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The use of low molecular weight heparin in pregnant women with mechanical and bio-prosthetic heart valves: An eight-year experience at an academic hospital

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The use of low molecular weight heparin in pregnant women with mechanical and bio-prosthetic heart valves: An eight-year experience at an academic hospital



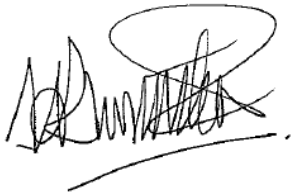
Haroun A. Rhemtula

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Science in Medicine

Johannesburg, 2024

Declaration

I, Haroun Rhemtula declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Science in the branch of Obstetrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



……

30 day of October 2024 in Johannesburg

Dedication

To my parents, Dr Aziz Rhemtula and Mrs. Shirin Rhemtula (both late).

To all women with cardiac disease and those with mechanical prosthetic heart valves who embark on the risky journey of pregnancy.

May the Almighty always protect you and your

unborn offspring as you bring forth new life into this world.

Presentations and publication arising from the research project

Presentations

1. H Rhemtula. Mechanical prosthetic heart valves and the use of anticoagulation in pregnancy. Women in Thrombosis Congress 2018, Johannesburg, South Africa

2. H Rhemtula. Mechanical prosthetic heart valves and the use of anticoagulation in pregnancy. Women in Thrombosis Congress 2019, Johannesburg, South Africa

3. H Rhemtula. Mechanical prosthetic heart valves and the use of anticoagulation in pregnancy. Women in Thrombosis Congress 2020, Johannesburg, South Africa

4. H Rhemtula. The heart of the matter. 5th Cardiovascular Disease in Pregnancy Symposium 2021, Cape Town, South Africa

5. H Rhemtula. The use of low molecular weight heparin in pregnant women with mechanical prosthetic heart valves. An eight-year experience at an academic hospital. University of the Witwatersrand Research Day 2023, Johannesburg, South Africa

6. H Rhemtula. Management of Metallic Valves in Pregnancy: Is Warfarin the only option in 2024? Imperial Obstetric Medicine Symposium 2024, Johannesburg, South Africa

7. H Rhemtula. Optimization of cardiac risk: Maternal and Fetal considerations. Path Africa Conference 2024, Cape Town, South Africa

Publications

1. Warfarin Anticoagulation and Fetal Central Nervous System Abnormalities: a Case Report. Schapkaitz E, *Rhemtula H*, Monaheng R, Louw M, Gerber A, Masebe M, Sithole J. Clin Lab. 2021 Jun 1;67(6).

Abstract

Pregnancy in women with mechanical prosthetic heart valves (MPHV) is a significant contributor to maternal morbidity and mortality worldwide. This requires individualized management to safely balance the maternal and fetal risks associated with the various anticoagulation strategies. A descriptive cross-sectional study was performed to review the maternal and fetal outcomes in pregnant women with prosthetic heart valves managed according to a protocol recommending low molecular weight heparin (LMWH) throughout pregnancy in order to provide guidance on the management of this high risk population. Fifty pregnancies with MPHV and three with tissue valves, on anticoagulation for comorbid atrial fibrillation, attending the Specialist Cardiac Antenatal Clinic at the Charlotte Maxeke Johannesburg Academic Hospital between 1 July 2015 and 30 June 2023 were included. The majority were of African ethnicity at a mean age of 33 ± 6 years. Anti-Xa adjusted enoxaparin was commenced at 10.5 ± 5.6 weeks' gestation until delivery in 48 (90.6%) pregnancies and warfarin was continued in 5 (9.4%) pregnancies. The live birth rates on enoxaparin and warfarin were 56.3% (95% confidence interval [CI] 42.3-69.3) and 20.0 % (95% CI 2.0-64.0) respectively. There were 12 (22.6 %) miscarriages at a mean of 11.3 ± 3.7 weeks' gestation, 4 (7.5%) intra-uterine fetal deaths on warfarin and 2 (3.8%) warfarin embryopathy/fetopathy. The rates of antepartum/secondary postpartum bleeding and primary postpartum bleeding were 29.4% (95% CI 18.6-43.1) and 5.9% (95% CI 1.4-16.9) respectively. Maternal complications included anaemia (n=11, 20.8%), arrhythmia (n=2,3.8%), heart failure (n=2, 3.8%) and para-valvular leak (n=2, 3.8%). There was one (1.9%) mitral valve thrombosis and one (1.9%) stuck valve in pregnancies who defaulted warfarin prior to pregnancy. There were no maternal deaths. Multidisciplinary management of pregnant women with MPHV with anti-Xa adjusted

LMWH throughout pregnancy represents an effective anticoagulation option for low-middle-income countries.

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I would like to thank Professor Lawrence Chauke for the encouragement and support given to me for this project and his unwavering advocacy of me during its completion.

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I would also like to thank Professor Barry Jacobson for his continued support of the common vision that we have for anticoagulation of pregnant women with mechanical prosthetic heart valves. He remained encouraging and supportive throughout this journey and was available for consultation and advice.

