The management of pregnant women with mechanical heart valves is challenging. Recently, based on small numbers of patients and poor-quality data, correspondence from Aventis Pharmaceuticals Inc has described treatment “failures” and concerns about teratogenicity with the use of the low-molecular-weight heparin (LMWH) enoxaparin. The company issued a “Warning” that enoxaparin should not be used in patients with prosthetic heart valves and a “Precaution” about potential teratogenicity. This has created a huge problem for physicians managing pregnant women with prosthetic heart valves because the alternatives, unfractionated heparin and warfarin, are problematic. There have been case reports of failures (including death from thrombosed valves) with unfractionated heparin, whereas the package insert for warfarin states that the drug is contraindicated during pregnancy because of potential teratogenicity. Initially, LMWHs appeared suitable for pregnant patients with prosthetic heart valves. Unfortunately, the company correspondence, presumably supported by the Food and Drug Administration (FDA), raises medicolegal concerns with use of any LMWH. We believe that pharmaceutical companies and the FDA should not endorse scientifically unsupported claims that eliminate acceptable therapeutic options. This correspondence has created considerable confusion among patients and treating physicians and is likely to lead to frivolous lawsuits and preclude the performance of properly designed trials in pregnant women. We believe a consensus conference among experts in the field to identify key unresolved issues and a commitment by the FDA and industry to perform appropriate studies are now critical.
There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defects. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.

The warning was based on the results of a very small trial and an undisclosed number of postmarketing reports of thrombosed valves in patients receiving enoxaparin. The randomized controlled trial, conducted in South Africa and not sponsored by Aventis Pharmaceuticals, of pregnant women with prosthetic heart valves was stopped after 12 patients were enrolled. In this study, women were randomly allocated to receive enoxaparin (1 mg/kg twice daily) or a regimen consisting of unfractionated heparin (UFH) and warfarin given sequentally. Few details are available; however, according to Aventis Pharmaceuticals, 2 of 7 enoxaparin-treated women developed thrombosis and outflow obstruction of their prosthetic valves, causing maternal (and fetal) death. The postmarketing reports consisted of an undisclosed number of valve thromboses in enoxaparin-treated patients (including pregnant women) with prosthetic heart valves. Based on the small numbers in the trial, and the inability to determine accurate incidence rates from postmarketing data, the true incidence of valve thrombosis in enoxaparin-treated pregnant women with mechanical heart valves, and whether thrombosis rates are higher in such women than warfarin-treated nonpregnant patients, are unknown.

Teratogenicity can result from numerous causes, including use of drugs, or simply by chance. The company claims a “cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population,” thereby avoiding direct indictment of physicians who prescribe enoxaparin during pregnancy. However, the “Precaution” was presumably issued to minimize potential liability against Aventis Pharmaceuticals and has the potential to inhibit physicians from prescribing enoxaparin and other LMWHs in pregnant women. In view of the evidence that neither UFH nor LMWH crosses the placenta, an increase in teratogenicity seems biologically implausible.

Subsequently, a “Dear Health Care Professional” letter from Aventis summarizing the additions to the Waring and Precaution sections of the Lovenox prescribing information was disseminated, presumably supported by the Food and Drug Administration (FDA). Both the warning and the precaution are based on poor evidence and are likely to affect physicians’ practices, as well as the feasibility of further research into the management of pregnant women with mechanical heart valves. When an adverse pregnancy outcome occurs, the likelihood of medico-legal action against the attending physician is high, even if the care given was reasonable. Undoubtedly, many physicians will avoid enoxaparin (and other LMWHs) in pregnant women with mechanical heart valves and, perhaps, particularly unnecessarily, for other indications in pregnancy. Physicians who use an LMWH in pregnant women with mechanical heart valves face a high probability of being sued if an adverse experience occurs in the mother or the neonate.

So, how should pregnant women with mechanical prosthetic heart valves be managed?

Antithrombotic therapy is essential, because the risk of valve thrombosis and death or systemic embolism is high if it is not given. With currently used regimens (including warfarin, UFH, and LMWH, either alone or in sequence), pregnancy in a woman with a mechanical heart valve carries a risk of maternal mortality from valve thrombosis estimated at 1% to 4%. Many factors determine the risk of valve thrombosis, including valve type and position, presence of atrial fibrillation, left atrial size, history of previous thrombosis, number of mechanical valves, and adequacy of anticoagulation. Valve designs have changed significantly over the last few years and there is less thrombogenic potential associated with newer bileaflet valves. Management is problematic because these women require anticoagulant therapy and there are no controlled clinical trials to provide guidelines with respect to the optimal antithrombotic agent or the intensity of anticoagulant therapy. Unfortunately, pregnant women (and often women of childbearing potential) are usually excluded from trials that involve evaluation of drugs. Performing studies involving only pregnant women is extraordinarily difficult, because of “ethical” concerns, often resulting in the refusal of institutional ethical review boards to approve such studies. Consequently, the best available evidence for the management of most diseases in pregnant women is very poor, usually consisting of case reports, small series, and “expert opinion.” A further problem is the philosophy of most pharmaceutical companies of avoidance of the development of drugs for use in pregnancy because of medico-legal concerns and the perception that the potential profits are not worth the liability.

