The effect of warfarin dosage on maternal and fetal outcomes in pregnant women with prosthetic heart valves

P Soma-Pillay FCOG (SA)*, **Z Nene** MBChB (Medunsa)*, **T M Mathivha** MBChB FCP(SA)[†]
and **A P Macdonald** FCOG (SA) FRCOG*

*Department of Obstetrics and Gynaecology, Maternal and Fetal Unit; [†]Department of Cardiology, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa

Summary: There are several challenges in the management of pregnant women with mechanical heart valves. Pregnancy increases the risk of thromboembolism and there is currently no consensus on the safest anticoagulation method during pregnancy. The objective of the study was to determine the correlation between the warfarin dose and pregnancy outcome in pregnant women with prosthetic heart valves. Warfarin in pregnancy was associated with a low risk of valve thrombosis or maternal death. The risk for fetal abnormalities was not related to the maternal warfarin dosage. However, the risk for stillbirth was significantly increased with increasing doses of warfarin.

Keywords: cardiovascular, prosthetic heart valve, warfarin, stillbirth

INTRODUCTION

There are several challenges in the management of pregnant women with mechanical heart valves. Pregnant women are at risk of heart failure, thrombo-embolic complications, arrhythmia, infectious endocarditis and maternal death. The hypercoagulable state of pregnancy increases the thromboembolic risk and therefore the choice of anticoagulant is particularly important in pregnancy. There is currently no consensus on the safest and most efficacious anticoagulation method during pregnancy.

Warfarin (Aspen Pharmacare: Pharma, Johannesburg, South Africa) is regarded as the safest treatment option for the mother. Unfortunately, warfarin crosses the placenta and is associated with increased rates of fetal loss.¹ Warfarin is also associated with teratogenic lesions if used in the first trimester and the use later in gestation carries the risk of fetal haemorrhagic complications and maternal haemorrhage during labour. Long-term use of unfractionated heparin (Fresenius Kabi, South Africa) is safe for the fetus but is associated with the maternal complications of osteoporosis and thrombocytopenia. Low molecular weight heparins (LMWHs) have been included as therapeutic options in recent consensus guidelines and reports from case series with LMWH therapy in pregnancy suggest a risk for valve thrombosis ranging from 10% to 22%.^{1–4} There are no published randomized controlled trials comparing the different anticoagulant therapeutic regimens in pregnancy.

OBJECTIVES

The objective of the study was to determine the correlation between the warfarin dose and pregnancy outcome in pregnant women with prosthetic heart valves. These patients followed a local anticoagulation protocol and received obstetric care at the Steve Biko Academic Hospital, a tertiary referral hospital in Pretoria, South Africa.

PATIENTS AND METHODS

This was a prospective observational study of 62 pregnancies in 60 women between January 2005 and August 2009. All the patients were managed in a combined cardiac–obstetric unit and were treated according to the anticoagulation protocol shown in Table 1. (Aspirin was not used routinely as part of the anticoagulation protocol.)

A routine anatomy ultrasound was performed between 20 and 24 weeks on all fetuses. The study received ethical approval from the University of Pretoria Ethics Committee.

Maternal outcome was classified as a maternal death (death of a woman while pregnant or within 42 days of termination of pregnancy) or a near miss (a patient with an acute organ dysfunction that could result in death if not treated appropriately).⁵

Fetal outcome was analysed in three groups depending on the average daily maternal warfarin dose. The maternal warfarin dose was 5 mg or less in group 1, 5.1–7.4 mg in group 2 and 7.5 mg or more in group 3.

Fetal outcome was classified as live birth (babies above 500 g born alive), miscarriage (fetal loss <500 g) or stillbirth (a fetus weighing >500 g that was born dead). Weights rather than gestational age were used for definitions of fetal outcome because gestational age was often uncertain. The diagnosis of

Correspondence to: P Soma-Pillay, PO Box 2432, Midrand 1685, South Africa
Email: priya.somapillay@up.ac.za

Table 1 Prosthetic valves – management protocol at the Steve Biko Academic Hospital Cardiac-Obstetric Unit

