LMWH had not been adequately studied in pregnant women with mechanical prosthetic heart valves, thus amending their previous recommendation to avoid its use in all patients with prosthetic heart valves. A review of the history of LMWH and its use in pregnant women and nonpregnant patients with prosthetic heart valves will be briefly presented.

**LMWH in pregnant women without prosthetic heart valves.** The use of LMWH seemed to be effective in the prevention and/or treatment of deep vein thrombosis in pregnancy in several serial case studies (36–39). Just as important, it was felt that the use of LMWH did not seem to have detrimental effects on the mother or her fetus. A large review (40) done retrospectively of 624 pregnancies treated with enoxaparin reported the following: seven stillbirths, ten serious neonatal hemorrhages, and eighteen major congenital abnormalities, none of which were felt to be due to enoxaparin. Adverse maternal events included eleven cases of bleeding, six of bleeding at delivery, and two of serious maternal thrombocytopenia.

A prospective observational study (41) of low-dose aspirin plus either enoxaparin or heparin in women with recurrent pregnancy loss and antiphospholipid antibody syndrome was conducted with 123 women. Aspirin therapy was initiated immediately, while enoxaparin or heparin was started at 7 weeks and continued until 34 weeks or delivery. With a mean duration of 27 weeks, there were no fetal deaths, bleeding complications, thrombocytopenia, or fractures.

**LMWH in nonpregnant patients with prosthetic heart valves.** There have been many reports on the use of LMWH, in several clinical settings, in patients with prosthetic heart valves. Its use in periprocedural management was reviewed in a cohort of 1,082 patients (42) who were prophylactically “bridged” from long-term oral coagulation on an outpatient basis. A total of 401 patients had mechanical or bioprosthetic valves, while the remaining 681 patients did not have valves and had other indications for anticoagulation, such as atrial fibrillation, recurrent venous thrombosis, cerebral emboli, transient ischemic attacks and other conditions. The last dose of LMWH was given

12 hours before the procedure, and the first injection was given 8–12 hours following the procedure, after hemostasis was secured. The use of LMWH heparin was overlapped with anticoagulation until a therapeutic INR was reached. The main results were that minor bleeding occurred in 7.6% of patients, major bleeding occurred in 0.27% of patients, and no thromboembolic events were seen in any patient during this bridging period.

In a similar review (43) of periprocedural bridging of 185 patients with mechanical valves, no prosthetic valve thrombosis was observed. Other reports of case series of patients agree that the use of LMWH for “bridging” while off chronic oral anticoagulation was at least as safe as unfractionated heparin, with the additional benefits of shorter length of hospitalization and lower costs (44); the use of LMWH included the immediate anticoagulation after mechanical valve surgery with subsequent administration of warfarin (45–47).

**LMWH in pregnant women with prosthetic heart valves.** There is very little published data concerning the use of LMWH in pregnant women with prosthetic heart valves. There are case reports or small case series on the use of LMWH in such circumstances, detailing incidences of valve thrombosis (48–51).

The study which led to the controversial labeling change by Aventis (maker of enoxaparin) was to have enrolled 110 patients in a randomized, open-label fashion, comparing enoxaparin with warfarin and unfractionated heparin in pregnant women with prosthetic heart valves (52). But after only 12 patients were enrolled, the safety committee terminated the study due to two deaths from prosthetic valve thrombosis in the enoxaparin group. A detailed report of the circumstances of the deaths of these two pregnant women revealed that one had a prosthetic mitral valve and the other had prosthetic valves in both the mitral and aortic positions. Although recommended therapeutic ranges for Factor Xa are 0.6–1.0 IU/mL (53), the data showed that both women had subtherapeutic levels of Factor Xa just before or at the time of death. As a result, critics of the labeling change believe that the level of anticoagulation with enoxaparin was not optimal and that, given the high risk of adverse outcome with unfractionated heparin in the same clinical setting, such a change was unwarranted and should not be applied to all patients with prosthetic heart valves, even if pregnant.

