Clinical and Applied Thrombosis/Hemostasis
http://cat.sagepub.com/

A Prospective Trial Showing the Safety of Adjusted-Dose Enoxaparin for Thromboprophylaxis of Pregnant Women With Mechanical Prosthetic Heart Valves

Rufaro Saeed Chitsike, Barry Frank Jacobson, Pravin Manga, Haroun Aziz Rhemtula, Serasheni Moodley and Gabrielle Dominique Toweel

CLIN APPL THROMB HEMOST published online 13 June 2010
DOI: 10.1177/1076029610371470

The online version of this article can be found at:
http://cat.sagepub.com/content/early/2010/06/07/1076029610371470

Published by:
SAGE
http://www.sagepublications.com

Clinical and Applied Thrombosis/Hemostasis
000(00) 1-7

DOI: 10.1177/1076029610371470
http://cath.sagepub.com

A Prospective Trial Showing the Safety of Adjusted-Dose Enoxaparin for Thromboprophylaxis of Pregnant Women With Mechanical Prosthetic Heart Valves

Chitsike Rufaro Saeed, FCPath (Haem)[1], Jacobson Barry Frank, FRCS, PhD[1], Manga Pravin, FRCP PhD[2], Rhemtula Haroun Aziz, FCOG[3], Moodley Serasheini, FCOG[3], and Toweel Gabrielle Dominique, FCOG[3]

Abstract

Objective: To determine whether dosage adjustment of enoxaparin during pregnancy, to maintain a peak anti-Xa of 1.0 to 1.2 U/mL, is safe for women with mechanical prosthetic heart valves (MPHV). **Design**: A prospective observational study. Setting: This study was performed at Charlotte Maxeke Johannesburg Academic Hospital from 2007 to 2009. **Population**: Fifteen women with MPHVs. **Methods**: Women were treated with enoxaparin with dosage adjustment to achieve a peak anti-Xa of 1.0 to 1.2 U/mL. **Main Outcome Measures**: Main outcomes measured were prosthetic valve thrombosis, bleeding, and maternal mortality. **Results**: There was no maternal mortality. None of the women developed valvular thrombosis during pregnancy. In all, 2 women developed epistaxis and another developed spotting per vaginum. **Conclusion**: Our data show that enoxaparin may be administered safely during pregnancy to pregnant women with MPHV when there is dosage adjustment throughout pregnancy to maintain an anti-Xa of 1.0 to 1.2 U/mL.

Keywords

mechanical prosthetic heart valves, pregnancy, enoxaparin

Introduction

Mechanical prosthetic heart valves (MPHV) are still in use in women of childbearing age. This is because these valves have excellent long-term durability, whereas the alternative bioprosthetic valves are associated with a high rate of structural valvular damage (SVD),[1] which is further accelerated by pregnancy.[2] The continued use of mechanical valves is despite the fact that bioprosthetic valves confer the significant advantage of not requiring anticoagulant prophylaxis. In contrast, mechanical prosthetic valves are associated with increased thrombogenicity requiring anticoagulant prophylaxis.

Mechanical prosthetic heart valves are of 3 main types, the cage-ball valves such as the Starr-Edwards valve, the tilting disc valves such as the Bjork-Shiley, and the Medtronic valves and the bileaflet valves such as the St Jude's Medical valve. Greater thrombogenicity is associated with the older generation valves (Starr-Edwards and Bjork-Shiley) compared to the newer generation valves (St Jude's Medical and Medtronic) and with a prosthetic valve in the mitral as opposed to the aortic position.[3]

Options for anticoagulation comprise oral coumarin therapy with warfarin and subcutaneous injection with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Warfarin therapy throughout pregnancy is believed to be most efficacious in the prevention of the maternal thromboembolic disease for patients with MPHV. Unfortunately evidence has shown that this drug may be associated with fetal morbidity and

[1] Department of Haematology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital and National Health Laboratory Service (NHLS), Johannesburg, South Africa
[2] Department of Cardiology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa
[3] Department of Obstetrics and Gynaecology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

