The Search for a Safe and Effective Anticoagulation Regimen in Pregnant Women With Mechanical Prosthetic Heart Valves*

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Pregnancy is associated with an increased risk of thrombosis in women with mechanical prosthetic heart valves (MPHV) (1). Effective anticoagulation therapy is, therefore, critical but remains challenging because both oral anticoagulants and heparins may be associated with important maternal and fetal complications (1,2).

Warfarin, a time-honored treatment for nonpregnant patients with MPHV has been also shown to be effective in the prevention of thromboembolic complications during pregnancy (1–3). Exposure to warfarin in the first 6 to 12 weeks of pregnancy, however, can be associated with a significant risk to the fetus, including spontaneous abortions and warfarin embryopathy (1,3). In addition, the use of oral anticoagulation therapy during pregnancy may also be associated with fetal hemorrhage, including intracranial bleeding (4), central nervous system abnormalities, and minor neurologic dysfunction and low intelligent quotients in later age (1). Although a number of recent studies have reported no untoward effects with the use of warfarin during pregnancy (5–7), others have clearly shown a high and unacceptable rate of fetal complications (8–13). Because of these risks, both women and physicians have been reluctant to use oral anticoagulation during the first trimester or at any time during pregnancy.

Is warfarin-related fetal risk dose dependent? Vitale et al. (12) in 1999 suggested a close relationship between warfarin dosage and fetal complications in pregnant women with MPHV. These investigators studied 58 pregnancies and showed that the majority of fetal complications were related to warfarin dose of >5 mg per day. Thirty-three gestations in women taking ≤5 mg were associated with 28 healthy babies (82%) in comparison to 22 fetal complications (fetal loss 76%, warfarin embryopathy 8%) in 25 women treated with >5 mg daily. The same group of investigators (11) later reported poor outcome in 30 of 71 pregnancies (fetal loss in 28 cases, and embryopathy in 2 cases). Multivariable analysis identified warfarin at daily dose >5 mg as a significant predictor (p < 0.001) of poor fetal outcome. This information resulted in a recommendation to consider the use of oral anticoagulation throughout pregnancy when warfarin dose is <5 mg daily by the recently published European Society of Cardiology guidelines (14) for the management of women with heart disease in pregnancy.

In this issue of the Journal, De Santo et al. (15) report additional 16 pregnancies in women who received therapeutic anticoagulation with a daily warfarin dose <5 mg before an aortic valve replacement and later received a new-generation MPHV. These patients, who continued to receive low-dose warfarin throughout pregnancy with very close follow-up, had no thromboembolic or hemorrhagic complications, and all had healthy babies. Patients were carefully monitored with weekly international normalized ratio (INR) determinations targeted by the investigators to be between 1.5 and 2.5.

Although these results are encouraging, they suffer from important limitations and, therefore, can have only limited clinical impact at the present time. The findings can be applied only to patients with new-generation aortic MPHV adequately anticoagulated with low-dose oral anticoagulation. In addition, as indicated by the investigators, the combined number of patients included in their 3 publications (11,12,15) is small and cannot be considered conclusive. A further concern is that, in spite of the absolute safety reported in the study by De Santo et al. (15), the results are not supported by other publications describing fetal complications with low-dose warfarin. Sadler et al. (10) reported 7 miscarriages in 11 women treated with <5 mg warfarin daily compared to 5 miscarriages in 11 women treated with >5 mg daily. Shannon et al. (9) reported spontaneous abortion in 8 of 10 women receiving warfarin during the first trimester; 6 of these were treated with ≤5 mg per day and the other 2 received 6 mg. In addition, 1 case of warfarin embryopathy was associated with a warfarin dose of 5 to 6 mg per day. McIntiottck et al. (16) reported 2 perinatal deaths and 2 stillbirths as a result of fetal intracerebral hemorrhage in women taking warfarin at daily doses of 4 mg and 5 mg, respectively, and an infant death due to warfarin embryopathy in a woman taking 6 mg per day until week 34. Mehdiriratta et al. (13) reported a case of severe
growth retardation and warfarin embryopathy in a patient treated with warfarin 3 mg per day throughout pregnancy.

De Santo et al. (15) used a relatively low INR goal between 1.5 and 2.5 on the basis of recent studies showing a low incidence of thromboembolic events among nonpregnant patients with new-generation MPHV (17,18). Because pregnant patients were not included in these studies, the safety of this approach for pregnancy remains unproven. For this reason, and until more data are available, it seems advisable to follow the American College of Cardiology/American Heart Association guidelines (19) and use a warfarin dose during pregnancy aiming to achieve an INR level of ≥2.5 even in patients with new-generation MPHV in the aortic position.

Another limitation associated with the protocol presented by De Santo et al. (15) is a mandatory cesarean section delivery in all patients. Although relatively safe, a cesarean delivery is associated with a substantial increase in short- and long-term risks, including surgery-related infections, bleeding, thromboembolism, pain, and damage to pelvic organs, and later, increased risk of miscarriage, ectopic gestation, placenta previa, and placenta accreta (20).

Because of the remaining concern regarding fetal effects of warfarin, recent guidelines recommendations to use low-dose warfarin, if therapeutically effective, throughout pregnancy (14) seem premature and require further validation.

The only patient reported by De Santo et al. (15) to have valve thrombosis was treated with low-molecular-weight heparin at a dose titrated to achieve peak anti-Xa levels of 0.7 to 1.2 IU/ml, as recommended by recent guidelines (14,19). These guidelines, however, ignore the manufacturer recommendations to monitor both peak and trough levels (21). The importance of measuring trough levels was first demonstrated by Barbour et al. (22), who evaluated 138 levels, which were later confirmed by Friedrich and Hameed (23), who studied 15 pregnant subjects receiving therapeutic doses of enoxaparin given twice daily. While all peak levels at 3 to 4 h were between 0.5 IU/ml and 1.0 IU/ml, 20% at 8 h and 73% at 12 h were subtherapeutic. The relationship between 177 paired peak and trough levels of anti-Xa during pregnancy were further studied by our group (24); in 26 pregnant patients receiving adjusted-dose enoxaparin given every 12 h, peak levels of 0.7 to 1.2 IU/ml were associated with subtherapeutic trough level (<0.6 IU/ml) in >50% of the cases, and only 7 (6%) determinations, 6 of them with trough levels >0.8 IU/ml, had peak levels >1.5 IU/ml. These data, in addition to documented risk of valve thrombosis with subtherapeutic pre-dose anti-Xa levels (2), support the importance of routine measurement and maintenance of trough levels at therapeutic range in pregnant women with MPHV ≥0.6 IU/ml in lower risk women, and ≥0.7 IU/ml in high-risk women (Table 1) (25). Peak levels should also be monitored to detect excessive anticoagulation (i.e., anti-Xa >1.5 IU/ml), which requires switching to 8-hourly dosing.

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