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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 Pre-Operative Counseling Protocol

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Objectives This pilot prospective observational study aimed to evaluate the maternal and fetal outcomes of pregnancies under low-dose oral anticoagulation therapy after aortic mechanical replacement.

Background Need for valve replacement is still an issue for young women with native valve disease who are planning on future pregnancy. Choice of replacement device is a challenging clinical task.

Methods A comprehensive pre-operative counseling protocol to guide choice of replacement device was developed. The pre-operative anticoagulation trial to determine the warfarin daily dosage needed to reach target international normalized ratio (INR) represented the main stem of such protocol. Pregnancies on low-dose anticoagulation therapy (target INR: 1.5 to 2.5) were allowed in a highly selected subset of mechanical aortic valve recipients.

Results Twenty-two patients of 40 originally referred for native valve disease surgery requiring valve replacement, safely underwent the pre-operative anticoagulation challenge. No maternal or fetal complications were detected in 16 pregnancies under low oral anticoagulation. Patterns of warfarin daily dosage and induced INRs were characterized during pregnancy.

Conclusions In this small sample observational study, a pre-operative anticoagulation therapy trial helped young women scheduled for valve replacement to acquire complete information as to the choice of prosthetic device. In selected third-generation mechanical aortic prosthesis recipients, low-dose anticoagulation therapy seems safe and feasible for both mother and fetus. Further studies are needed to validate this approach. (J Am Coll Cardiol 2012;59:1110–5) © 2012 by the American College of Cardiology Foundation

Young women with native valve disease planning on pregnancy should undergo a thorough risk assessment to decide whether an intervention is necessary before pregnancy and eventually to define its timing and the type of surgical therapy (1,2). When native valve stenosis needs pre-pregnancy intervention, there is a consensus that mitral balloon valvuloplasty is the best option for mitral stenosis, whereas choice of a prosthetic valve for aortic disease is still highly debated (2–4). Pregnancy in women with a bioprosthesis is associated with early and late structural valve deterioration, implying high reoperation rate. Pregnancy with a mechanical valve has a high maternal complication rate, including valve thrombosis and death. Coumarin derivatives are relatively safe for the mother, with a lower incidence of valve thrombosis than unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), but carry the risk of embryopathy (5,6).

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Less thrombogenic materials and an improved valve and hinge design in modern bileaflet prostheses have reduced the propensity for thrombus formation and the need for aggressive anticoagulation therapy. As for nonpregnant last-generation prosthetic heart valve patients, low-dose anticoagulation therapy has been well recognized as 1 of the possible means to improve quality of anticoagulant prophy-

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laxis (7,8). However, because pregnancy prompts a hypercoagulable state, the feasibility of low-dose anticoagulation therapy in the peculiar setting of the heart valve prosthesis patient management during pregnancy is still undemonstrated. Since 2000, after our original findings suggesting a probable dose-dependency of warfarin embryopathy (5,9), a dedicated multidisciplinary program of pre-operative counseling for women referred for valve surgery who were contemplating a future pregnancy has been adopted in our department. A multistage protocol for the choice of prosthetic valve type and for management of anticoagulation therapy during pregnancy has been developed. The aim of this paper is to report maternal and fetal outcomes of women undergoing pregnancies after mechanical aortic valve replacement under low-dose anticoagulation therapy.