Corresponding Author:
Chitsike Rufaro Saeed, Room 4, Area 454, NHLS Haematology Laboratory, Charlotte Maxeke Johannesburg Academic Hospital, PO Box 1038, Johannesburg, 2000, South Africa
Email: rufaro.chitsike@gmail.com

mortality described in the literature as "warfarin embryopathy."[4] Unfractionated heparin is an alternative therapy in women who elect to avoid treatment with warfarin, especially during the first-trimester. However, 2 retrospective surveys reported a high incidence of valve thrombosis in pregnant women with old-generation MPHV treated with fixed- or adjusted-dose subcutaneous UFH.[5,6] The efficacy of adjusted-dose subcutaneous heparin has not been definitively established though.

Low-molecular-weight heparins are glycosaminoglycan molecules that exert their anticoagulant activity by binding to antithrombin and causing a conformational change that greatly enhances the ability of antithrombin to bind to and inhibit the action of the activated coagulation factor X (factor Xa). The LMWHs have generated a significant amount of interest in recent years, the reason for this is 2-fold: first, the improved pharmacokinetics and side effect profile of the LMWHs compared to UFH and second, the potential benefits in pregnancy. Low-molecular-weight heparins have been shown to cause less heparin-induced thrombocytopenia than UFH. In addition, a study done in pregnancy showed that LMWH usage was associated with significantly less osteoporosis when compared to UFH usage.[7] A number of studies done on LMWH use in pregnancy show that the LMWHs are generally safe when administered for thromboprophylaxis in pregnancy.[8] Low-molecular-weight heparin has an average molecular weight of 5000 and has been shown not to cross the placenta; hence, its use in pregnancy is safe for the foetus.[9] When monitoring of anti-factor Xa (anti-Xa) levels are indicated, such as for maternal patients with MPHV, the peak anti-Xa activity should be measured 3 to 4 hours after subcutaneous LMWH injection.

Reports of treatment failure such as thrombosis of prosthetic heart valves in pregnant women on LMWH in addition to concerns about possible teratogenicity raised questions regarding the safety of LMWH. This resulted in a "warning" being issued by a LMWH manufacturer regarding the use of LMWH in pregnant women with MPHV.[10] As LMWH does not cross the placenta, it is implausible that it causes fetal morbidity or mortality.[9] Subsequent to the warnings release, a cardiology consensus statement regarding the use of LMWH in pregnancy was issued stating it "should more appropriately be considered an unproven and imperfectly studied alternative among a trio of suboptimal and potentially unfavorable options (warfarin, UFH, and LMWHs)."[11] A number of reviews have stated that there are presently no good data documenting the use of LMWH in pregnant women with MPHV and there have been calls for appropriately designed studies to investigate this therapeutic option. One review concluded that LMWH could be the best option of the 3 treatment options available but that all 3 options have still been understudied.[11] More recently, the earlier warning by the LMWH manufacturer has been rephrased to "use of Lovonox (LMWH) for thromboprophylaxis in pregnant women with MPHV has not been adequately studied."[12] The 8th American College of Chest Physicians (ACCP) guidelines recommend the use of LMWH at a dose aiming to achieve peak anti-Xa levels of $\sim$1.0 U/mL as one of the treatment options.[13]

Objective

To determine whether the use of the LMWH, enoxaparin, is safe for pregnant women with MPHV during pregnancy when used with dosage adjustment to maintain a peak anti-Xa of 1.0 to 1.2 U/mL. Key outcomes measured were prosthetic valve thrombosis, bleeding, and maternal mortality.

Materials and Methods

This was a prospective observational study performed at Charlotte Maxeke Johannesburg Academic Hospital from 2007 to 2009. Our sample consisted of 15 consecutive pregnant women. The women in our study were 18 years and older with known MPHV in the mitral and/or aortic position (single or double). Most of these women were either attending the anticoagulation clinic at Charlotte Maxeke Johannesburg Academic Hospital or Chris Hani Baragwanath Hospital for monitoring of warfarin therapy efficacy prior to conception. Written informed consent was obtained prior to any protocol-specific procedures. Other inclusion criteria included cardiac assessment to confirm clinical stability, sinus rhythm as well as ability to administer medication subcutaneously at home and a normal platelet count for pregnancy ($>100 \times 10^9$/L).