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Nomenclature

AF	Atrial fibrillation
CD	Cardiac disease
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CI	Confidence interval
HIV	Human immunodeficiency virus
INR	International normalised ratio
LMWH	Low molecular weight heparin
MPHV	Mechanical prosthetic heart valves
RHD	Rheumatic heart disease
SA	South Africa
SD	Standard deviation
VKA	Vitamin K antagonists

CHAPTER 1

INTRODUCTION

1.1 Background

Cardiac disease (CD) in pregnancy contributes significantly to maternal morbidity and mortality worldwide (1). In South Africa (SA), CD, in the Confidential Enquiry into Maternal Deaths in 2021, was the most common non-obstetric cause of death. In the category of medical and surgical disease, CD accounted for 28.2% of the deaths in this group (2). Despite improvements in the socio-economic status of South Africans since 1994, rheumatic heart disease (RHD) continues to be the most prevalent CD in pregnancy, followed by cardiomyopathy (3). The majority of women of childbearing age who undergo heart valve replacements in SA, receive second or third generation mechanical prosthetic heart valves (MPHV). This is due to their greater durability and hemodynamic characteristics as compared to bio-prosthetic valves. The advantages of MPHV are nonetheless offset by the requirement for lifelong anticoagulation with vitamin K antagonists (VKA).

1.2 Physiological changes during pregnancy

In pregnancy, many factors such as the physiological changes in coagulation and fibrinolysis result in a hypercoagulable state which is associated with an increased risk of valve thrombosis and systemic thrombo-embolism (4). Normal pregnancy is characterised by an increase in concentrations of coagulation factors VII, VIII, IX, X, XII, as well as a rise in fibrinogen and von Willebrand factor (5). Physiological anticoagulants decrease too with pregnancy

progression, with a significant reduction in protein S activity (6, 7). The risk of thrombosis is highest in the immediate postpartum period and slowly decreases back to pre-pregnancy levels by 8 to 12 weeks' post-partum (8). In accordance with these observations, one might expect most thrombotic complications to occur in the post-partum period. However, in women with MPHV, this often occurs in the first trimester (9). Valve thrombosis may occur earlier in pregnancy due to sub-therapeutic anticoagulation during transition from VKA to heparins in the early stages of pregnancy (10). In addition, some women may discontinue VKA once a diagnosis of pregnancy is made due to concerns about the teratogenic effects of these agents. This may occur prior to the initiation of another anticoagulant agent, leading to lapses in anticoagulation.

Physiological changes during pregnancy also include a decrease in systemic vascular resistance, a 30-50% increase in cardiac output (due to an increase in stroke volume and pulse rate), and an increase in blood volume/red cell mass (11). During delivery, because of auto transfusion of blood from the uterus and pain-related sympathetic stimulation, cardiac output increases even further (11). This puts more strain on the heart and can exacerbate any previously present CD. Genitourinary system changes include an increase in the renal plasma flow rate at the end of the first trimester resulting in an increased glomerular filtration rate of about 50% (4,7). This increased glomerular filtration rate is maintained until the 36th week, dropping down towards pre-pregnancy levels thereafter (11).

1.3 Anticoagulant options

The choice of anticoagulation in women with MPHV during pregnancy is the most significant risk factor for thrombo-embolic complications. In the absence of randomized controlled trials, anticoagulant regimens have been based largely on prospective registries, observational studies and expert opinion (10, 12-16). A treatment regimen with low molecular weight heparin (LMWH) throughout pregnancy has been associated with the highest live birth rate as compared to VKA and sequential treatment with LMWH and VKA (12, 13, 15). VKA cross the placenta and have a dose-dependent relationship with increased adverse outcomes, such as miscarriage, stillbirth, and embryopathy, occurring predominantly at doses >5 mg daily. According to meta-analysis of 46 studies by D'Souza et al., of the anticoagulant agents in pregnancy, the rate of fetal wastage, defined as spontaneous abortion, therapeutic abortion, stillbirth, and neonatal death, was 19.2% in the low-dose (≤ 5 mg) warfarin group versus 63.9% in the high-dose group (12). Importantly, a heparin strategy in the first trimester followed by VKA in the remainder of pregnancy did not eliminate the risk of fetal wastage (22.7%), in contrast to a strategy of LMWH throughout pregnancy which was associated with a 12.2% rate of fetal wastage (12). Moreover VKA are not recommended in the first trimester owing to the highly variable rates of warfarin embryopathy (12, 17-19). Vitamin K antagonism suppresses carboxylation of gamma-carboxy- glutamic acid, a component of osteocalcin and other bone proteins, which may result in warfarin embryopathy, characterized by nasal cartilage hypoplasia. In the study by D'Souza et al., the live birth rate with LMWH was 92% (95% confidence interval [CI] 86.1–98.0) with no incidents of embryopathy or fetopathy. This was in contrast to the live birth rate of 79.9% (95% CI 74.3-85.6) with a 1.4% (95% CI 0.3-2.5) incidence of embryopathy or fetopathy with sequential therapy (12). LMWH does not cross the placenta, has higher bioavailability, less protein binding, is not teratogenic and offers several

advantages as compared to intravenous unfractionated heparin (20). Nonetheless, the changing pharmacodynamics of LMWH as a result of the increased volume of distribution and enhanced renal clearance during pregnancy requires close peak and/or trough anti-Xa monitoring (21, 22). LMWH, particularly at sub-therapeutic anti-Xa levels, has been associated with a higher incidence of maternal death, valve thrombosis and systemic thrombo-embolism (10, 23-25). D'Souza et al., reported a maternal mortality rate of 2.9% (95% CI 0.2-5.7) and 2.0% (95% CI 0.8-3.1) with the use of LMWH and sequential treatment respectively (12). Likewise, thrombo-embolic complications occurred in 8.7% (95% CI 3.9-13.4) and 5.8% (95% CI 3.8-7.7) with LMWH and sequential treatment respectively (12). Specifically, in a New Zealand study, by McClintock et al., 31 women had 47 pregnancies. In this series, 7 thrombotic complications occurred of which 5 were associated with enoxaparin treatment. These adverse outcomes were due to non-compliance and sub-therapeutic anti-Xa levels in each case (24). This emphasises the need for close monitoring and compliance which are essential for successful outcomes in pregnancy. Moreover, data from the United Kingdom Obstetric Surveillance System showed a maternal mortality rate of 9% with a severe morbidity risk of 41% in women with MPHV. Valve thrombosis occurred in 16% of patients while 9% had a cerebrovascular accident. Maternal mortalities occurred postpartum after discharge and in patients with double valve replacements, which have been associated with worse maternal outcomes (16). This study emphasises the need for close monitoring in a specialist centre to improve outcomes.