Abbreviations and Acronyms

INR = international normalized ratio

LMWH = low-molecular-weight heparin

UFH = unfractionated heparin

Methods

Algorithm for the choice of valve prosthesis. Patients with aortic disease not suitable for a valve repair procedure underwent an informative counseling on the choice of valve substitute and inherent drawbacks, both absolute (need for anticoagulation therapy versus risk of reoperation) and related to pregnancy (including reduced durability of biological prostheses and fetal toxicity of oral anticoagulants for mechanical devices). Information was given about the risks of maternal and perinatal morbidity and mortality, and the risks and benefits of each anticoagulant treatment option. Such counseling included also the advice that, theoretically, the safest option was to avoid pregnancy after surgery. To help in this decision process, patients, after written informed consent and a negative pregnancy test, underwent a pre-operative 3-month trial of anticoagulation therapy to evaluate the dose of warfarin needed to achieve the target international normalized ratio (INR). Since 2000, for selected patients after mechanical aortic valve replacement (negative anamnesis for thromboembolic events, normal left ventricular ejection fraction, left atrium diameter <47 mm, and sinus rhythm), it is our practice to prescribe an INR between 1.5 and 2.5, as described in the prospective trial by Torella et al. (8). Target INR for mitral valve replacement was 2.5 to 3.5. Young women achieving this target INR with a warfarin daily dose <5 mg were preferentially offered a third-generation mechanical device; however, in case of aortic prostheses, they were informed about the maternal hazard related to the use of a low-dose oral anticoagulation regimen during a hypercoagulable condition. Patients needing higher dosage were preferentially offered a bioprosthesis or, as a second choice, a mechanical device contingent with the advice that in both cases poor maternal and/or fetal outcomes were likely in case of a pregnancy.

Management of anticoagulation therapy during pregnancy. Women were advised to contact the outpatient clinic as soon as they missed a period, and to perform pregnancy tests every 3 days until positive or until menstruation. Upon confirmation of pregnancy, each pregnant woman completed written informed consent, whereby she chose 1 of the following treatment options: 1) heparin (either UFH or LMWH) during the first trimester, followed by oral anticoagulation therapy up to the 36th week, with subsequent replacement by heparin until delivery; 2) oral anticoagulation therapy throughout pregnancy, until the 36th week, followed by heparin until delivery (either UFH or LMWH); and 3) the Cotrufo protocol. As previously described (5,9), such a protocol, named after its original developer (Maurizio Cotrufo), was based on sodium warfarin administration throughout all pregnancy; the INR was estimated on a weekly basis at our outpatient clinic and recorded along with prescribed warfarin doses. Women with mechanical aortic valve replacements underwent low-dose anticoagulation therapy, as described in the preceding text. Echocardiographic follow-up was performed monthly to evaluate cardiac and prosthetic function. Patients were followed up by cardiologists and obstetricians at monthly intervals until the 37th week of gestation, when they were electively hospitalized until delivery. Cesarean delivery was scheduled before the end of the 37th gestational week. Cesarean section is indicated because of the risk of intracranial bleeding in the anticoagulated baby with vaginal delivery. Warfarin therapy was discontinued at least 2 days before surgery and restarted 1 day after surgery. During this perioperative period, heparin was not routinely administered, as collegially considered not necessary for a warfarin discontinuation of just 3 days, and INRs were checked daily. For patients presenting no or sluggish increase of INR after post-partum warfarin resumption, LMWH was added until the target INR was reached. The whole management algorithm described here complied with the principles of the Helsinki Declaration and received ethical approval from the local ethics committee.

Aim of the study and outcomes definitions. This study aimed to assess: 1) the results of a multistage counseling protocol for young women needing valve surgery; and 2) the rate of maternal thrombotic and hemorrhagic complications and pregnancy outcomes in women with third-generation mechanical aortic prostheses who received low-dose oral anticoagulation treatment with sodium warfarin throughout all pregnancy. Definition of maternal thrombotic and hemorrhagic complications followed current guidelines. Poor pregnancy outcome was defined as the occurrence of spontaneous abortion, stillbirth, or congenital birth defect. Ultrasound evaluations of the fetus were done at the third, fifth, and eighth months. Neonates underwent clinical examination soon after birth and at 4 and 12 months to ascertain or exclude the diagnosis of warfarin embryopathy. All eventual miscarriages and stillbirths were to be clinically evaluated by neonatologists; indication for a pathology examination was left to a case by case decision.

Statistical analysis. Data are expressed as mean ± SD for continuous variables and as percentages for categorical variables. The Wilcoxon matched pairs signed-rank test (for the INR variable) or the paired Student *t* test (for the dose variable) were used to compare the warfarin daily dose needed to achieve the target INR during pregnancy to that needed during the pre-operative anticoagulation trial as well as mean pre-operative INR to intrapregnancy outcomes. Statistical significance was set at 0.05. All analyses were performed with SPSS version 13.0 (SPSS, Inc., Chicago, Illinois).

