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EDITORIAL COMMENT

Anticoagulation Therapy for Pregnant Women With Mechanical Prosthetic Heart Valves

How to Improve Safety?*

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A considerable number of women in childbearing age undergoing a valve replacement receive mechanical prosthetic heart valves (MPHVs) because of their superior durability and hemodynamic characteristics (1,2), and therefore require lifelong anticoagulation (AC). Because of the hypercoagulable state of pregnancy (3), there is an increased risk of valve thrombosis (VT). The search for a safe and effective AC regimen has been challenging because both oral anticoagulants (vitamin K antagonists [VKAs]) and heparins may be associated with important maternal and fetal complications (4,5). In this issue of the *Journal*, Steinberg et al. (6)

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attempt to compare the efficacy and safety of various AC regimens by a meta-analysis of 800 pregnancies in women with MPHVs included in 18 studies published between 2003 and 2013. The studies were selected to exclude high-risk patients with old-generation valves or mechanical tricuspid and pulmonic valves with no report of right ventricular function and those treated with a fixed dose of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) without monitoring of the AC activity. A similar but less restrictive meta-analysis has been recently published by D'Souza et al. (7), including data obtained from 46 different publications. The results of both meta-analyses include a considerable number of single-center series of small sample sizes limited by incomplete reporting of quality of AC, reporting bias, or the lack of control groups or head-to-head comparisons between the different AC regimens. Any conclusions or recommendations based on the results of these analyses should therefore take into consideration the serious limitations of the data.

The reports, however, confirm that a continued administration of a VKA throughout pregnancy is associated with the lowest risk of maternal complications, including maternal death, VT, and systemic thromboembolism (TE). However, this was achieved at a very high cost of excessive risk of fetal complications. The study by Steinberg et al. (6) reports fetal complications in about 40% of the cases, including spontaneous abortions, fetal death, and congenital defects. Because of the high risk to the fetus, a VKA throughout pregnancy seems advisable only in women with old generation PHV in the mitral position or when other optional therapies are not available.

Use of sequential treatment when either UFH or LMWH was used during the first trimester, followed by a VKA during the second and third trimesters, also was associated with a high risk of fetal loss (1). These results clearly suggest that the detrimental effect of a VKA on fetal outcome is not limited to the first trimester. In addition, the use of a VKA during pregnancy has also been shown in other publications to lead to intracranial bleeding (8), central nervous system abnormalities, minor

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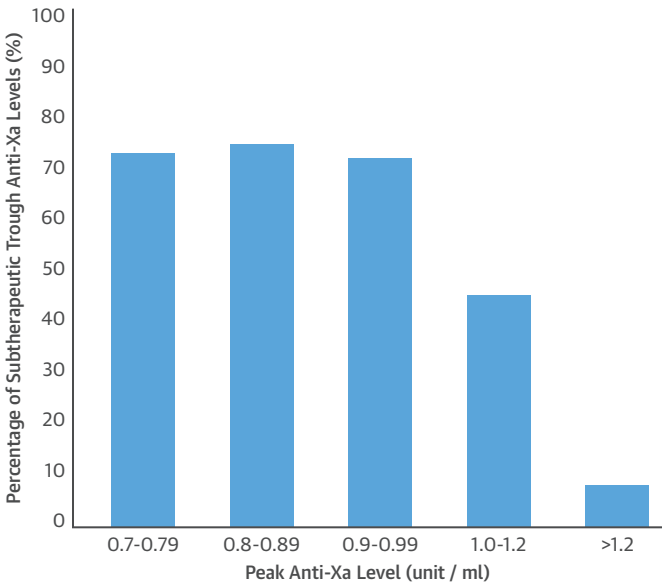
neurologic dysfunction, and low intelligent quotients at later age (4). Despite the Class I recommendations by both the American and European guidelines for the use of a VKA during the second and third trimesters (9,10), there is a need to clearly inform women about the risk-benefit ratio associated with this approach.

