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EDITORIAL COMMENT

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).

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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. McLintock 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. Mehndiratta et al. (13) reported a case of severe

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Table 1 Our Recommended Approach to Anticoagulation Therapy for Women With MPHV During Pregnancy

Higher Risk	Lower Risk
Old-Generation MPHV in Mitral Position, MPHV in Tricuspid Position, Atrial Fibrillation, History of TE on Heparin	New-Generation MPHV in Mitral Position and MPHV in Aortic Position
Warfarin (INR 2.5 to 3.5) for 35 to 36 weeks followed by IV UFH (aPTT >2.5) to parturition + ASA 81 to 100 mg/day	LMWH SQ Q12 h (trough anti-Xa ≥0.6 IU/ml, peak anti-Xa <1.5 IU/ml) to 35 to 36 weeks, then UFH IV (aPTT >2.0) to parturition
OR	OR
LMWH SQ Q12 h (trough anti-Xa ≥0.7 IU/ml, peak anti-Xa <1.5 IU/ml) or UFH SQ Q12 h or IV* (mid interval aPTT >2.5) for 12 weeks, followed by warfarin (INR: 2.5 to 3.5) to 35 to 36 weeks, then UFH IV (aPTT >2.5) to parturition + ASA 81 to 100 mg/day.	LMWH SQ Q12 h (trough anti-Xa ≥0.6 IU/ml, peak anti-Xa <1.5 IU/ml) or UFH SQ Q12 h or IV* (mid interval aPTT >2.0) for 12 weeks followed by warfarin (INR: 2.5 to 3.0) until 35 to 36 weeks, then UFH IV (aPTT >2.0) to parturition

*IV preffered.

aPTT = activated partial thromboplastin time; ASA = acetylsalicylic acid; INR = international normalized ratio; IV = intravenous; LMWH = low-molecular-weight heparin; MPHV = mechanical prosthetic heart valve; Q = every; SQ = subcutaneous; TE = thromboembolism; UFH = unfractionated heparin.

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 peak and 112 trough anti-Xa levels in 13 pregnancies and found only 9% of trough levels at >0.5 IU/ml. Even when peak levels were between 0.75 IU/ml and 1.0 IU/ml, only 15% of trough levels were >0.5 IU/ml. These findings 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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REFERENCES

1. Elkayam U, Singh H, Irani A, Akhter MW. Anticoagulation in pregnant women with prosthetic heart valve. J Cardiovasc Pharmacol Ther 2004;9:107–15.
2. McLintock C. Anticoagulant therapy in pregnant women with mechanical prosthetic heart valves: no easy option. Thromb Res 2011; 127:56–60.
3. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 2000;160:191–6.
4. Kawamata K, Neki R, Yamanaka K, et al. Risks and pregnancy outcome in women with prosthetic mechanical heart valve replacement. Circ J 2007;71:211–3.
5. Al-Lawati AA, Venkitraman M, Al-Delaime T, Valliathu J. Pregnancy and mechanical heart valves replacement; dilemma of anticoagulation. Eur J Cardiothorac Surg 2002;2:223–7.
6. Meschengieser SS, Fondevila CG, Santarelli MT, Lazzari MA. Anticoagulation in pregnant women with mechanical heart valve prostheses. Heart 1999;82:23–6.
7. Geelani MA, Singh S, Verma A, Nagesh A, Betigeri V, Nigam M. Anticoagulation in patients with mechanical valves during pregnancy. Asian Cardiovasc Thorac Ann 2005;13:30–3.
8. Sillesen M, Hjortdal V, Vejlstrup N, Sørensen K. Pregnancy with prosthetic heart valves—30 years' nationwide experience in Denmark. Eur J Cardiothorac Surg 2011;40:448–54.

9. Shannon MS, Edwards MB, Long F, Taylor KM, Bagger JP, De Swiet M. Anticoagulant management of pregnancy following heart valve replacement in the United Kingdom, 1986–2002. J Heart Valve Dis 2008;17:526–32.
10. Sadler L, McCowan L, White H, et al. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. Br J Obstet Gynecol 2000;107:245–53.
11. Cotrufo M, De Feo M, De Santo LS, et al. Risk of warfarin during pregnancy with mechanical valve prostheses. Obstet Gynecol 2002;99: 35–40.
12. Vitale N, De Feo M, De Santo LS, et al. Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol 1999;33:1637–41.
13. Mehndiratta S, Suneja A, Gupta B, Bhatt S. Fetotoxicity of warfarin anticoagulation. Arch Gynecol Obstet 2010;282:335–7.
14. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J 2011 Oct 13 [E-pub ahead of print].
15. De Santo LS, Romano G, Della Corte A, et al. Mechanical aortic valve replacement in young women planning on pregnancy: maternal and fetal outcomes under low oral anticoagulation. A pilot observational study on a comprehensive preoperative counseling protocol. J Am Coll Cardiol 2012;59:1110–5.
16. McLintock C, McCowan LM, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. BJOG Int J Obstet Gynaecol 2009; 116:1585–92.
17. Koertke H, Zittermann A, Wagner O, et al. Efficacy and safety of very low-dose self-management of oral anticoagulation in patients with mechanical heart valve replacement. Ann Thorac Surg 2010;90:1487–93.
18. Torella M, Torella D, Chiodini P, et al. Lowering the intensity of oral anticoagulant therapy in patients with bileaflet mechanical aortic valve replacement: results from the LOWERING-IT trial. Am Heart J 2010;160:171–8.
19. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA2006 guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol 2008;52:e1–142.
20. Ecker JL, Frigoletto FD Jr. Cesarean delivery and the risk-benefit calculus. N Engl J Med 2007;356:885–8.
21. Physicians' Desk Reference. Montvale, NJ: PDR Network, 2011:3023.
22. Barbour LA, Oja JL, Schultz LK. A prospective trial that demonstrates that dalteparin requirements increase in pregnancy to maintain therapeutic levels of anticoagulation. Am J Obstet Gynecol 2004;191: 1024–9.
23. Friedrich E, Hameed AB. Fluctuations in anti-factor Xa levels with therapeutic enoxaparin anticoagulation in pregnancy. J Perinatol 2010; 30:253–7.
24. Fan J, Goland S, Khatri N, Elkayam U. Monitoring of anti-Xa in pregnant patients with mechanical prosthetic valves receiving low molecular weight heparin: peak or trough levels (abstr)? Circulation 2011;122:A18219.
25. Elkayam U, Bitar F. Valvular heart disease and pregnancy. Part II: prosthetic valves. J Am Coll Cardiol 2005;46:403–10.
26. Yinon Y, Siu SC, Warshafsky C, et al. Use of low molecular weight heparin in pregnant women with mechanical heart valves. Am J Cardiol 2009;104:1259–63.

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