### Current Guidelines: European Society of Cardiology and American College of Cardiology/American Heart Association

The current guidelines by the European Society of Cardiology (ESC) (54) and the American College of Cardiology/American Heart Association (ACC/AHA) (55) recommend the use of warfarin as the anticoagulation of choice for pregnant women with mechanical prosthetic heart valves, for the first 35 weeks of pregnancy (Table 1) (55). The ACC/AHA report also suggests that if women who are at high risk for thromboembolism (history of thromboembolism and/or older generation mechanical prosthesis in the mitral position) choose not to take warfarin during the first trimester, then unfractionated heparin should be given continuously intravenously, with a target of aPTT of 2–3 times control. Women at low risk for thromboembolism who choose not to take warfarin should receive adjusted-dose subcutaneous heparin to achieve a desired aPTT of 2–3 times control. Women who choose not to take warfarin in the first trimester must be made fully aware that unfractionated heparin is less safe for them, with higher risks of both thrombosis and bleeding, than warfarin, and that any risk to the mother also puts the health of the baby at risk.

**TABLE 1**  
*Recommendations for Anticoagulation during Pregnancy: Weeks 1 through 35 in Patients with Mechanical Prosthetic Valves*

Indication	Class
Whether to use heparin or continue warfarin during the first trimester must be discussed fully with the patient and her partner. If she chooses to use heparin for the first trimester, she must 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.	I
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) aPTT to 2–3 times control.	
Transition to warfarin can occur thereafter.	I

Adapted with permission from Bonow RO, et al. Guidelines for the management of patients with valvular heart disease. *Circulation* 1998; 98(18):1949–1984 (55).

After the 36th week of pregnancy (Table 2) (55), the guidelines recommend the cessation of warfarin with the substitution of unfractionated heparin. If warfarin is continued up until delivery, cesarean section should be performed. Finally, once it has been determined that there is no significant bleeding, heparin should be resumed 4–6 hours after delivery and warfarin begun orally.

The ACC/AHA report cautions against the use of LMWH simply because of the lack of data available in the management of pregnant patients with prosthetic heart valves.

### Conclusions

Given the lack of data, definitive management of pregnant patients with prosthetic heart valves who need anticoagulation remains particularly challenging. There is, however, general agreement on certain aspects of this entity.

- There is insufficient data to compare or advocate use of warfarin, unfractionated heparin, or LMWH, since there is evidence to suggest that any option or combination of these choices has potentially adverse outcomes for both the mother and fetus. All patients should be advised of the potential risks to the patient and fetus with all options of anticoagulation. The importance of educating the patient on the risks and benefits of each option cannot be overstated; the patient needs to have this information to make a decision with which she is most comfortable.

**TABLE 2**

*Recommendations for Anticoagulation during Pregnancy: After the 36th Week, in Patients with Mechanical Prosthetic Valves*

Indication	Class
Warfarin should be stopped no later than week 36 and heparin substituted in anticipation of labor.	IIa
If labor begins while the patient is still on warfarin, a cesarean section should be performed.	IIa
In the absence of significant bleeding, heparin can be resumed 4–6 hours after delivery, and warfarin begun orally.	IIa

Adapted with permission from Bonow RO, et al. Guidelines for the management of patients with valvular heart disease. *Circulation* 1998; 98(18):1949–1984 (55).

- ACC/AHA guidelines recommend that warfarin be used as the choice of anticoagulation in weeks 1–35, since there is evidence to show that use of unfractionated heparin as a substitute early on increases the risk of harm to the mother; at week 36 and afterwards, heparin may be used instead of warfarin, but if warfarin is continued, caesarian section is recommended at the time of delivery to avoid excessive bleeding (55).
- ACC/AHA guidelines recommend that patients who choose not to take warfarin during the first trimester, and patients who are at high risk for thromboembolism (history of previous thromboembolic disease or older generation prosthetic valve at the mitral position) should receive intravenous unfractionated heparin with a target aPTT of 2–3 times control. Patients who are at low risk should receive subcutaneous heparin with a target aPTT of 2–3 times control (55).
- There is insufficient data as to the use of LMWH in pregnancy (55).

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