Vitale et al. (11) in 1999 reported a close relationship between warfarin dosage and fetal complications. The information, which was based on a small number of patients, resulted in a controversial recommendation to consider the use of a VKA when the dose of warfarin required to achieve a therapeutic level is <5 mg/day (4,9,10). A recent review by Hassouna and Allam (12) in 2014 attempted to summarize published data of 494 eligible pregnancies of women with MPHVs treated with a low-dose VKA reported in 11 studies. Despite low-quality information provided in most of these publications, the data seem to support a reduced rate of fetal complications compared with a high VKA dose but also point out the limitations of this approach. The ability to use this regimen is limited to women who achieve therapeutic AC with a constant low-dose VKA without the need for a dose increase during pregnancy. A recent study by Hassouna et al. (13) reported the need to switch low-dose warfarin to phenindione in more than a quarter of patients between the fifth and 12th weeks of gestation because of failure to achieve target international normalized ratio (13). Other limitations include a higher fetal loss compared with that seen with LMWH (6,7) as well as a high rate of cesarean section deliveries. Although information regarding warfarin embryopathy was not included in most studies, occasional cases of embryopathy have been reported (4,12). It should be noted that the recent report of the registry of pregnancy and cardiac disease, which included 212 women with MPHV, did not find reduced fetal loss with low-dose VKA compared with high-dose VKA (1). I agree with the statement made by D'Souza et al. (7) that because of the limitations of the reports of patients treated with low-dose VKA and the inconsistency of the data, the safety of this approach requires further validation.

Subcutaneous (SC) UFH was considered the drug of choice for prevention of TE in pregnancy (3). The drug does not cross the placenta and is therefore safe for the fetus. Treatment with SC UFH during pregnancy was, however, associated with high incidence of TE, including VT and maternal mortality (14,15). The use of SC UFH for thromboprophylaxis in pregnant women with MPHVs is no longer recommended by the U.S. guideline (9). The recommended use of dose-adjusted, continuous intravenous UFH is probably more effective (16) but logistically more complicated and requires a meticulous management of a central line for the prevention of endocarditis.

LMWH is an attractive alternative to UFH and similarly does not cross the placental barrier. In addition, it has several potential advantages, which include superior absorption and bioavailability, 2- to 4-fold longer half-life, more predictable and stable dose response, less bleeding, and a lower risk of heparin-induced thrombocytopenia and osteopenia (3). The meta-analyses by Steinberg et al. (6) and D'Souza et al. (7) found LMWH, used throughout pregnancy, to be associated with the highest rate of live birth but at the same time with a higher incidence of maternal complications, including TE events, compared with VKA. However, a critical review of the data clearly shows that most if not all of the TE events were due to subtherapeutic AC secondary to inappropriate dosing, poor monitoring, or poor patient compliance. Van Hagen et al. (1) have reported mechanical VT in 10 patients, of which 6 were treated with LMWH prior to 14 weeks gestation. Anti-factor Xa levels were not checked, not reported, or

FIGURE 1 Percentage of Subtherapeutic Trough Anti-Factor Xa Levels According to Peak Anti-Factor Xa Level Categories



Subtherapeutic trough anti-factor Xa levels (<0.6 IU/ml) were recorded in 80% of 126 paired measurements with peak levels of 0.7 to 1.2 IU/ml. It was found in 73% of 11 measurements with peak levels of 0.7 to 0.79 IU/ml, 74% of 23 with peak levels of 0.8 to 0.89 IU/ml, 72% of 29 with peak levels of 0.9 to 0.99 IU/ml, and 44% of 63 with peak levels of 1.0 to 1.2 IU/ml. Subtherapeutic levels were also measured in a few of an additional 42 cases with peak levels of >1.2 IU/ml. Reprinted with permission from Goland et al. (25).

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TABLE 1 Our Recommended Approach to AC Therapy With LMWH Throughout Pregnancy for Women With MPHVs

1. Counseling risks and benefits of various AC regimens and determining likelihood of the patient and family to follow very strict follow-up and treatment regimens
2. Baseline transthoracic echocardiogram and BNP or NT-proBNP levels
3. Switch from VKA to LMWH in the hospital when INR <3.0, starting enoxaparin at 1 mg/kg every 12 h with daily monitoring of anti-factor Xa levels with dose adjustment to achieve a trough level of ≥0.6 IU/ml for low-risk patients and ≥0.7 IU/ml for high-risk patients* with peak level (4–5 h after administration) not exceeding 1.5 IU/ml.†
4. Aspirin 75–100 mg/day
5. Weekly clinical assessments and monitoring of trough and peak anti-factor Xa levels
6. Return to clinic for monitoring of anti-factor Xa levels in 2–3 days after dose adjustment
7. Repeat echocardiogram and BNP or NT-proBNP levels in case of worsening symptoms
8. Hospitalization at 36–37 weeks for switching from LMWH to IV UFH at a dose adjusted to anti-factor Xa level of 0.8–1.0 IU/ml or APTT of >2.5
9. Induction of labor at 38 weeks
10. Stop IV UFH on onset of labor or >6 h prior to regional anesthesia
11. Vaginal delivery unless fetal indications for a cesarean section delivery or maternal instability
12. Resume UFH in 2–12 h, depending on risk of bleeding, and continue for 24–48 h before start of VKA
13. Start VKA in the hospital after a wait of 24–48 h
14. Continue IV UFH in the hospital until INR is therapeutic

*Mitral, tricuspid, and pulmonic mechanical valves; previous thromboembolism; atrial fibrillation; ventricular systolic dysfunction; or hypercoagulable condition other than pregnancy. †In the infrequent case of peak anti-factor Xa level >1.5 IU/ml, total daily dose is divided into 3 parts given every 8 h each.