Results

Patient population. Between January 2000 and December 2010, 40 young women were referred for treatment of valvular heart disease: 5 required balloon mitral valvuloplasty, 9 underwent mitral valve repair, 2 had mitral valve replacement, 4 had aortic valve repair, and 20 needed aortic valve replacement. Women judged suitable for heart valve replacement did not experience any complication while undergoing the planned anticoagulation trial. Those affected by mitral valve disease reached target INR with warfarin daily doses >5 mg and decided to be implanted with a bioprosthesis. Between patients needing aortic valve replacement, 17 achieved a target INR with a warfarin daily dose <5 mg and 3 with a daily dose >5 mg. All 17 women achieving target INR with low-dose warfarin opted for a mechanical replacement. Of patients needing higher warfarin daily dose, 1 requested a bioprosthesis and 2 requested a mechanical device. Choice of a mechanical replacement by these 2 patients had the following motivation: intention of the one to undergo a future pregnancy on LMWH regimen, and the decision by the other to avoid pregnancy and opt for an international child adoption. Figure 1 reports the management algorithm of the whole subset of patients referred for native valve disease.

Pregnancies with a prosthesis. There were 20 pregnancies after valve replacement surgery. Three patients with a bioprosthesis (2 mitral, 1 aortic) had 3 healthy fetuses, and none of them experienced structural valve degeneration so far (mean follow-up 59 months, minimum 36 months and maximum 84 months). Seventeen patients with a mechanical aortic valve had 17 healthy babies. One pregnancy, as per patient preference, was carried out under LMWH and was complicated by valve thrombosis at the 11th week. The patient had been compliant with medication, and LMWH dose was adjusted to achieve peak anti-Xa levels of 0.7 to 1.2 U/ml 4 h post-dose, with anti-Xa levels checked weekly. The patient underwent successful emergency reoperation at our department, the fetus survived the procedure, and the pregnancy was successfully concluded under warfarin therapy. Sixteen pregnancies were conducted according to the Cotrufo protocol with low-dose anticoagulation therapy.

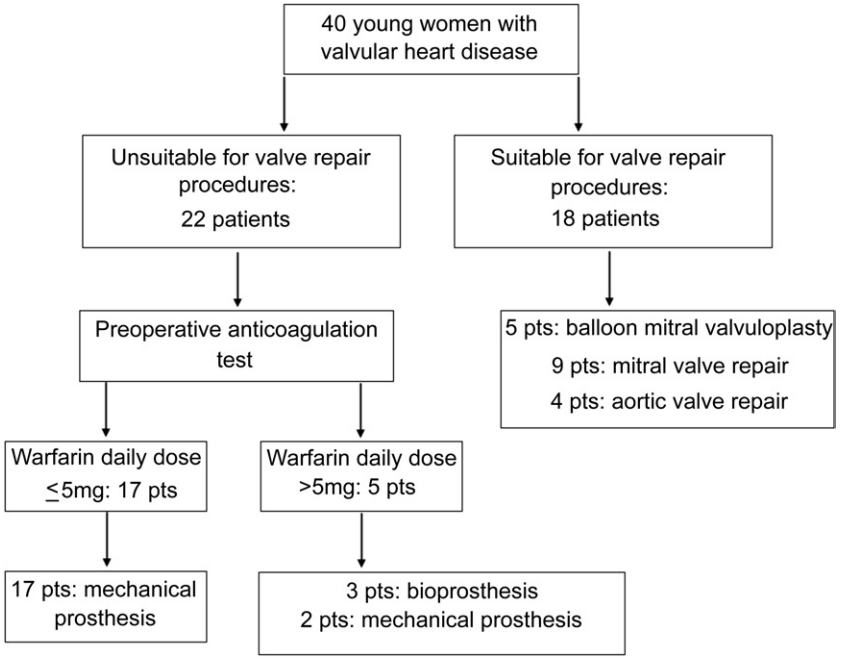

Figure 1 Flowchart of Therapeutic Options for Young Women

Patients (pts) unsuitable for valve repair underwent a pre-operative anticoagulation test to find out the warfarin dosage needed to achieve postoperative target international normalized ratio (INR). Results of this anticoagulation test helped patients in choosing prosthetic type. Patients in need of a warfarin daily dosage <5 mg preferred mechanical prostheses.