Women with cardiac instability, infective endocarditis, a known thrombophilic state, an inherited condition predisposing to bleeding, and any women with hemolysis were excluded from our study. Women were removed from therapy for noncompliance on treatment or inability to administer medication at home and the development of thrombocytopenia. Any women who were treated with enoxaparin for 2 weeks or less were not included in the write up of this study. Aspirin was not routinely given to the women in our study. Any other medication inhibiting platelet function such as other nonsteroidal anti-inflammatory drugs and medication that would interact with enoxaparin or interfere with evaluation of the clinical response (systemic glucocorticoids and thrombolytics) were not administered.

The experimental protocol observed was as follows. Women were admitted as soon as they discovered they were pregnant or whenever they presented to the hospital during pregnancy. All patients signed written consent to take part in the study. Women were started at a dose of enoxaparin calculated at 1 mg/kg twice daily. The dose of enoxaparin was then adjusted to achieve a peak anti-Xa level (3 hours postdose) of more than 1.0 U/mL and less than 1.2 U/mL. The women were taught how to inject themselves in the hospital and were then discharged home where they injected themselves twice a day (12 hourly) with enoxaparin until just prior to delivery. The women attended the antenatal clinic weekly, where they had a full clinical examination and blood was taken for peak anti-Xa levels, which was measured at the NHLS (National Health Laboratory Service) Hematology Coagulation Laboratory at Charlotte Maxeke Johannesburg Academic Hospital. The dose of enoxaparin was adjusted weekly to maintain the therapeutic peak anti-Xa level of 1.0 to 1.2 U/mL for the duration of pregnancy.

Anti-Xa values outside the target range would result in an either upward or downward adjustment in the dose of enoxaparin by 10 mg. An echocardiogram to exclude valvular thrombosis was performed monthly.

"Major" bleeding was defined as bleeding resulting in a drop in the hemoglobin concentration by $\geq$2 g/dL or as bleeding requiring transfusion of at least 2 units of packed red blood cells. Bleeding not fulfilling these criteria was defined as "minor."

A prospective control arm of pregnant women taking warfarin was not undertaken as we felt it was unethical to purposefully expose fetuses to a drug with known teratogenic potential.

Results

A total of 18 consecutive women met the inclusion criteria and consented to be part of the study. In all, 2 of these women were not included in the write up of this study as they were treated with adjusted-dose enoxaparin therapy for 2 weeks or less before delivery. A further patient was not included in the write up of this study due to insufficient data. All 3 of these patients did not develop any thrombotic or hemorrhagic complications during enoxaparin exposure in pregnancy. No patient who met the inclusion criteria declined to be part of the study. An additional maternal patient with a MPHV did not meet the inclusion criteria as she was younger than 18 years of age.

Table 1 illustrates baseline information of our patient group including the type of mechanical prosthetic valve present. It also shows the duration of the various anticoagulation therapies used during pregnancy.

The average age was 26.3 years (median 24 years); there were 6 primigravidas and 9 multigravidas. All of the women were New York Heart Association (NYHA) class 1 to 2. One woman had epilepsy and was being treated with carbamazepine (patient 1), whereas another patient (patient 13) had human immunodeficiency virus (HIV) infection and was receiving antiretroviral therapy. In all, 6 of the 15 women had double prosthetic valves with an aortic MPHV in addition to a mitral MPHV. All the women had bileaflet MPHV (second-generation valves). The average time to presentation to our unit and conversion to enoxaparin was 14.7 weeks (median 17 weeks). The total combined period of time that our women were exposed to adjusted-dose enoxaparin during pregnancy was 344 weeks.

Two women were not on any anticoagulation during pregnancy prior to presentation for 15 weeks (patient 2) and 23 weeks (patient 7).

Figure 1 shows the duration of adjusted-dose enoxaparin exposure relative to the duration of prior anticoagulation given in pregnancy.

Figure 2 shows the average anti-Xa readings recorded throughout pregnancy with the 95% confidence interval. All the average readings recorded were maintained within the target range of 1 to 1.2 U/mL throughout pregnancy.

