

**Editorial Comment****Anticoagulation in Pregnant Women With Prosthetic Heart Valves: A Double Jeopardy\***

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Young women with a prosthetic heart valve often wish to bear children (1). Pregnancy in such patients is associated with increased risk due to various causes, including increased blood volume and hemodynamic burden, hypercoagulable state of pregnancy leading to increased incidence of thromboembolic events and the exposure of the fetus to cardiovascular drugs required to treat maternal disease. Oral anticoagulant agents have been considered contraindicated in pregnancy because of their reported teratogenic effect and resulting abnormalities. In contrast, heparin does not cross the placenta because of its large molecule, and recent experience (2) in a large number of patients who received heparin during pregnancy has shown a normal fetal and neonatal outcome without an increase in maternal bleeding complications. Although subclinical reduction in bone density is a potential consequence of long-term heparin therapy in pregnancy, it is usually reversible, and the risk of symptomatic bone fracture is small (3). For all these reasons, it is not surprising that the use of heparin has been preferred during pregnancy in patients requiring anticoagulation therapy (4). In this issue of the Journal, Salazar et al. (5) describe their prospective experience with 40 pregnancies in 37 women with prosthetic heart valves who received subcutaneous heparin from the 6th week to the end of the 12th week and for the last 2 weeks of gestation. The authors report fatal valve thrombosis during heparin therapy in two cases and conclude that subcutaneous heparin is not effective in the prevention of mechanical valve thrombosis during pregnancy. On the basis of their findings, the authors recommend the use of oral anticoagulation throughout pregnancy with a change to heparin only during the last 2 weeks of gestation. These group of investigators have had a long-standing interest in the management of pregnant patients with prosthetic heart valves. Their previous publications (6,7) had a substantial impact on the care of such patients, and their present report is likely to have a similar effect. For this reason, the results of the study should be analyzed very carefully and in context of other available data.

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Considering the important clinical implications of their recommendations, Salazar et al. (5) could be criticized for overinterpreting information obtained in only a small number of patients. The authors have used the results of a recent European survey (8) that evaluated 12 cases of mechanical valve thrombosis during pregnancy, 16 of which occurred during subcutaneous heparin therapy, to defend their conclusions. Although these data may indeed suggest failure of subcutaneous heparin to provide adequate protection against valve thrombosis during pregnancy, the results of such surveys are unfortunately limited by the retrospective design and the inherent susceptibility to providing incomplete and biased information (3).

Both the studies by Salazar et al. (5) and Sbarouni et al. (8) reported the occurrence of valve thrombosis in patients with older generation mechanical prosthesis, such as Starr-Edwards and Björk-Shiley valves, and in all cases the prosthetic valve involved was in the mitral position. Should the recommendations to use Coumadin during most of the pregnancy, including the first trimester, be extended to newer, less thrombogenic prosthetic heart valves and to valves in the aortic position? The answer to these questions is difficult, mainly for lack of sufficient information. However, Sarel et al. (9) reported a low incidence of thromboembolism despite inadequate anticoagulation during 50 pregnancies in women with 60 mechanical valves. The majority of these patients had newer generation mechanical prostheses (Medtronic-Hall and St. Jude Medical) and were treated with Coumadin during the first two trimesters of gestation and heparin during the last trimester. Measured prothrombin ratio was found to be within the therapeutic range in only 39% of cases. These data may indicate a lower likelihood of thromboembolic events during pregnancy in patients with newer generation prosthetic heart valves.

A reported high rate of valve thrombosis during heparin therapy may be due to inadequate heparin dose or lack of stringent monitoring of activated partial thromboplastin time (aPTT). Although the authors state that valve thrombosis occurred despite adequate heparin dosing, data are not provided. In addition, the minimal target aPTT ratio of 1.5 used by these investigators has recently been suggested to be too low (3). Similarly, no information regarding adequacy of heparin dose and aPTT monitoring in cases with valve thrombosis is provided by Sbarouni et al. (9). In addition, anecdotal information clearly demonstrates that valve thrombosis during pregnancy is not unique to heparin and can also occur in patients receiving Coumadin therapy, especially when adequate monitoring is not available (10-12).