Prior to the development of LMWHs, 2 regimens were commonly recommended in pregnant women with mechanical heart valves: (1) warfarin, for most of the pregnancy, usually with substitution of UFH between 6 and 12 weeks of gestation (to avoid warfarin embryopathy; see below) and near term (to avoid neonatal hemorrhage), and (2) UFH throughout pregnancy. Evidence supporting the use of these regimens is poor and is derived from case reports, case series, small cohort studies, and questionnaires. Further, the use of both warfarin and UFH is problematic during pregnancy. Warfarin crosses the placenta and can cause fetal abnormalities as well as hemorrhage, particularly during and immediately after delivery. Although UFH does not cross the placenta and does not harm the fetus, it must be given parenterally (usually by subcutaneous injection twice daily) and like warfarin can cause maternal hemorrhage, and also can cause maternal osteoporosis and thrombocytopenia.

Many experts have suggested that LMWHs may be a suitable option for prophylaxis of systemic embolism in pregnant women with mechanical heart valves. Like UFH, they do not cross the placenta and, therefore, it seems biologically implausible that they could be teratogenic. In support of this, a recent overview found no increase in teratogenicity with LMWH use during pregnancy. Further, when compared with UFH, LMWHs have distinct advantages, including the potential for subcuta-
neous administration once, rather than twice, daily possibly less bleeding for an equivalent antithrombotic effect, less osteoporosis, and less heparin-induced thrombocytopenia. In addition, because they produce a predictable antithrombotic effect when given to patients subcutaneously on a weight-adjusted basis, no laboratory monitoring is required in this patient population. However, the pharmacokinetics of LMWHs are different in pregnant than in nonpregnant subjects because of changes in volume of distribution resulting from an increase in plasma volume and changes in renal clearance of LMWH. Consequently, although empiric, we recommend periodic anti-factor Xa level monitoring, with dose adjustments to ensure a consistent anticoagulant effect. Nevertheless, many experts were hopeful that LMWHs would improve the management of pregnant women with mechanical heart valves. Until properly designed, adequately powered trials of currently available agents are performed or new antithrombotics suitable for use in pregnant women are developed, recommendations for the management of pregnant women with mechanical heart valves must be based on case reports, case series, and expert consensus.

BASIS FOR RECOMMENDATIONS

To make sensible recommendations, the following questions should be addressed. For warfarin: (1) What are the true incidence and the clinical impact of warfarin embryopathy? (2) Does warfarin truly cause other fetal problems when given to pregnant women? For UFH and LMWH: (1) What is the true incidence of failure (valve thrombosis)? (2) What is the incidence of other adverse experiences (bleeding, osteoporosis, thrombocytopenia)? For LMWH: Does LMWH truly cause fetal problems when given to pregnant women?

Warfarin

Warfarin is the drug of choice in nonpregnant patients with mechanical heart valves and is highly effective in preventing thromboembolic complications. In pregnant women, it can cause a specific embryopathy, consisting of nasal hypoplasia and epiphyseal stippling, albeit only when administered between 6 and 12 weeks of gestation. In a recent critical review of the available published literature, the authors estimated that the true incidence of warfarin embryopathy with exposure between 6 and 12 weeks of gestation was low (<5%); this contrasted with estimates of 30% or higher. Further, in recent follow-up studies of children born with warfarin embryopathy, major morbidity was uncommon, and many of these infants developed normally.

Other problems, such as fetal central nervous system abnormalities, have been reported in association with warfarin use at any stage of pregnancy. However, these events are rare and it is unclear whether the incidence of any of these complications is higher than in pregnancies not associated with warfarin use. Finally, since warfarin crosses the placenta, maternal use can cause fetal hemorrhage, particularly during labor and immediately after delivery. However, this is likely to be rare and can be avoided by using a heparin (instead of warfarin) for the last part (2-4 weeks) of pregnancy.