Figure 3 shows the average enoxaparin doses in milligrams recorded throughout pregnancy with the 95% confidence interval.

Table 2 demonstrates adverse maternal outcomes. Maternal morbidity was expressed as valve thrombosis, bleeding, and cardiac, obstetric, or other complications. Maternal mortality is also recorded.

None of the women developed prosthetic valve thrombosis during pregnancy and there was no maternal mortality. Patient 9 developed asymptomatic pannus that was detected postdelivery by echocardiography. She subsequently also developed valvular thrombosis on the same valve 4 weeks later, which was associated with significant shortness of breath. This occurred 2 days after the enoxaparin was stopped, despite the patient being therapeutic on warfarin therapy at the time (6 weeks postpartum). She had an uneventful valve replacement.

Patient 13 developed numbness and tingling of the left arm. This lasted about 6 hours and occurred at 19 weeks of gestation. On further enquiry, it was revealed that she had suffered similar events since childhood prior to the insertion of the prosthetic valve. For completeness, echocardiography was carried out, which revealed a normal functioning valve with no evidence of valvular thrombosis. A normal D-dimer level also confirmed the absence of thrombotic event. Her anti-Xa level at the time was 1.18 U/mL. This episode did not recur during her pregnancy.

Patient 11 had 4 episodes of epistaxis while on enoxaparin in this pregnancy. She presented with a history of epistaxis since childhood. Each episode of epistaxis in this pregnancy involved the left nostril (this was the same nostril from which she had had a long history of bleeding) and occurred when the ambient temperature was high. The severity of the bleeding varied from a few drops to an episode, which required nasal packing with gauze soaked with zinc oxide paste in the casualty department. However, the patient did not fulfill the criteria for major bleeding. A peak anti-Xa taken soon after presentation revealed an anti-Xa of 1.35 U/mL, mildly greater than the therapeutic range. She was subsequently treated with saline nasal drops and chloramphenicol ointment and her enoxaparin dose was adjusted downward to return into the therapeutic range. This patient developed mild itching at the site of enoxaparin injection. This may have represented a mild allergy to the drug. This was treated with a topical antihistamine ointment with some improvement. Patient 15 had no previous history of epistaxis, however, developed an episode of epistaxis during her pregnancy. The bleeding was defined as minor; however, she required nasal packing. A peak anti-Xa revealed a result of 1.79 U/mL at the time of bleeding. Her dose of enoxaparin was reduced to achieve the target anti-Xa level. She did not have any further epistaxis during her pregnancy. One woman developed spotting with a few drops of blood passed per vaginum (patient 1). No other potential side effects of enoxaparin use were noted such as heparin-induced thrombocytopenia and there was no clinical evidence of vertebral osteoporosis.

Discussion

The use of LMWH in pregnant women with mechanical prosthetic valves has been a subject of much controversy. A review

Table 1. Baseline Information and Duration of Anticoagulation

Patient Number	Age (yrs)	Weight (kg)	Parity	Type of Mechanical Prosthetic Valve	Prior Anticoagulation in Pregnancy	Enoxaparin Duration (Adjusted-Dose)
1	33	71	Multi	MVR MIRA, AVR MIRA	Warfarin weeks 1-17	Weeks 18-38
2	18	60	Primi	MVR St Jude Medical	Warfarin weeks 1-20	Weeks 21-38
3	24	72	Primi	MVR St Jude Medical	Warfarin weeks 1-4, LMWH fixed dose weeks 5-20	Weeks 21-32
4	32	74	Multi	MVR St Jude Medical, AVR St Jude Medical	Warfarin weeks 1-12, Nil for weeks 13-27	Weeks 28-38
5	20	63	Multi	MVR MIRA	Warfarin weeks 1-22	Weeks 23-40
6	40	86	Multi	MVR St Jude Medical, AVR St Jude Medical	Warfarin weeks 1-23	Weeks 24-37
7	28	89	Multi	MVR MIRA, AVR St Judes Regent	Nil for weeks 1-22	Weeks 23-39
8	22	69	Multi	MVR Silzone St Judes Medical	Warfarin weeks 1-27	Weeks 28-38
9	23	70	Multi	MVR Carbomedics Orbis	Warfarin weeks 1-10	Weeks 11-38
10	32	90	Primi	MVR St Jude's Medical	Warfarin weeks 1-5	Weeks 6-39
11	27	72	Multi	MVR MIRA	Warfarin weeks 1-9	Weeks 10-38
12	21	61	Primi	MVR Carbomedics Orbis, AVR Carbomedics	Warfarin weeks 1-5	Weeks 6-38
13	31	93	Multi	MVR St Judes Medical	Warfarin weeks 1-5	Weeks 6-38
14	23	60	Primi	MVR MIRA, AVR MIRA	Warfarin weeks 1-5	Weeks 6-36
15	21	57	Primi	MVR Silzone St Judes Medical	Warfarin weeks 1-4	Weeks 5-38