Based on current evidence, the best practice guidance from the American College of Cardiology/American Heart Association, British Society for Haematology and European Society of Cardiology guidelines recommend sequential treatment with switching to VKA between 12 and 36 weeks' gestation (Class I recommendation) (26-29). Adequate counselling

of women is required about the risk–benefit ratio associated with this treatment approach owing to the risks of central nervous system complications, miscarriages and stillbirths with VKA during the second and third trimesters (10). In order to safely balance the maternal and fetal risks associated with the various anticoagulation strategies, individualized management should be optimized at a specialist centre by a multidisciplinary team (26). The choice of anticoagulation should be considered in conjunction with risk factors for thrombo-embolism, namely the type, location and functioning of the MPHV; CD including heart failure, atrial fibrillation (AF) and infective endocarditis as well as a history of systemic thrombo-embolism. (26). Economic factors such as the availability and cost of treatment, access to laboratory testing and specialist care; compliance with treatment as well as maternal anticoagulant preference are also important considerations (30).

The preferred approach at the Specialist Cardiac Antenatal Clinic in Johannesburg South Africa has been a protocol of LMWH throughout pregnancy following the first publication of 15 women with MPHV in 2011 (31). This protocol has been designed to prevent maternal complications and includes regular review of patients' cardiovascular systems; close monitoring of peak anti–Xa levels as well as patient education (32).

1.4 Study Aim and Objectives

To review maternal and fetal outcomes in pregnant women with MPHV managed according to a protocol recommending LMWH throughout pregnancy in order to provide guidance on the management of this high risk population.

The objectives of this study are to:

- To review the maternal complications in pregnant women treated with LMWH
- To review the fetal complications in pregnant women treated with LMWH
- To review the anticoagulant characteristics of LMWH throughout pregnancy
- To investigate the cost implications of using LMWH throughout pregnancy, as compared to VKA

CHAPTER 2

METHODOLOGY

2.1 Study site

The study was performed at a quaternary teaching hospital attached to one of South Africa's nine medical schools in South Africa. The Department of Obstetrics and Gynaecology at the study site, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), provides quaternary services. It also serves as a referral centre for six regional and for districts hospitals as well as ten Midwife Obstetric units spread across three health districts. The study site delivers between 8000 to 9000 women per annum.

2.2 Study design and population

A retrospective study of pregnant women with MPHV and bio prosthetic heart valves attending the Specialist Cardiac Antenatal Clinic at CMJAH was performed. This is a referral clinic for women with CD in Johannesburg, South Africa including; RHD, cardiomyopathy, arrhythmia, congenital heart disease, pulmonary hypertension and hypertensive heart disease. Approximately 100 women attend the clinic per year, of which a 10% are women with prosthetic heart valves. All pregnant women with MPHV and bio prosthetic heart valves who required anticoagulation during the study period were included.

2.3 Data collection

The Department of Obstetrics and Gynaecology is organised into specialised units.

Details of women with CD receiving pregnancy care at the study site are kept in a

unit register. This information was used to retrieve clinical records from the Hospital Patient

Records Department. Data was collected using a purposefully designed Excel spread sheet.

The clinical records were reviewed of consecutive pregnant women with prosthetic heart valves requiring anticoagulation, between 1 July 2015 and 30 June 2023. The following patient information was collected: demographics, relevant cardiac, obstetric, delivery and postpartum information. Corresponding data on maternal and fetal outcomes were also collected. Antepartum and postpartum bleeding was assessed using the International Society of Thrombosis and Haemostasis Scientific and Standardization Subcommittee on Control of Anticoagulation bleeding assessment tool for minor, clinically relevant non-major and major bleeding events related to the use of anticoagulants during pregnancy and the postpartum period (33). Postpartum haemorrhage referred to bleeding by visual estimation during the first 24 hours (primary) or from 24 hours to six weeks after delivery (secondary). All bleeding events were evaluated by the researchers. Echocardiograms were routinely performed to assess for subclinical valve thrombosis, which is most often an incidental finding. Electrocardiograms and echocardiograms were collected at baseline and 36 weeks' gestation.

The data was anonymized and coded once all relevant information was collected. Permission to conduct the study was obtained from the Head of the Department of Obstetrics and Gynaecology and the Chief Executive Officer at the study site. This study was approved by the University of Witwatersrand Human Research and Ethics Committee (M-180901). Informed consent was not obtained from the study participants as the study was performed retrospectively.

All women were managed by a multi-disciplinary team which consisted of an obstetrician, cardiologist, obstetric medicine physician and haematologist. The choice of anticoagulation was considered in conjunction with risk factors for thrombo-embolism, economic factors and maternal preferences. In women receiving enoxaparin 12-hourly throughout pregnancy, doses were adjusted to achieve a peak anti-Xa of >1.0-1.2 IU /mL for valves in the mitral position and >0.8-1.2 IU/mL in the aortic position, 3 - 4 hours post injection. Thereafter anti-Xa levels were monitored weekly. In women receiving warfarin daily, doses were adjusted to achieve an international normalised ratio (INR) range of 2.5-3.5 (target 3.0). A cardiac and anaesthetic review was performed prior to a scheduled delivery (Appendix A).