1. Unfractionated twice daily subcutaneous heparin (titrated to a therapeutic thromboplastin time; PTT maintained between 70 and 90 seconds) given when possible from pregnancy detection until 12 weeks gestation
2. Warfarin from weeks 12 to 36. The international normalized ratio (INR) was maintained at 2.5–3.5
3. **Week 36**
 - (a) Warfarin stopped and patients re-started on twice daily unfractionated subcutaneous heparin
 - (b) Delivery by elective caesarean section at 38 weeks with the morning dose of heparin withheld. Planned elective caesarean section ensures that the patient is transferred to a prebooked cardiac ICU postdelivery
 - (c) Subcutaneous heparin re-started six hours after delivery
 - (d) Warfarin was resumed the morning after delivery if there were no bleeding complications. INR maintained between 2.5 and 3.

warfarin embryopathy was made if the mother was exposed to warfarin in the first trimester with the presence of midline hypoplasia in the fetus/newborn.

Statistical analysis

The data were analysed using SPSS for Windows Version 17 (SPSS Inc, Chicago, IL, USA). Descriptive statistics in the form of means and standard deviations frequencies and percentages were used to describe the population. Chi-square tests and where appropriate Fisher's exact tests were used to establish if differences between the three dosage groups were statistically significant. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Sixty-two pregnancies were managed during the study period. Fifty-one patients had mitral valve, two aortic and nine double-valve prostheses. Most of our study population have had prosthetic valve replacements as a consequence of childhood rheumatic heart disease. Unfortunately, we were unable to obtain information about the valve type because most patients had their valve replacement surgery at other health institutions and we were unable to obtain the surgical notes. Forty-one (66%) women booked after the first trimester and were exposed to warfarin during this period. Seventeen (27%) patients were referred from the Pretoria/Tshwane District while the remaining patients were from other districts or provinces within the referral system. The baseline characteristics of the study population are shown in Table 2.

Maternal outcome

There were no maternal deaths or cases of valve thromboses. There were six (9.7%) maternal near misses. Four mothers developed cardiac failure and were treated medically. There were two cases of bleeding problems related to anticoagulation therapy postcaesarean section requiring massive blood transfusions and re-look laparotomies.

Fetal outcome

Forty-one fetuses were exposed to warfarin in the first trimester and there were five (12%) cases of warfarin embryopathy. The

Table 2 Baseline characteristics of study population

Age of patient	Years
Mean (SD)	23 ± 6.48
Minimum	14
Maximum	41
Obstetric history	N (%)
Primigravida	17 (27%)
Multigravida	45 (73%)
Gestational age at booking	Weeks
Mean (SD)	16 ± 9.19
Minimum	6
Maximum	38
Area of residence	
Tshwane District	17 (27%)
Referral from other centres	45 (73%)
Position of prosthetic valve	
Mitral	51
Aortic	2
Double valve	9

average daily warfarin dose, the average international normalized ratio (INR) and the highest recorded INR for each of these patients is shown in Table 3.

There was no significant difference in the live birth rate, average birth weights or miscarriage rates between the three warfarin dosage groups. The stillbirth rate increased with increasing doses of warfarin. Overall, there was a significant difference in the stillbirth rate between the groups. The difference between groups 1 and 3 (*P* = 0.008) was significant but not between groups 1 and 2 and groups 2 and 3. The average INR recorded for each group was also similar. Table 4 records the number of patients and the fetal outcomes.

DISCUSSION

Only 27% of our patients reside locally and the remaining patients live in areas where health centres do not have the facilities to manage cardiac complications such as cardiac failure or valve thrombosis. We also do not have facilities for monitoring anti-Xa, which is required if LMWH is used. Compliance with twice daily injections and testing of anti-Xa levels are critical when using LMWH. We are therefore unable to offer pregnant patients LMWH as a treatment option, even though studies using LMWH report lower fetal complication rates.¹ It is important that our institution follows an anticoagulation protocol where the mother is at lowest possible risk for valve thrombosis.