Abbreviations: AVR, aortic valve replacement; LMWH, low-molecular-weight heparin; Multi, multigravida; MVR, mitral valve replacement; Primi, primigravida.

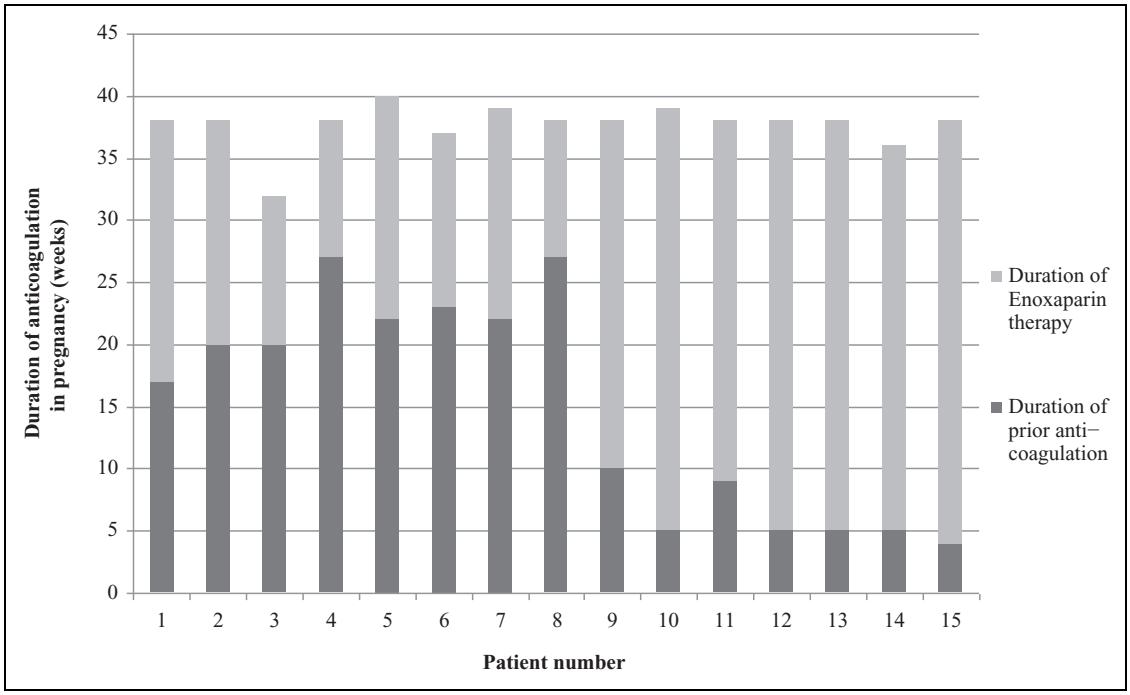

Figure 1. Duration of enoxaparin and prior anticoagulation in pregnancy.

of 81 pregnancies in 75 women with MPHV treated with LMWH during pregnancy done by Oran et al[14] reported an 8.6% rate of valve thrombosis. This rate of valve thrombosis is unacceptably high especially as valve thrombosis in these women is often associated with maternal and fetal mortality. However, careful review of the cases of valve thrombosis reported by Oran et al indicated a consistent pattern; most, if not all, of these cases were associated with an inadequate dose of LMWH, lack of monitoring, or subtherapeutic anti-Xa levels.