Venous blood for anti-Xa and INR measurements was collected in 3.2% sodium citrate (Becton-Dickinson, Oxford, UK). Analysis was performed on the STA-R Max ® automated coagulation analyser (Diagnostica Stago, Asnières sur Seine, France) at the CMJAH laboratory.

2.4 Data analysis

The statistical unit of analysis was pregnancy. Data was exported from the Excel spread sheet and analysed using Statistica 13.2 software (Palo Alto, California, USA). Comparisons for continuous measurements were performed using a one-way ANOVA test with Sheffes's post hoc test or a Kruskal-Wallis test. Comparisons for categorical measurements were performed using chi-square test or Fisher's exact test when necessary. The median time to intra-uterine fetal deaths were estimated using the Kaplan-Meier method. Statistical significance was set at p value of <0.05.

CHAPTER 3

RESULTS

3.1 Baseline characteristics

The baseline characteristics of the 53 pregnancies in 51 women are described in Table 1. There were 50 pregnancies with MPHV and three with tissue valves, on anticoagulation for comorbid AF. Associated co-morbidities included chronic hypertension (17.0%), previous cerebrovascular event (5.7%), epilepsy (1.9%) and human immunodeficiency virus (HIV) (22.6 %). The majority living with HIV (n=8, 66.7%) were virologically suppressed on first line antiretroviral therapy for a mean ± standard deviation (SD) duration of 3.5 ± 1.1 years. The baseline cardiac characteristics are described in Table 2. There were 10 (18.9%) pregnancies with double valve replacements in the aortic and mitral valve positions. Echocardiograms were performed at baseline at a mean gestational age of 11.1 ± 6.0 weeks and at 36 weeks' gestation.

Table 1. Baseline characteristics

Characteristics	
Number of pregnancies	53
Demographics	
Gestation age at presentation (weeks), mean ± SD	11.1 ± 6.0
Age at study entry (years), mean ± SD	32.8 ± 5.7
BMI (kg/m^2), mean ± SD	29.8 ± 6.3
African ethnicity (n,%)	52 (98.1)
Married/stable relationship (n,%)	16.0 (30.2)
Employed (n,%)	15.0 (28.3)
Smoker (n,%)	2.0 (3.8)
Parity, median [IQR]	1.0 [1.0]
Gravidity, median [IQR]	3.0 [2.0]
Previous history of late miscarriages (n,%)	7.0 (13.2)
Previous history of stillbirth/neonatal death	7.0 (13.2)
Baseline laboratory characteristics	
HIV infected (n,%)	12.0 (22.6.)
CD4 count of HIV infected (x 10^6/L), mean ± SD (ref: 561-2051)	420.2 ± 175.7
HIV viral load of HIV infected, (>50 copies/ml) (n,%)	4.0 (33.3)
Syphilis (n,%)	0.0 (0.0)
White cell count (x 10^9/L), mean ± SD (ref: 3.9-12.6)	7.4 ± 3.0
Haemoglobin (g/dL), mean ± SD (ref: 11.6-16.4)	11.6 ± 2.0
Platelet count (x 10^9/L), mean ± SD (ref: 186-454)	250.0 ± 68.9
Urea (mmol/L), mean ± SD (ref: 2.1-7.1)	3.0 ± 1.1
Creatinine (umol/L), mean ± SD (ref: 64-104)	62.2 ± 12.4
Thyroxine (pmol/L), mean ± SD (ref: 12-22)	15.0 ± 2.3
Thyroid stimulating hormone (mIU/L), mean ± SD (ref: 0.2-4.2)	2.1 ± 1.0
Key: SD, standard deviation, IQR, inter-quartile range; BMI, body mass index; HIV, human immunodeficiency virus	

Table 2. Baseline cardiac characteristics

Cardiac Characteristics	
Number of pregnancies	53
Valve type (n, %)	
Mechanical	50.0 (94.3)
Tissue	3.0 (5.7)
Reason for valve replacement (n, %)	
Rheumatic heart disease	52.0 (98.1)
Congenital heart disease	1.0 (1.9)
Valve position (n, %)	
Mitral	32.0 (60.4)
Aortic	10.0 (18.9)
Mitral and aortic	10.0 (18.9)
Pulmonary	1.0 (1.9)
Age at valve replacement (years), mean ± SD	24.3 ± 9.0
Interval from valve replacement to current pregnancy (years), mean ± SD	8.7 ± 6.8
New York Heart Association functional class (n, %)	
I/II	51.0 (96.2)
III/IV	2.0 (3.8)
Modified world health organisation class (n, %)	
II	3.0 (5.7)
III	49.0 (92.5)
IV	1.0 (1.9)
Vital signs, mean ± SD	
Heart rate (bpm)	87.1 ± 10.7
SBP (mmHg)	119.6 ± 13.6
DBP (mmHg)	71.7 ± 11.1
Baseline ECG (n, %)	
Sinus rhythm	46.0 (86.8)
Atrial fibrillation	7.0 (13.2)
Baseline Echocardiogram	

Left ventricular ejection fraction (%), mean ± SD	56.5 ± 10.9
Left atrium (mm), mean ± SD	42.7 ± 11.6
Tricuspid annular plane systolic excursion (mm), mean ± SD	18.8 ± 4.3
Pulmonary artery pressure (mm), mean ± SD	31.5 ± 8.4
Inferior vena cava collapsing (n, %)	53.0 (100.0)
Paravalvular leaks (n, %)	2.0 (3.8)
Valve thrombosis (n, %)	1.0 (1.9)
Stuck valve leaflet (n, %)	1.0 (1.9)
Co-morbidities (n, %)	
Chronic hypertension	9.0 (17.0)
Previous cerebrovascular event	3.0 (5.7)
Epilepsy	1.0 (1.9)
Cardiac medications (n, %)	
Aspirin	2.0 (3.8)
Digoxin	3.0 (5.7)
Diuretics	26 (49.1)
ACE inhibitor	9.0 (17.0)
Beta-blocker	21.0 (39.6)
Calcium channel blocker	6.0 (11.3)
Key: SD, standard deviation, bpm,beats per minute, SBP, systolic blood pressure, DBP, diastolic blood pressure, ECG, electrocardiogram	