Pregnancies in women with mechanical aortic valve replacement under low dose anticoagulation therapy. Aortic valve replacement in this subset was always performed with a St. Jude prosthesis. Mean age at pregnancy was 26.9 ± 3.4 years (range 22 to 36 years). No maternal thromboembolic or hemorrhagic complications were observed. There were 16 full-term healthy babies. Mean dose of warfarin during pre-operative anticoagulation test was 4.1 ± 0.7 mg to maintain a mean INR of 2.2 ± 0.5 IU (median 2.05 IU; interquartile range: 2.0 to 2.2 IU). Mean warfarin dosage during pregnancy was 4.1 ± 0.4 to maintain a mean INR 1.9 ± 0.3 (median 1.9; interquartile range: 1.8 to 2.0). The difference between pre-pregnancy and intrapregnancy mean doses of warfarin was 0.1 ± 0.7 (95% confidence interval: −0.3 to 0.5; p = 0.63). In particular, on average, 7 patients took a lower dose, 7 a higher dose, and 2 the same. The difference between pre-pregnancy and intrapregnancy mean INR was −0.26 ± 0.25 (95% confidence interval: −0.12 to −0.4; p = 0.001). Thirteen patients had a mean INR lower than that measured before pregnancy, whereas 3 had the same. Oral anticoagulation management in this closely followed study population was of high quality; 90.2% of a total of 592 INR measurements were inside the therapeutic corridor. Adherence to the anticoagulation protocol during pregnancy is reported in Figure 2. Mean INR after the 2-day period of pre-partum withdrawal of warfarin was 1.39 (median 1.4; interquartile range: 1.3 to 1.4).

Discussion

The main findings of the present observational study are these: 1) multistage counseling may help in the choice of valve substitute and subsequent management of pregnancy; and 2) low-dose anticoagulation therapy under strict surveillance appears feasible and safe in highly selected patients with third-generation aortic mechanical devices. Consistent with the literature and despite advances in valve repair procedures, valve replacement surgery, in our tertiary care, university-affiliated cardiac surgery center, was needed in 55% of young women of childbearing age (22 of 40 patients) with the highest proportion in those affected by aortic disease (1–4). Need for multidisciplinary counseling in this setting was authoritatively underlined by Hanania in 2002 (10). In a clinical situation implying tremendous ethical issues and several medicolegal drawbacks, physicians must intervene in the discussion and break the syllogism of the long-lasting equation that "heparin protects the fetus and aggravates maternal risk, while oral anticoagulants protect the mother and aggravate fetal risk."

In the real world, such counseling has to face both the limited follow-up data and the lack of consensus documents. Indeed, guidelines on the antithrombotic therapy in patients with mechanical heart valve replacements by the American College of Cardiology/American Heart Association and by the European Society of Cardiology disagree on many fundamental issues, including the risk categorization of different mechanical prostheses and the management of anticoagulation therapy during pregnancy (11,12). Such discrepancies, together with the limited experience of most of cardiac surgery centers, has led to under-care of patients. In an impressive study by Shannon et al. (13), the anticoagulant management of pregnancy after heart valve replacement in the United Kingdom between 1986 and 2002 was reviewed. The study results illustrated the diverse and uncertain manners in which heart valve recipients were managed during pregnancy (13).