For this reason, strict monitoring of anti-Xa levels was performed in our study and the dose of LMWH was subsequently

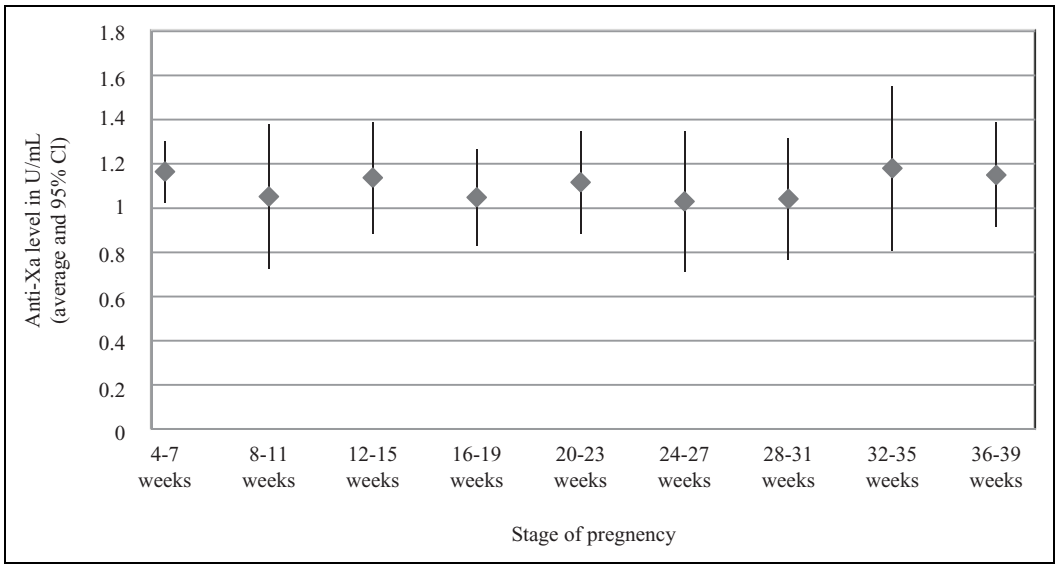

Figure 2. Variation of anti-Xa levels throughout pregnancy.

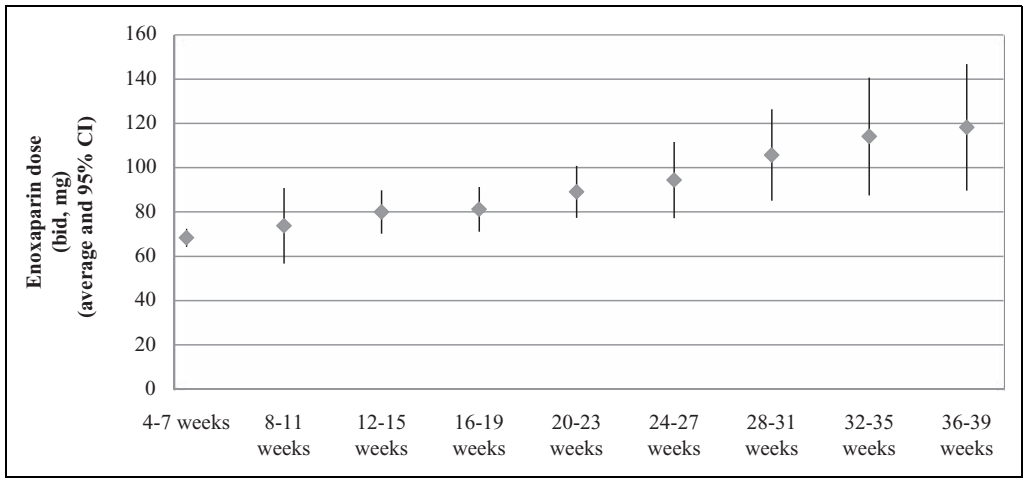

Figure 3. Variation of enoxaparin dose throughout pregnancy.

adjusted to maintain the high level of anticoagulation required to keep the anti-Xa at 1.0 to 1.2 U/mL throughout pregnancy.