Unfractionated Heparin

Since it does not cross the placenta, UFH is not teratogenic. However, multiple reports of thrombosed valves with the use of UFH, causing maternal morbidity and mortality, have raised serious concerns about its effectiveness. One plausible explanation for the failure of UFH is inadequate dosage. It is known that low-dose heparin (5000 IU every 8-12 hours subcutaneously) is inadequate for prevention of thrombosis of mechanical prosthetic heart valves during pregnancy; it is unclear whether 12-hourly subcutaneous UFH adjusted to prolong a mid-interval activated partial thromboplastin time (aPTT) result to 1.5 to 2.5 times control is adequate. After initial heparin therapy, this regimen has been shown to be as effective as warfarin (with a target international normalized ratio [INR] of 2.0-3.0) for the prevention of recurrence in nonpregnant patients with acute venous thromboembolism. However, based on several considerations, this regimen of UFH might be less effective in pregnant women with mechanical heart valves. First, 1.5 times control, the usual lower limit of the therapeutic range, corresponds to subtherapeutic heparin levels (anti-factor Xa levels <0.3 U/mL) using most currently available aPTT reagents. Second, except for patients who have bileaflet mechanical aortic valves and do not have atrial fibrillation, the recommended target INR range for patients with mechanical heart valves (2.5-3.5) is higher than the corresponding target INR range for the treatment of acute venous thromboembolism (2.0-3.0), suggesting that more intense antithrombotic therapy is appropriate. Further, although warfarin, with a target INR of 2.0 to 3.0, is highly effective in the long-term treatment of acute venous thromboembolism, even with the use of a more intense warfarin regimen (INR of 2.5-3.5), the addition of aspirin to the warfarin regimen improves efficacy for patients with mechanical heart valves (albeit at the cost of an increase in the rate of minor bleeding). Given this information, we recommend that if subcutaneous UFH is used to prevent thrombosis in pregnant women with mechanical heart valves, the starting dose should be high (17 500-20 000 U every 12 hours) and adjusted aggressively to achieve a mid-interval aPTT of at least 2.0 times control or a result that corresponds to an anti-factor Xa heparin level of at least 0.3 to 0.5 U/mL. Finally, adjunctive aspirin therapy should be considered in high-risk women, such as those with previous systemic embolism and those with atrial fibrillation.

The rate of major bleeding in pregnant patients treated with UFH has been reported to be approximately 2%, which is consistent with the reported rates of bleeding associated with heparin therapy in nonpregnant patients and with warfarin therapy when used for the treatment of deep vein thrombosis. Unfortunately, adjusted-dose subcutaneous UFH can cause a persistent anticoagulant effect at the time of delivery, which can complicate its use prior to labor. Approximately 3% of non-pregnant patients receiving UFH develop immune, IgG-mediated thrombocytopenia, which is frequently complicated by extension of preexisting venous throm-
boembolism or new arterial thrombosis. In pregnant women, the true incidence of IgG-mediated thrombocytopenia is unknown. Long-term heparin therapy has been reported to cause osteoporosis in both laboratory animals and humans. Further, symptomatic vertebral fractures have been reported to occur in about 2% to 3% of patients receiving UFH for periods of 1 month or more and significant reductions in bone density have been reported in up to 30% of patients receiving long-term UFH.

Low-Molecular-Weight Heparin

The true incidence of valve thrombosis in enoxaparin- (or other LMWH-) treated pregnant women with mechanical heart valves and the optimal LMWH treatment regimen for their patients are unknown. Based on published data, there have been a small number of patients treated with LMWH, most successfully. The small numbers of patients with valve thrombosis in the randomized trial of enoxaparin (2 of 7, 29%) have very wide confidence intervals (4%-71%) and, when combined with the limitations of the postmarketing data, preclude an accurate estimate of the true rate of fatal and nonfatal valve thrombosis despite the information contained in the recent “Precaution” and “Dear Health Care Professional” letter.1

The potential for teratogenicity of LMWHs lacks biologic plausibility because it has been demonstrated that these agents do not cross the placenta. In support of this, a recent comprehensive overview concluded that there was no teratogenicity associated with LMWHs.9

OTHER ISSUES

Warfarin, with a target INR of 2.5 to 3.5 (except in patients with uncomplicated bileaflet mechanical aortic valves), is standard antithrombotic therapy for nonpregnant patients with mechanical prosthetic heart valves. It is highly likely that warfarin therapy is safe during pregnancy when used up to 6 weeks of gestation and from 12 weeks of gestation until just prior to (≥2 weeks) delivery. It is also likely that both the incidence and the morbidity of warfarin embryopathy have been overestimated with warfarin use between 6 and 12 weeks of gestation; the true incidence is probably less than 5% and the morbidity is low.2,8-11

However, the use of warfarin during pregnancy has important medicolegal implications (especially in North America) as the package insert for the most commonly prescribed brand (Coumadin; DuPont Pharma, Wilmington, Del) states that warfarin is contraindicated during pregnancy.