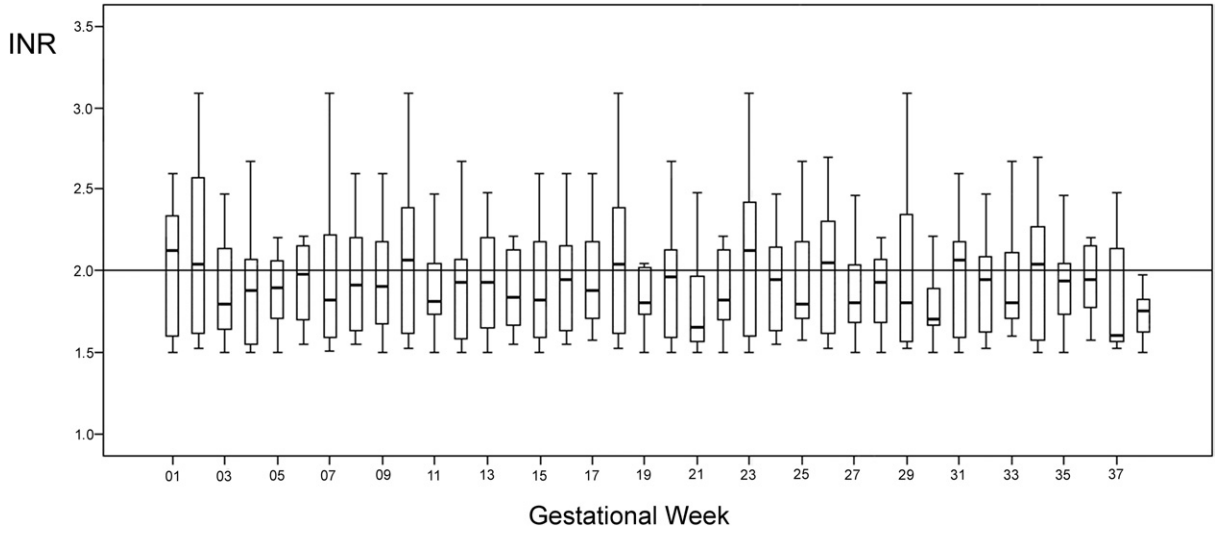

Figure 2 Adherence to Anticoagulation Therapy During Pregnancy

Boxes represent interquartile range for international normalized ratio (INR), **black line** represents mean INR values, **whiskers** represent 95% confidence interval INR.

At our department, the multistage counseling initially devoted to patients who had already undergone a valve replacement and wanted to have pregnancies has been lately applied to women referred for surgical treatment (9). Patient information incorporated both the institutional experience and up-to-date literature review. Choice of prosthesis was originally aided by a pre-operative anticoagulation test that aimed to give hints on future warfarin dosage. Despite inherent challenges and limitations, all patients facing the need for replacement surgery promptly consented to this pre-operative evaluation. Despite aiming at a low-intensity anticoagulation target, in this pilot sample, oral anticoagulation therapy of <5 mg per day was feasible only in 17 of 20 patients needing aortic replacement and, so far, in none of those needing mitral replacement surgery. Subsequent patient choice reflected the patient's preference as well as completeness of informative counseling (i.e., avoidance of pregnancy, pregnancy after bioprosthesis implantation, pregnancy under LMWH or oral anticoagulation therapy) and equidistance of counselors.

Coming to the evaluation of pregnancy outcomes, just a few words may be said on usage of bioprostheses and bridging anticoagulation therapy with LMWH. Patients undergoing pregnancies after tissue replacement did not experience structural valve deterioration and entered a close echocardiographic follow-up of prosthesis function in the long term. Absence of structural deterioration may be quite the reflection of short absolute length of follow-up. As to the inherent merits of LMWH anticoagulation therapy, no conclusion may be drawn from a single case experience, but the observation is that the outcome of such a case is consistent with those recently reported by others (14,15). Recent publications have differed in their recommendations with regard to anti-Xa levels and with target post-dose levels of 0.7 to 1.2 IU/ml or peak anti-Xa levels of 1.0 IU/ml. By contrast, Elkayam and Bitar (3) recommended target pre-dose trough levels of 0.6 IU/ml and 0.7 IU/ml and biweekly monitoring to enhance anticoagulation efficiency. Even apparently insignificant divergences from this latter protocol (i.e., pre-dose anti-Xa level of 0.4 to 0.7 IU/ml and peak dose of 0.7 to 1.2 IU/ml with monthly monitoring), have led to suboptimal maternal outcomes (enoxaparin-related maternal thromboembolism: 10.6%, 95% confidence interval: 4.3% to 22.6%) in recent case series (16). Similarly, it cannot be excluded that in the single case of LMWH use in the present series, additional monitoring of trough levels, beside peak levels, of anti-Xa could have possibly avoided the thrombotic complication observed (17,18). Physicians preferring LMWH administration to pregnant patients with mechanical heart valves commit themselves to the very delicate task of ensuring absolute adherence to the best evidence-derived protocols.