3.2 Anticoagulation characteristics

In 48 pregnancies, anti-Xa adjusted enoxaparin was commenced at 10.5 ± 5.6 weeks' gestation at diagnosis of pregnancy either at the anticoagulation clinic or first antenatal clinic visit. (Table 3). Mean enoxaparin doses in the second and third trimesters were higher than first trimester doses ($p<0.002$ and $p<0.03$ respectively). Similarly, anti-Xa levels in the second and third trimesters increased as compared to the first trimester ($p<0.001$ and $p<0.008$ respectively) (Figures 1 and 2). Warfarin was continued in five pregnancies. There were 10 (18.9%) pregnancies in women with mitral and aortic valve replacements for RHD detailed in Table 4.

Table 3. Anticoagulation characteristics

Characteristics	
Number of pregnancies	53
Pregnancy	
Gestational age first antenatal visit (weeks), mean ± SD	11.1 ± 6.0
Warfarin dose at conception, n (%) [a] ≤ 35 mg/week > 35 mg/week	 22.0 (47.8) 24.0 (52.2)
International normalized ratio at first visit, mean ± SD	1.9 [1.2]
Gestational age enoxaparin commenced (weeks), mean ± SD [b]	10.5 ± 5.6
Delivery	
Enoxaparin discontinued prior to delivery (hours) , mean ± SD	20.4 ± 7.7
Enoxaparin restarted after delivery (hours) , mean ± SD	11.2 ± 6.8
Enoxaparin dose after delivery (mg), median [IQR]	60.0 [7.5]
Warfarin restarted after delivery (days) , mean ± SD	3.0 ± 1.0
International normalized ratio at discharge, mean ± SD	2.4 ± 0.5
Time to achieve a therapeutic International normalized ratio at discharge (days), mean ± SD	7.0 ± 2.0
Warfarin weekly dose at discharge (mg), median [IQR]	42.5 [10.0]
Key: SD, standard deviation, IQR, inter-quartile range [a] in 50 pregnancies- 1 switched to enoxaparin pre-conceptually; 2 defaulted anticoagulation prior to conception	

[b] in 48 pregnancies

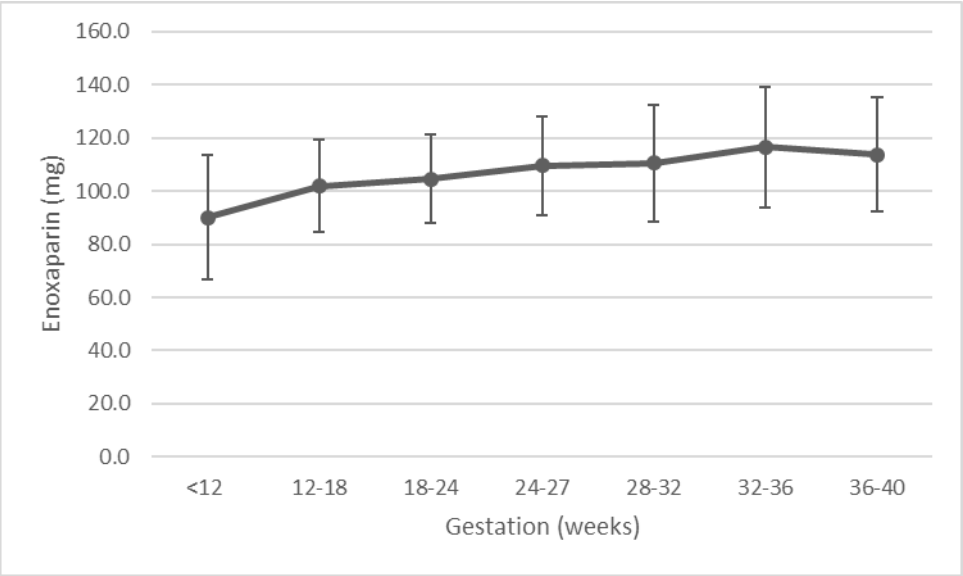


Figure 1. Mean enoxaparin dose over the three trimesters ($p<0.004$)

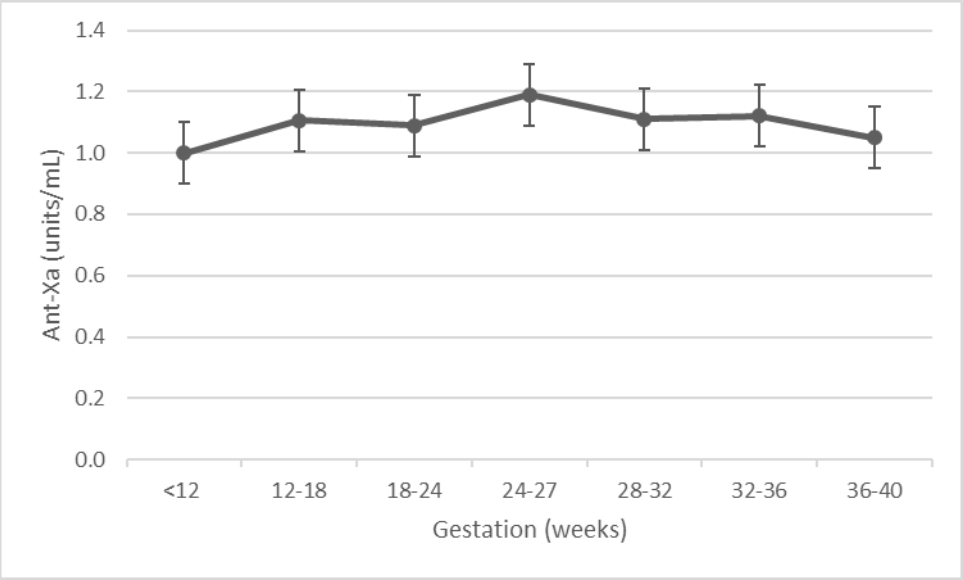


Figure 2. Mean anti-Xa levels over the three trimesters ($p<0.001$)