AC = anticoagulation; APTT = activated partial thromboplastin time; BNP = brain natriuretic peptide; INR = international normalized ratio; IU = international units; IV = intravenous; LMWH = low-molecular-weight heparin; MPHVs = mechanical prosthetic heart valves; NT-proBNP = N-terminal pro-B-type natriuretic peptide; UFH = unfractionated heparin; VKA = vitamin K antagonist.

intermittently subtherapeutic. Quinn et al. (8) reported VT in 1 of 12 patients on LMWH. This patient had a Bjork-Shiley valve in the mitral position with a history of TE complication due to thrombophilia who received dalteparin during pregnancy without anti-factor Xa monitoring. Abildgaard et al. (17) reported VT in 2 of 12 women on LMWH; both patients were infrequently monitored and the peak anti-factor Xa levels were subtherapeutic, at 0.67 and 0.71 IU/ml. Previous reports not included in the Steinberg et al. meta-analysis have also demonstrated a close relationship between TE complications in pregnant women with MPHVs treated with LMWH and subtherapeutic AC (18,19). Oran et al. (18) reported VT in almost 9% of pregnancies in women with MPHVs and 12% incidence of overall TE complications. Nine of 10 women with VT received a fixed dose of LMWH, one of whom had monitoring of anti-factor Xa, but no further information was provided. McLintock et al. (19) reported on 37 pregnancies treated predominately with enoxaparin. Five developed TE complications, all of which were due to noncompliance or subtherapeutic AC. Two patients reported by Yinon et al. (20) and De Santo et al. (21) developed VT on LMWH despite guideline-recommended peak anti-factor Xa levels; however, trough anti-factor Xa levels were not measured in both patients. The importance of measuring trough anti-factor Xa has been clearly demonstrated by several investigators (22–24). Barbour et al. (22) evaluated 138 peak and 112 trough anti-factor Xa levels in 13 pregnancies and found trough levels of 0.5 to 1.0 IU/ml in only 15% when peak levels were 0.75 to 1.0 IU/ml. Friedrich and Hameed (23) found subtherapeutic anti-factor Xa levels in 20% of cases 8 h after administration when peak levels at 3 to 4 h were between 0.5 and 1.0 IU/ml. A recent publication by our group reported the relationship between 177 paired peak and trough anti-factor Xa levels during pregnancy in 26 women receiving dose-adjusted SC enoxaparin given every 12 h. Peak anti-factor Xa levels between 0.7 to 1.2 IU/ml were achieved in 123 of the measurements, but in 80% of them the trough levels were found to be subtherapeutic (<0.6 IU/ml), including >40% of cases with peak levels of 1.0 to 1.2 IU/ml (**Figure 1**) (25). These data in addition to reports of VT with "therapeutic peak levels" (20,21) clearly support the rational for mandatory measurement of trough anti-factor Xa levels to guide dose adjustments of LMWH in pregnant women with MPHVs (3,4). Peak levels should also be measured to prevent excessive AC and increased risk of bleeding. **Table 1** describes the protocol used for more than 2 decades, with minor modifications, at the University of Southern California for the management of pregnant women with MPHV (3,4,26). Our preferred approach has been the use of LMWH throughout pregnancy. The protocol has been designed to maximize efficacy and prevent complications and includes patient education; in-hospital change from warfarin to LMWH and from LMWH to UFH; level of AC according to risk of TE complication (similar to guideline-recommended dose adjustment of VKA in nonpregnant patients with MPHVs) (9); close monitoring of patients' symptoms to detect early signs of hemodynamic changes; weekly monitoring of both trough and peak anti-factor Xa levels to assure patient compliance and allow quick changes in dose as required; monitoring intravenous UFH AC by measuring anti-factor Xa, rather than activated partial thromboplastin time, which results in a more expeditious achievement of therapeutic AC; more consistent therapeutic levels;

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and fewer lab tests and dose changes (27); in addition, avoidance of unnecessary cesarean section deliveries to reduce risk of bleeding complications; and early resumption of AC therapy with UFH after the delivery and initiation of VKA therapy after a wait of 24 to 48 h to assure safety.

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