The risk for thromboembolism was determined from pooled estimates and reported in two studies. The study by Chan *et al.*⁶ was based on a literature search prior to 1998 and that of Abildgaard *et al.*⁷ covered the period 1998–2008. The risk of thromboembolism if oral anticoagulants were used throughout

Table 3 Cases of warfarin embryopathy

Patient	Average dose of warfarin (mg)	Average INR	Highest INR
1	6	3.0	6.1
2	5	2.6	3.2
3	3.5	3.1	4.9
4	7.5	3.0	4.2
5	7.5	2.3	4.4

INR, international normalized ratio

Table 4 Maternal warfarin dose and fetal outcome

	Group 1	Group 2	Group 3	P value
Maternal warfarin dose	5 mg or less <i>n</i> = 28	5.1–7.4 mg <i>n</i> = 21	7.5 mg or more <i>n</i> = 13	
Live births (<i>n</i>)	19 (68%)	13 (62%)	6 (46%)	0.413
Average birth weight (kg) (SD)	2.9 ± 0.84	2.78 ± 0.83	2.7 ± 1.22	
Pregnancy loss	9 (32%)	8 (38%)	6 (46%)	0.389
Miscarriages (<i>n</i>)	8 (29%)	5 (24%)	1 (7.7%)	0.16
Stillbirths (<i>n</i>)	1 (3.6%)	3 (14%)	5 (38.5%)	0.012
Average INR	2.5	2.8	2.7	

INR, international normalized ratio
Value in bold is statistically significant

pregnancy was similar in both studies: 2.4% and 3.9%, respectively. If warfarin was replaced by unfractionated heparin in the first trimester, the risk of thromboembolism increased to 9.2% and 10.3%, respectively. In our study, 41 (66%) women booked after the first trimester and were therefore treated with warfarin throughout pregnancy. There were no cases of valve thrombosis in our study and the risk of maternal death or thrombosis is lower in our study than that reported previously.

Studies reporting maternal and fetal outcomes using LMWHs are based on limited data from observational studies and case reports. In the largest study (*n* = 47) of consecutive pregnancies in women with mechanical valves treated with enoxaparin, the risk for valve thrombosis was 10.6%.¹ The authors of this study stated that non-compliance with LMWH or low anti-Xa levels contributed to the development of thrombosis in five pregnancies. Other studies have reported valve thrombosis rates of 7%, 8.6%, 22% and 4%.^{4,8–10} The HIP-CAT study was the only randomized controlled trial comparing enoxaparin to unfractionated heparins. This study was also affected by problems of compliance and low anti-Xa levels and the study was stopped after two out of seven patients in the enoxaparin group died of valve thrombosis. The United States Food and Drug Administration requested that this information be added to the package insert.¹¹ Some experts have suggested LMWHs should not be used in high-risk patients with first-generation mechanical valves in the mitral position, and that if LMWHs are used this should be done in a setting with close clinical follow-up and appropriate laboratory testing.^{1,12} The case of valve thrombosis and maternal death in the study by Yinon occurred in a patient with a second-generation mechanical aortic valve with close monitoring of anti-Xa levels that were in the therapeutic range.

Cases fatality rates of between 40% and 50% after valve thrombosis have been reported with the use of heparins.⁴ We therefore believe that in our clinical situation where access to tertiary health-care facilities for the majority of our patients is limited, warfarin throughout pregnancy or in combination with unfractionated heparin is a safer option for the mother.

There were two (3.2%) cases of postcaesarean section bleeding related to anticoagulation therapy. Again, this risk is lower than the reported bleeding risks of 17% and 13% associated with LMWHs.^{1,10}

The risk of warfarin-related embryopathy was 12% and this risk was present irrespective of the maternal warfarin dose. This risk is higher than the 3.4% and 6.4% previously reported by Vitale *et al.*¹³ and Chan *et al.*⁶ The rate of embryopathy in our

study was 5% if the warfarin dose was 5 mg or less and 7% for patients using >5 mg of warfarin. In the study by Vitale *et al.*,¹³ cases of embryopathy were found only in women taking a daily dose of more than 5 mg of warfarin. Unfortunately, this finding was not confirmed in our study and two patients with average daily dosages of 3.5 and 5 mg of warfarin had babies diagnosed with warfarin-related embryopathy.