Table 4. Anticoagulation characteristics pregnancies in women with mitral and aortic valve replacements

Characteristics	
Number of pregnancies	10
Pregnancy	
Warfarin dose at conception, n (%)*	
≤ 35 mg/week	3.0 (30.0)
> 35 mg/week	5.0 (50.0)
International normalized ratio at first visit, mean ± SD	1.7 ± 0.4
Gestational age enoxaparin commenced (weeks), mean ± SD	9.4 ± 4.7
First-trimester anti-Xa levels, mean ± SD	1.1 ± 0.1
Second-trimester anti-Xa levels, mean ± SD	1.2 ± 0.2
Third-trimester anti-Xa levels, mean ± SD	1.2 ± 0.1
Delivery**	
Enoxaparin discontinued prior to delivery (hours) , mean ± SD	21.3 ± 5.9
Enoxaparin restarted after delivery (hours) , mean ± SD	13.0 ± 5.9
Enoxaparin dose after delivery (mg), median [IQR]	60.0 [0.0]
Warfarin restarted after delivery (days) , mean ± SD	2.9 ± 1.1
International normalized ratio at discharge, mean ± SD	2.8 ± 0.7
Time to achieve a therapeutic International normalized ratio at discharge (days), mean ± SD	5.4 ± 1.9
Warfarin weekly dose at discharge (mg), median [IQR]	42.5 [10.0]
Live births (n, %)	7 (70.0)
Miscarriage (n, %)	1 (10.0)
Termination of pregnancy (n, %)	1 (10.0)
Key: SD, standard deviation, IQR, inter-quartile range *Enoxaparin preconception in 1 pregnancy and 1 defaulted warfarin preconception **1 delivery at another centre.	

3.3 Maternal and fetal outcomes

The live birth rate was 52.8% (95% confidence interval [CI] 39.7-65.6) (Table 5.). The live birth rates on enoxaparin and warfarin were 56.3% (95% CI 42.3-69.3) and 20.0 % (95% CI 2.0-64.0) respectively. The miscarriage rate was 22.6% (95% CI 13.3-35.7) at a mean gestation of 11.3 ± 3.7 weeks, of which 6 (11.3 %) were anembryonic pregnancies. These pregnancies which resulted in miscarriage were switched from warfarin to anti-Xa adjusted enoxaparin at 9.0 ± 4.1 weeks' gestation. There were four (7.5%) intra-uterine fetal deaths on warfarin (Table 6 and Figure 3.). These occurred in a pregnancy on warfarin 52.5mg weekly with AF at 32 weeks' gestation; a pregnancy on warfarin 40 mg weekly with AF at 26 weeks' gestation; an unbooked pregnancy on warfarin 25mg weekly which presented with a birth before arrival of 1800g and a pregnancy with a previous cerebrovascular event on warfarin 40mg weekly which presented at 21 weeks' gestation with an intra-uterine fetal death. There were no intra-uterine fetal deaths on enoxaparin. Warfarin therapy was associated with mid-facial hypoplasia on ultrasound in a pregnancy on a weekly warfarin dose of 25mg until 8 weeks' gestation. In another on a weekly warfarin dose of 52.5mg, ultrasound scan at 11 weeks' gestation revealed a posterior encepholocele associated with over-anticoagulation (INR 6.78). On post-mortem histological assessment no cerebellar or cerebral tissue was present in the skull confirming anencephaly (34).

There was one (1.9%) mitral valve thrombosis at first presentation and one (1.9%) stuck valve during pregnancy on echocardiography which occurred in pregnancies who defaulted warfarin. Of the 46 (86.8%) pregnancies in sinus rhythm at presentation, one developed AF at 23 weeks' gestation. Additionally, another developed a supraventricular tachycardia at 35 weeks'

gestation. The patient failed cardioversion with the administration of intravenous adenosine. It was effectively controlled with amiodarone. There were no maternal deaths.

The incidence of antepartum/secondary postpartum bleeding in 51 pregnancies was 29.4% (95% CI 18.6-43.1) of which 9.8% (95% CI 3.8-21.4) were classified as major bleeds (two patients delivered at another center) (Table 7.). The incidence of primary postpartum bleeding was 5.9% (95% CI 1.4-16.9) of which 3.9% (95% CI 0.3-14.0) were major bleeds. Secondary postpartum, self-limited oozing from the surgical site was observed in three (5.9 %) pregnancies. The dose of enoxaparin was reduced in two.