Our data show that enoxaparin may be efficacious in the prevention of cardiac valve thrombosis in this high-risk group of women when associated with anti-Xa monitoring and dosage adjustment. A similar finding has been shown by 2 other studies also performed in maternal patients with MPHV in Auckland[15] and in London.[16] The Auckland study used adjusted-dose enoxaparin therapy to achieve a peak anti-Xa of 0.7 to 1.2 U/mL at 4 hours postdose. This was a large study ($n = 47$) that showed a 10.6% rate of valve thrombosis related to enoxaparin therapy. The reasons outlined for valvular thrombosis were subtherapeutic anti-Xa levels and poor compliance. The London study used adjusted-dose dalteparin and enoxaparin to achieve a peak anti-Xa of 1 to 1.2 U/mL throughout pregnancy 4 hours postdose. This study showed an 8.3% (1/12) rate of valve thrombosis. The reason stated for this was that the patient had a subtherapeutic anti-Xa level and frequent monitoring of the anti-Xa was not possible. A further complicating factor was that this patient also had an underlying thrombophilic state (heterozygous prothrombin G20210A gene mutation). It is not clear though how often patients had anti-Xa monitoring in this study. Possible reasons why the rate of valvular thrombosis observed in our study was lower than that observed in these studies could be that there was a higher target range for the peak anti-Xa in our study in comparison to the Auckland study and more frequent anti-Xa monitoring was performed in our study (weekly as opposed to monthly). Both these factors could have reduced the likelihood of our patients developing subtherapeutic anti-Xa levels and subsequent valve thrombosis. Trough anti-Xa levels were, however, not measured in our study and there are currently no good data to show how frequently anti-Xa levels should be monitored for this patient group. More frequent antenatal visits may have also

Table 2. Maternal Morbidity and Mortality

	Maternal Morbidity			
Patient Number	Valve Thrombosis	Bleeding	Cardiac/Obstetric/Other Complications	Maternal Mortality
1	Nil	1 episode spotting per vagina	Nil	Nil
2	Nil	Nil	Nil	Nil
3	Nil	Nil	Nil	Nil
4	Nil	Nil	Nil	Nil
5	Nil	Nil	Nil	Nil
6	Nil	Nil	Nil	Nil
7	Nil	Nil	Nil	Nil
8	Nil	Nil	Nil	Nil
9	Nil	Nil	Valvular pannus	Nil
10	Nil	Nil	Nil	Nil
11	Nil	Epistaxis	Itchiness at enoxaparin injection site	Nil
12	Nil	Nil	Nil	Nil
13	Nil	Nil	Left arm numbness	Nil
14	Nil	Epistaxis	Nil	Nil
15	Nil	Nil	Nil	Nil

helped with patient compliance. The limitations of our study though are that there was no control group and it was not composed of a large sample size. The results of these studies would support the recommendation of LMWH as a treatment option for this patient group in the 8th ACCP guidelines as no patients developed valvular thrombosis on enoxaparin while the anti-Xa was in the therapeutic range.

Elkayam et al make a distinction between the risk posed to pregnant women with first-generation prosthetic valves in the mitral position compared to the risk posed to those with second-generation prosthetic valves in the mitral position or any mechanical prosthetic valve in the aortic position. They suggest that the former group have a higher risk of thrombosis than latter group.[3] All the women in our study had second-generation prosthetic valves and based on this risk stratification, despite still being high-risk they are at a lower risk than the above described group of women with older generation prosthetic valves. Appropriate studies are required to assess the efficacy of LMWH in pregnant women with the first-generation prosthetic valves. However, due to their greater thrombogenicity, these first-generation prosthetic valves are no longer as commonly used as the second-generation prosthetic valves in our center.

Maintenance of the anti-Xa at 1.0 to 1.2 U/mL throughout pregnancy results in a high degree of anticoagulation, thus a higher theoretical risk of bleeding. Over-anticoagulation can result in bleeding as was observed in one of our patients. None of the women in our study, however, developed a major bleed requiring blood transfusion as a complication of enoxaparin therapy during their pregnancy. In all, 1 of the 2 women with epistaxis already had a predisposition to nose bleeding which was exacerbated by the enoxaparin. The general lack of bleeding is a positive finding which further supports the use of enoxaparin in the women studied.