The miscarriage rate was 22% (*n* = 14) and this was consistent with rates of 24%, 33.9% and 37.9% reported by Chan *et al.*⁶ and Vitale *et al.*¹³ There was no statistically significant difference in the miscarriage rate between the three groups. The average birth weight, risk for embryopathy and the live birth rate were also not affected by the maternal warfarin dose. Like our study, the study by Sadler *et al.*¹⁴ could also not confirm the association between lower dose warfarin and improved fetal outcome for all parameters. The only dose-dependent difference in fetal outcome observed was that of stillbirths. If the maternal warfarin dose was <5 mg a day, the stillbirth rate was 3.6% and this rose to 38.5% if the warfarin dose was 7.5 mg or more per day (*P* = 0.01).

In the study by Vitale *et al.*, there was a lower fetal complication rate of 15% if the maternal warfarin dose was <5 mg per day and this risk increased to 88% when the dose was more than 5 mg per day. This observed difference was statistically significant and the complications included birth defects, spontaneous miscarriage and stillbirths. Similarly, for stillbirths in our study, 8/9 cases occurred with >5 mg of warfarin. The stillbirth rate was 3.6% for women using <5 mg of warfarin and 24% (*P* = 0.026) for women with higher doses of warfarin.

Warfarin exposure during the second and third trimesters of pregnancy is associated with central nervous system abnormalities and fatal haemorrhage in the fetus.^{12,15} The immature liver enzyme system and the low levels of vitamin K-dependent clotting factors in the fetus result in higher levels or overdosing of the fetus with oral anticoagulants, leading to haemorrhage.¹³ The increased stillbirth rates with higher doses of warfarin found in our study are therefore most likely due to haemorrhage in the fetus.

Limitations of the study

Post-mortems could not be performed on all the babies who were stillborn because most of these infants were macerated at birth and we were therefore unable to determine the cause of the death. Complications such as miscarriages, stillbirths and maternal morbidity/mortality could have been missed if patients did not present to their local health institution.

CONCLUSION

Warfarin in pregnancy is associated with low risks of valve thrombosis and maternal death. In a population where access to health care is difficult, warfarin is a safer option for the mother than heparin. The risk for fetal embryopathy is not related to the maternal warfarin dosage and embryopathy occurs also with low-dose warfarin. However, the risk for stillbirth is significantly increased with increasing doses of warfarin. Patients should be informed prior to conception about the risks of warfarin for the fetus and strict INR control in a high-risk cardiac obstetric unit is advised.

Conflict of interest: None.

REFERENCES

- 1 McLintock C, McCowan L, North R. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. *BJOG* 2009;**116**:1585–92
- 2 Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 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. *J Am Coll Cardiol* 2008;**52**:e1–142
- 3 Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. American College of Chest P. Venous thromboembolism, thrombophilia, antithrombotic therapy and pregnancy: American College of Chest Physicians Evidenced-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;**133** (6 suppl):844S–86S
- 4 James AH, Brancizio 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
- 5 Mantel GD, Buchmann EJ, Rees H, Pattinson RC. Severe acute maternal morbidity: a pilot study for a definition of a near miss. *BJOG* 1998;**105**:985–90
- 6 Chan WSC, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Int Med* 2000;**160**:191–6
- 7 Abildgaard U, Sandset PM, Hammerstrom J, Gjestvang FT, Tveit A. Management of pregnant women with mechanical heart valve prosthesis: thromboprophylaxis with low molecular weight heparin. *Thrombosis Res* 2009;**124**:262–7
- 8 Rowan JA, McCowan LME, Raudkivi PJ, North RA. Enoxaparin treatment in women with mechanical heart valves during pregnancy. *Am J Obstet Gynecol* 2001;**185**:633–7
- 9 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. *Thrombo Haemost* 2004;**92**:747–51
- 10 Yinon Y, Siu SC, Warshafsky C, Maxwell C, McLeod A, Colman JM. Use of low molecular weight heparin in pregnant women with mechanical heart valves. *Am J Cardiol* 2009;**104**:1259–63
- 11 Lovenox (enoxaparin sodium injection). Aventis Pharmaceuticals. See <http://products.sanofi-aventis.us/lovenox/lovenox.html#Boxed%20warning> (last checked 20 August 2010)
- 12 Elkayam U, Bitar F. Valvular heart disease and pregnancy: part II: prosthetic valves. *J Am Coll Cardiol* 2005;**46**:403–10
- 13 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
- 14 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* 2000;**107**:245–25
- 15 Hall JG, Pauli RM, Wilson KM. Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980;**68**:122–40

(Accepted 12 December 2010)