Table 5. Obstetric and delivery characteristics

Characteristics	
Number of pregnancies	53
Maternal complications	
Arrhythmia (n, %)	2 (3.8)
Heart failure (n, %)	2 (3.8)
Pre-eclampsia and FGR (n, %)	3 (5.7)
Anaemia (requiring transfusion) (n, %)	11 (20.8)
Number of hospital admissions antepartum, median [IQR]	1 [1]
Embryopathy (n, %)	1 (1.9)
Fetopathy (n, %)	1 (1.9)
Delivery characteristics	
Live births (n, %) [a]	28 (52.8)
Intra-uterine fetal death (n, %)	4 (7.5)
Miscarriage (n, %)	12 (22.6)
Termination of pregnancy (n, %)	7 (13.2)
Gestational age delivery (weeks), mean ± SD [b]	35.8 ± 2.9
Birthweight (g), mean ± SD [b]	2407.1 ± 634.4
Apgar at 5 minutes, mean ± SD [b]	9.0 ± 0.9
Mode of delivery [b]	
Normal vaginal delivery (induction of labour) (n, %)	5 (17.9)
Normal vaginal delivery (spontaneous) (n, %)	2 (7.1)
Elective caesarean section (n, %)	11 (39.3)
Emergency caesarean section (n, %)	10 (35.7)
Anesthesia (n, %) [c]	
General	11 (52.4)
Epidural	3 (14.3)
Spinal	7 (33.3)
Estimated blood loss at delivery (mL), median [IQR] [b]	450 [425]
Wound sepsis (n, %)	1 (2.0)
Postpartum characteristics [a]	
Hospital duration after delivery, mean ± SD	9.3 ± 3.9
Breastfeeding (n, %)	20 (71.4)
Contraception (n, %)	
Contraceptive injection	20 (39.2)

Bilateral Tubal Ligation	12 (23.5)
Contraceptive implant	2 (3.9)
Intrauterine contraceptive device	1 (2.0)

Key: SD, standard deviation, IQR, inter-quartile range; FGR, fetal growth restriction

[a] 2 deliveries at another centre.owing to a hospital fire which disrupted services at CMJAH

[b] of live births

[c] of caesarean deliveries

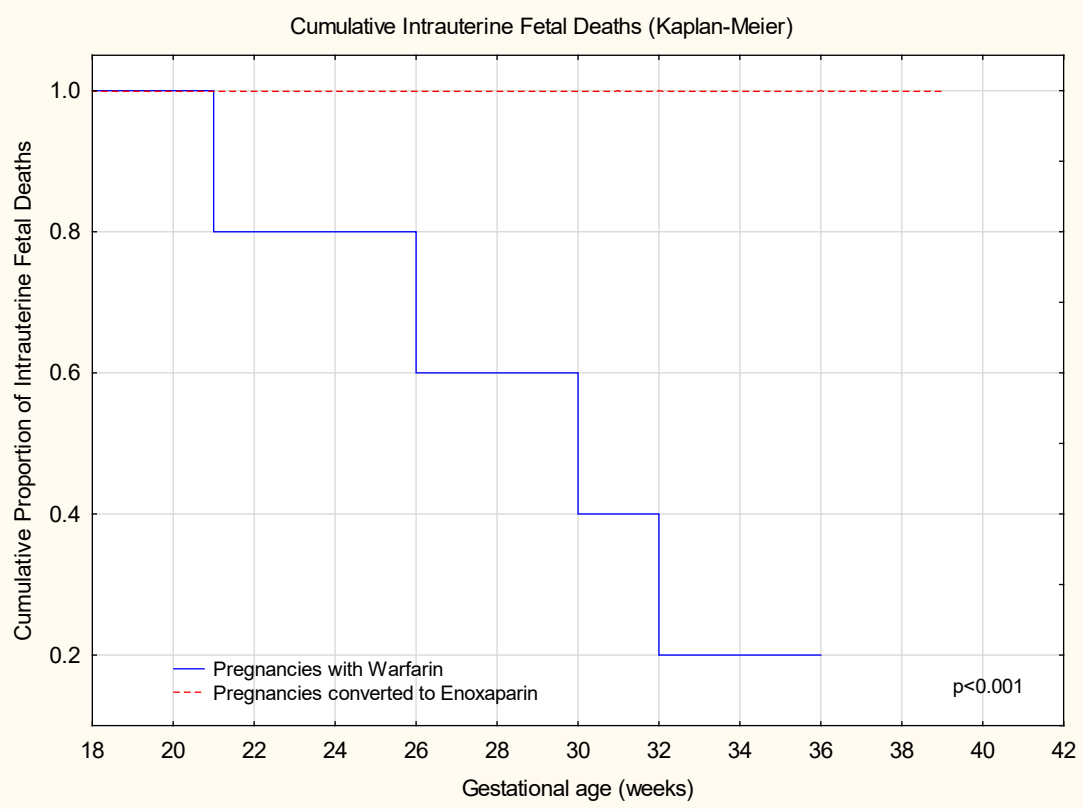


Figure 3. Kaplan–Meier curves of adjudicated intrauterine fetal deaths in the overall study period

Table 6. Outcomes on Warfarin

Diagnosis	**Indication for warfarin**	**Outcome**
Mitral valve replacement and atrial fibrillation	Atrial fibrillation	Intra-uterine fetal death at 32 weeks' gestation
Mitral valve replacement	Unbooked	Live birth at 36 weeks' gestation
Mitral valve replacement and atrial fibrillation	Atrial fibrillation	Intra-uterine fetal death at 26 weeks' gestation Midfacial hypoplasia
Mitral valve replacement and pacemaker for heart block	Unbooked	Intra-uterine fetal death at 30 weeks' gestation
Mitral valve replacement and stroke	Previous cerebrovascular event	Intra-uterine fetal death at 21 weeks' gestation