As far as the rationale for low anticoagulation after aortic mechanical replacement is concerned, since the pioneering experience by Saour et al. (19), for more than a decade several follow-up series have reported that less intensive oral anticoagulation therapy than previously recommended results in a lower incidence of bleeding complications without a significant increase of thromboembolic events. More recently, several large-scale, multicenter, randomized, prospective studies have validated a policy of low or even very low intensity anticoagulation therapy for patients with mechanical heart valves (8,20–22).

Ours is the first report on outcomes of very low anticoagulation therapy during pregnancy with a mechanical aortic prosthesis. The excellent results of this small sample of highly selected, closely monitored pregnant women may certainly give rise to several questions, above all, questions about: 1) reliability of pre-operative anticoagulation challenge; and 2) and the inherent merits of low-dose anticoagulation therapy, low warfarin daily dose, and quality of anticoagulation therapy management. As to the first, validation of the ability of pre-operative anticoagulation pattern to predict dose-response effect of warfarin during pregnancy is beyond the scope of this observational study. Nevertheless, taking into account sample size, as shown in Figure 1, managing anticoagulation within target INR without exceeding 5 mg warfarin per day was feasible in all patients who opted for receiving aortic valve replacement. As to the second, absence of maternal thromboembolic events certainly depends on a composite of patient profile, prosthesis characteristics, and close anticoagulation surveillance; similarly, lack of fetal complications results from the additive effects of low target INR and low warfarin daily dose.

Study limitations. Several study limitations deserve considerations for a thorough data interpretation. First, the magnitude of the study sample may raise concerns. Overall patient population is certainly limited, and the subgroup undergoing low-dose anticoagulation therapy is even smaller. Nevertheless, both because available data in literature are few and somewhat contradictory and because inclusion criteria and management protocol of the present study were stringent, even the analysis of a small series may add importantly to the knowledge of the topic. Second, dose dependency of warfarin fetal complications was originally suggested by our group and later supported by reports from others (23,24) published in lower visibility journals. Overall, the evidence of the safety of low-dose warfarin is currently based on low numbers: the present study itself, as none of the patients requiring >5 mg warfarin daily chose to become pregnant on warfarin, could not provide any further support to that theory. Conversely, it must be acknowledged that Sadler et al. (25) showed miscarriage in 7 of 11 women whose maximum dose of warfarin was <5 mg compared to 5 of 11 women who received >5 mg. Therefore, although the low-dose warfarin proposal was incorporated in the current European guidelines (12), the level of clinical evidence of such advice is low, as well as that assigned to the other available advices, because of the generalized lack of definitive data. Third, when applying our protocol, the inherent risks of a cesarean delivery at the 37th week should be considered, including, in addition to neonatal prematu-

rity, maternal hemodynamic fluctuations, larger blood loss, pain, infections, respiratory complications, damage to pelvic organs, and potential unfavorable effects on future reproductive health (26,27). Finally, although no prosthetic degeneration was observed after pregnancy, the shortness of follow-up of our patients receiving bioprostheses hampers a sound conclusion on the safety of this alternative option.

For all the aforementioned limitations, the present pilot study results should be viewed with due caution, and they surely need verification in a larger study sample.