Sbarouni et al. (9) reported no embryopathies in a group of 46 women who were treated with warfarin during the first gestational trimester and state that embryopathy is rare when a dose of warfarin is well controlled. In contrast, a careful evaluation in two other studies resulted in diagnosing signs of embryopathy in as many as 29% (6) and 67% (13) of newborns, respectively. The authors (5) indicate that many children with Coumadin embryopathy have only minor abnormalities. How-

ever, this can hardly be used as reassurance because the severity of the syndrome in an individual case is unpredictable, and many women are more likely to accept a possible increased risk to themselves before accepting the risk of "only" minor abnormalities in their children (1). In recent weeks, we consulted on two pregnant patients with prosthetic valves. The first had a Björk-Shiley valve in the mitral position due to an episode of bacterial endocarditis and the second a St. Jude valve in the tricuspid position due to Ebstein's anomaly. The latter patient developed valve thrombosis during gestation and was treated successfully with urokinase. Both patients and their physicians were informed of the reports by Salazar et al. (7) and Sbarouni et al. (8), and both elected to be treated with heparin. This experience suggests the need for an alternative drug regimen for high risk patients who may not wish to receive Coumadin during the first gestational trimester.

The use of a bioprosthetic valve can obviate the need for prolonged anticoagulation and, therefore, may seem a more appropriate choice in a woman with no other reason for anticoagulation during the childbearing age. However, several reports (5,8) have provided clear evidence for pregnancy-related accelerated bioprosthetic valve failure. Thirty-five percent of valves in the study by Sbarouni et al. (8) and 47% of valves in the study by Badduke et al. (14) demonstrated pregnancy-related structural deterioration requiring valve reoperation. Although the risk of mortality associated with a valve re-replacement has not been systematically evaluated in women of childbearing age, it has been reported to be 8.7% by one group (14).

**Summary and recommendations.** Anticoagulation in a patient with a mechanical heart valve during pregnancy presents a double jeopardy with risk both to the mother and the fetus. The study by Salazar et al. (5) and a recently published survey (8) have reported increased incidence of valve thrombosis in women treated with subcutaneous heparin and led to the recommendations to use Coumadin throughout pregnancy. However, exposure of the fetus to Coumadin may result in severe fetal consequences due to teratogenic effects and intracranial bleeding (4). The data presented and other available information are limited by either a small number of patients or by a retrospective design and possible selective and incomplete reporting. Any recommendations at the present time, therefore, cannot be definitive, are temporary and need to be further validated. Women with older generation prosthetic valves in the mitral position should be informed of the potential risk of valve thrombosis with heparin therapy and should consider the use of Coumadin throughout gestation with heparin before delivery. In high risk women who choose not to take Coumadin during the first trimester, in-hospital continuous intravenous heparin treatment, at least between weeks 6 and 12, seems justified. In patients with older generation prosthetic valves but in the aortic position and those with newer generation heart valves in any position, subcutaneous heparin should be used during the first trimester and in the last part of gestation. The dose of heparin should be adjusted to prolong the midinterval aPTT twice to three times control

value, and adequacy of anticoagulation should be monitored at least once every 1 to 2 weeks. Administration of heparin by subcutaneous infusion with a programmable pump has been demonstrated to achieve more even control with fewer complications than intermittent subcutaneous injection technique (15) and should be considered in patients with prosthetic valves.

Low molecular weight heparin may be an attractive drug for use during pregnancy. Similar to standard unfractionated heparin, it does not cross the placenta, and at the same time, it may provide additional benefits, including reduced incidence of heparin-induced thrombocytopenia, osteoporosis and bleeding complications, and no blood test is required to monitor its safety (16). The drug has been used effectively and safely to treat deep vein thrombosis during pregnancy, but data in patients with a prosthetic valve are not available. Because a small dose of aspirin is safe during pregnancy (3), it may be used in addition to anticoagulation to maximize the antithrombotic effect. The concomitant use of dipyridamole is not recommended because of high fetal loss demonstrated in one study (9).

Premature labor frequently occurs in women with prosthetic heart valves. In the study by Salazar et al. (5), 36% of the neonates were born before the 37th week of gestation, and one neonate died of cerebral hemorrhage that occurred during labor due to Coumadin treatment. These data suggest the need to substitute Coumadin with a therapeutic dose of heparin no later than 35 or 36 weeks of gestation to avoid the onset of labor during Coumadin therapy. In patients with older generation mitral prosthesis in the hospital, intravenous heparin therapy until term may be advisable to minimize the risk of valve thrombosis. Cesarean section should be used as a mode of delivery in patients who go into labor during treatment with oral anticoagulation to prevent fetal cerebral hemorrhage during vaginal delivery.

The present study by Salazar et al. (5) is another attempt to resolve the difficult issue of anticoagulation in patients with a mechanical heart valve during pregnancy. However, this attempt fails to provide clear guidelines for the treatment of such patients. In addition, the recommendations by the authors for the use of Coumadin, a drug declared by its manufacturer contraindicated during pregnancy, also present a double jeopardy for physicians, who may be blamed for using the drug or for not using it during pregnancy. A strong plea should therefore be made for a large, prospective, randomized and well controlled study to evaluate the efficacy and safety of various anticoagulation regimens in women with prosthetic heart valves during pregnancy.

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