Warfarin therapy for pregnant women with MPHVs is efficacious in the prevention of cardiac valve thrombosis with the reported overall maternal mortality reported as 2.9%.[17] Until a randomized controlled study is done to compare the use of adjusted-dose enoxaparin to warfarin, it will be difficult to say that enoxaparin is at least as efficacious as warfarin in the prevention of maternal thromboembolic disease in this patient group. Studies such as this one are, however, beginning to show that adjusted-dose enoxaparin may have a significant role to play for these patients in both maternal thromboprophylaxis as well as the prevention of fetal morbidity and mortality related to oral anticoagulant use.

Conclusion

Our data show that enoxaparin may be administered safely in pregnant women with MPHV when there is dosage adjustment throughout pregnancy to maintain an anti-Xa of 1.0 to 1.2 U/mL. Women with a significant bleeding tendency from prior to starting anticoagulation should be monitored closely to exclude bleeding as a complication of LMWH therapy.

Authors' Note

Ethical clearance for the study was granted by the University of the Witwatersrand Medical Human Research Ethics Committee on February 1, 2007, reference number M060822.

Acknowledgments

The authors would like to thank Dr NE Gregersen for her contribution to the perinatal assessment of neonates, Dr KM Vanderdonck for her

assistance with obtaining information about valve types, and the Charlotte Maxeke Johannesburg Academic Hospital NHLS Hematology Coagulation Laboratory for the processing of the anti-Xa tests.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References

1. Lee CW, Wu CC, Lin PY, Hsieh FJ, Chen HY. Pregnancy following cardiac prosthetic valve replacement. *Obstet Gynecol*. 1994; 83(3):353-356.
2. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J*. 1994;71(2):196-201.
3. Elkayam U, Bitar F. Valvular heart disease in pregnancy. *J Am Coll Cardiol*. 2005;46(3):403-410.
4. Hall JG, Paul RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med*. 1980;68(1): 122-140.
5. Hanania G, Thomas D, Michel PL, et al. Pregnancy in patients with heart valve prosthesis a French retrospective cooperative study (155 cases). *Arch Mal Coeur Vaiss*. 1994;87(4):429-437.
6. Salazar E, Izaguirre R, Verdejo J, Mutchinick O. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechanical cardiac valve prosthesis. *J Am Coll Cardiol*. 1996;27(7):1698-1703.
7. Barbour LA, Kick SD, Steiner JF, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. *Am J Obstet Gynecol*. 1994;170(3):862-869.
8. Ensom MHH, Stephenson MD. Low-molecular-weight heparins in pregnancy. *Pharmacotherapy*. 1999;19(9):1013-1025.
9. Forestier DF, Daffos F, Capelia-Pavlovsky M. Low molecular weight heparin (PK 10169) does not cross the placenta during the second trimester of pregnancy: study by direct foetal blood sampling under ultrasound. *Thromb Res*. 1984;34(6):557-560.
10. *Lovenox injection (package insert)*, Aventis Pharmaceuticals, Bridgewater, NJ (2002).
11. Anticoagulation and enoxaparin use in patients with prosthetic heart valves and/or pregnancy, *Clinical Cardiology Consensus Reports* 3, American Health Consultants, Atlanta, GA (2002), pp. 1–20.
12. Lovenox Injection [packet insert]. Bridgewater, NJ: Aventis Pharmaceuticals; 2004.
13. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Antithrombotic and thrombolytic therapy, 8th ed. ACCP Guidelines: venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy. *Chest*. 2008;133(6 suppl):844S-886S.
14. Oran B, Lee-Parritz A, Ansell J. Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. *Thromb Haemost*. 2004;92(4):747-751.
15. McLintock C, McCowan L, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. *BJOG*. 2009;116(12):1585-1592.
16. Quinn J, Von Klemperer K, Brooks R, Peebles D, Walker F, Cohen H. Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience. *Haematologica*. 2009; 94(11):1608-1612.
17. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves. *Arch Intern Med*. 2000; 160(2):191-196.