Conclusions

Comprehensive pre-operative counseling is mandatory for young women with valvular heart disease planning on future pregnancy as valve replacement surgery is still an issue for this subset. Availability of a broad state-of-the-art surgical armamentarium, advanced expertise of anticoagulation therapy protocols, and close long-term follow-up capabilities are prerequisites for counseling pregnancy management and ensuring good late maternal outcomes. In this pilot observational study, the required dose of warfarin emerging from a pre-operative anticoagulation trial was added to the factors helping young women scheduled for valve replacement to receive individualized information guiding the choice of prosthetic device. Obviously, it should not be the only factor to consider, inasmuch as women needing >5 mg daily could choose to have pregnancies with mechanical valves as well and to receive heparin-based protocols instead of oral anticoagulation therapy. Alternatively, considering the recent spreading of percutaneous techniques of valve implantation, a woman could choose to have a bioprosthesis and to undergo valve-in-valve implantation in case of pregnancy-related bioprosthetic degeneration.

For a highly selected and relatively small number of third-generation mechanical aortic valve recipients, low-dose anticoagulation therapy was associated with no maternal or fetal complications. Further studies are needed to validate this approach.

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REFERENCES

1. Elkayam U, Bitar F. Valvular heart disease and pregnancy. Part I: native valves. J Am Coll Cardiol 2005;46:223–30.
2. Pieper PG, Balci A, Van Dijk AP. Pregnancy in women with prosthetic heart valves. Neth Heart J 2008;16:406–11.
3. Elkayam U, Bitar F. Valvular heart disease and pregnancy. Part II: prosthetic valves. J Am Coll Cardiol 2005;46:403–10.
4. Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. Circulation 2003;107:1240–6.
5. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol 1999;33:1637–41.
6. Shlebak A, Malik I. Managing heparin anticoagulation in patients with prosthetic cardiac valves: balancing the risk. Heart 2009;95:1643–5.
7. Herijgers P, Verhamme P. Improving the quality of anticoagulant therapy in patients with mechanical heart valves: what are we waiting for? Eur Heart J 2007;28:2424–6.
8. 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.
9. Cotrufo M, de Luca TS, Calabrò R, Mastrogiovanni G, Lama D. Coumarin anticoagulation during pregnancy in patients with mechanical valve prostheses. Eur J Cardiothorac Surg 1991;5:300–4.
10. Hanania G. Management of anticoagulants during pregnancy. Heart 2001;86:125–6.
11. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. Executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2006;48:598–675.
12. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28:230–68.
13. 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.
14. James AH, Brancazio LR, Gehrig TR, Wang A, Ortel TL. Low-molecular-weight heparin for thromboprophylaxis in pregnant women with mechanical heart valves. J Matern Fetal Neonatal Med 2006;19:543–9.
15. 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.
16. McLintock C, McCowan L, North R. 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. Friedrich E, Hameed AB. Fluctuations in anti-factor Xa levels with therapeutic enoxaparin anticoagulation in pregnancy. J Perinatol 2010;30:253–7.
18. 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.
19. Saour JN, Sieck JO, Mamo LA, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. N Engl J Med 1990;322:428–32.
20. Hering D, Piper C, Bergemann R, et al. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German experience with low-intensity anticoagulation study. Chest 2005;127:53–9.
21. Koertke H, Zittermann A, Tenderich G, et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J 2007;28:2479–84.
22. 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.
23. Dong L, Shi Y, Tian Z. The follow up of 12 pregnant women with anticoagulation therapy after mechanical heart valve replacement. Zhonghua Fu Chan Ke Za Zhi 2001;36:465–7.
24. 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.
25. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. BJOG Int J Obstet Gynaecol 2000;107:245–53.
26. Ecker JL, Frigoletto FD Jr. Cesarean delivery and the risk-benefit calculus. N Engl J Med 2007;356:885–8.
27. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. N Engl J Med 2010;362:529–35.

Key Words: low-dose oral anticoagulation ■ pregnancy ■ prosthetic heart valves.