Neither UFH nor LMWH crosses the placenta and both are highly unlikely to be teratogenic. Reports of treatment failures with UFH and LMWH, resulting in thrombosed valves and sometimes death, have been published, leading many to conclude that these agents should not be used in pregnant patients with mechanical prosthetic heart valves. Many of these failures were associated with inadequate dosing (eg, UFH, 5000 U every 12 hours or “prophylactic” doses of LMWH). The true incidence of failure with either drug, given in adequate doses, is unknown and it is unclear whether the risk is higher than that associated with warfarin adjusted to target an INR of 2.5 to 3.5. If UFH or LMWH is used, sufficient doses must be initiated and the doses adjusted according to the results of appropriate laboratory tests, preferably anti-factor Xa levels or, with UFH, the aPTT.

To summarize, there are still 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. Based on the above considerations, UFH and LMWH are unlikely to be teratogenic. Although warfarin almost certainly can cause an embryopathy if given between 6 and 12 weeks of gestation, it has probably been overestimated in frequency and clinical impact. If UFH is used, it should be initiated in high doses (17 500-20 000 U every 12 hours) and adjusted according to a 6-hour postinjection aPTT (minimum target of twice control) or anti-factor Xa heparin level (minimum target of 0.3 U/mL). If an LMWH is used, it should also be initiated in high doses and adjusted according to a 6- to 6-hour postinjection anti-Xa heparin level (minimum target of 0.5 U/mL). In addition, for some high-risk patients (eg, those with a history of systemic embolism), aspirin, 80 to 325 mg/d, should be administered in an attempt to reduce the risk of thrombosis, recognizing that it increases the risk of bleeding.20

TREATMENT RECOMMENDATIONS

Women with mechanical heart valves should be carefully counseled about the risks associated with available anticoagulant options prior to, or shortly after, becoming pregnant. The practice of substituting warfarin with UFH or an LMWH between 6 and 12 weeks of gestation probably eliminates the risk of warfarin embryopathy (or other teratogenic effects) but might subject women to an increased risk of thromboembolism if inadequate doses are used.

One of the following approaches is recommended:

1. “Aggressive” adjusted-dose UFH throughout pregnancy; ie, administered subcutaneously every 12 hours in doses adjusted to maintain the mid-interval aPTT at a minimum of twice control or an anti-factor Xa heparin level of at least 0.3 U/mL.

2. Adjusted-dose LMWH throughout pregnancy; ie, administered subcutaneously every 12 hours in doses adjusted to maintain a 4- to 6-hour postinjection anti-factor Xa heparin level at a minimum of 0.5 U/mL.

3. UFH or LMWH (as above) until the 13th week of pregnancy, then warfarin with a target INR of 2.5 to 3.5 until the middle of the third trimester, followed by reinitiation of UFH or LMWH until delivery.

With any of the 3 above regimens, adjunctive aspirin therapy should be considered. Long-term anticoagulants should be resumed post partum with all regimens.

CONCLUSIONS

The management of pregnant women with mechanical valves is a particularly difficult challenge. The paucity of methodologically sound studies has hampered the devel-
velopment of definitive treatment recommendations. With the information contained in the package insert for warfarin, the concern about treatment failures with UFH, and the recent “Warning,” “Precaution,” and “Dear Health Care Professional” letter from Aventis Pharmaceuticals, physicians treating these patients have been left without a widely accepted treatment option and their medicolegal exposure is very high. The precaution about teratogenic effects also unnecessarily complicates the treatment and prophylaxis of venous thromboembolism during pregnancy. In addition, this new “information” will undoubtedly hamper the feasibility of conducting clinical trials designed to improve the management of pregnant women with mechanical valves. Pharmaceutical companies and the FDA have a responsibility to disseminate information about drugs that affect patient safety. However, the FDA and other regulatory agencies must not endorse scientifically unsupported claims that have the potential to “close the door” on acceptable therapeutic options. In this instance the result has been confusion and worry among patients and treating physicians, and will likely lead to frivolous lawsuits and the abandonment of research designed to improve the management of pregnant women with mechanical heart valves.

In our opinion, the next steps should include (1) a consensus among experts in the field to systematically gather the best available evidence and generate recommendations for the management of pregnant women with mechanical heart valves; (2) identification of key unresolved issues that will lead to the performance of appropriate studies to address these issues; and (3) a commitment by the FDA (and industry) to support appropriately designed trials to solve, rather than create problems. The status quo is unacceptable.

Accepted for publication December 3, 2002.

Dr Ginsberg is a Career Investigator of the Heart and Stroke Foundation of Ontario and the recipient of a Research Chair from the Canadian Institutes of Health Research/Astra Zeneca. Dr Bates is the recipient of a New Investigator Award from the Canadian Institutes of Health Research/Astra Zeneca.

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