Table 7. Maternal Bleeding events

	Description
Antepartum/secondary postpartum	
Major Bleeding	Pregnancy with aortic valve replacement Vaginal bleeding (clots) at day 10 post emergency CS and transfusion. INR 4.58 and Hb 7.3 g/dl on warfarin 42.5 mg/week.
	Pregnancy with mitral valve replacement Antepartum placenta praevia at 30 weeks on enoxaparin 90 mg sc bd
	Pregnancy with mitral valve replacement Antepartum haematuria on warfarin 35 mg/week at 11 weeks. INR 6.78. Received fresh frozen plasma.
	Pregnancy with tissue valve replacement and AF Postpartum vaginal bleeding 17 days post NVD on enoxaparin 40 mg sc bd. Evacuation of retained products of conception performed.
	Pregnancy with aortic valve replacement Vulval haematoma 2 days post NVD on enoxaparin 60 mg sc bd. 300ml of blood expelled.
Clinically relevant non major bleeding	Pregnancy with mitral valve replacement Antepartum epistaxis requiring admission at 25 weeks on enoxaparin 100 mg sc bd
	Vaginal bleeding related to early pregnancy loss x 7
Minor bleeding	Pregnancy with mitral valve replacement Antepartum vaginal bleeding prompting a face-to-face evaluation at 34 weeks on enoxaparin 120 mg sc bd
	Pregnancy with aortic valve replacement Antepartum vaginal bleeding prompting a face-to-face evaluation at 28 weeks on enoxaparin 120 mg sc bd
Primary postpartum	
Major Bleeding	Pregnancy with mitral valve replacement Postpartum blood loss ≥1000 mL at 28 weeks' gestation leading to transfusion post emergency CS for a non-reassuring fetal heart rate. Enoxaparin interval to delivery 12h.
	Pregnancy with mitral valve replacement Postpartum blood loss ≥1000 mL leading to transfusion and surgical evacuation of pelvic haematoma post assisted spontaneous NVD at 36 weeks' gestation in unbooked pregnancy on warfarin 42.5 mg/week.
Minor bleeding	Pregnancy with mitral valve replacement

	Postpartum blood loss ≥1000 mL post elective CS for cardiac indications. Enoxaparin interval to delivery 24h.
Key: CS, caesarean section; INR, international normalised ratio; NVD, normal vaginal delivery	

3.4 Delivery characteristics

Indications for caesarean section in 21/28 (75.0 %) pregnancies, included previous caesarean section (n=4,19.0 %), cardiac reasons (n=9, 42.9 %) and obstetric reasons (n=8, 38.1%). After delivery, 47 (92.2%) women were admitted to high care and four (7.8%) neonates were admitted to the neonatal intensive care unit for respiratory distress. There was one early neonatal death (day 2) secondary to severe pre-eclampsia with fetal affectation and growth restriction. An emergency caesarean section was performed at 31 weeks' gestation for severely abnormal dopplers and fetal distress. All neonates born to mothers living with HIV tested negative on HIV polymerase chain reaction.

3.5 Cost of enoxaparin versus warfarin

Table 8. describes the cost of enoxaparin as compared to warfarin throughout pregnancy in the South African public sector.

Table 8. Cost comparison of warfarin versus enoxaparin in the antepartum period

	Warfarin and IV UFH*	**Enoxaparin***
Price per drug	Warfarin 7.5mg 0-6 weeks and 12-36 weeks: R 238.28 IV UFH 6-12 weeks and 36-38 weeks: R 1,282.80	Warfarin 7.5mg until 6 weeks R 45.82 Enoxaparin 100mg bd 6-38 weeks: R 137,449.91
Cost laboratory test	INR x 8: R 934.65 aPTT x 112: R 13,192.09	Anti-Xa x 32: R 18,307.23
Average travel cost clinic visits	x 7: R 549.67	x 32: R 2,471.94
Loss of income	x 63: R 9,162.23	x 32: R 4,631.54
Hospital admission Conversion warfarin to enoxaparin first trimester Conversion warfarin to enoxaparin third trimester	 x42 days R 107,747.87 x 14 days: R 35, 906.81	 X 3 days: R 7,688.73 -
Total	**R 169,014.40**	**R170,595.17**
Key: IV UFH, intravenous unfractionated heparin; INR international normalized ratio, aPTT, activated partial thromboplastin time *based on mean dose of patient population		

CHAPTER 4

DISCUSSION

In this study of consecutive pregnancies in women from a single centre in South Africa with MPHV, RHD was the most common indication for heart valve replacement. The majority of were of African ethnicity and with a mean age of 33 years. This cohort was older than that described by Chitsike et al., (mean age of 26 years) and Sliwa et al., (mean age of 29) from this region (31, 35). The rates of HIV were consistent with the national antenatal rates of HIV infection. The majority were virologically suppressed on first line antiretroviral therapy. No participants tested positive for syphilis. Only 28% were gainfully employed and 30% were in a stable or married relationship. Owing to the socially disadvantaged backgrounds of this cohort it was not feasible for all women to book for antenatal care as soon as pregnancy was confirmed. Access to specialised services in academic hospitals and the loss of income as a result of frequent hospital visits are also important factors which impact on the management of pregnant women with MPHV.

Pregnancy in individuals with MPHV is considered very high risk and the majority were classified as modified World Health Organisation risk category III (27). In this category, the parturient is at increased risk of both maternal mortality and severe morbidity. Of the participants with MPHV for RHD, as expected 60% were in the mitral position. In addition, there were 10 (19%) women with double valve replacements in both the mitral and aortic valve positions. These women were managed with LMWH throughout pregnancy and this was continued until delivery. Peak anti-Xa levels, monitored weekly, were maintained between the recommended range of >1.0 to 1.2 U/mL implying a high degree of anticoagulation. The live

birth rate was 56% on enoxaparin. Factors that increase the risk of valve thrombosis and systemic thrombo-embolism include first generation valves, mechanical valves in the mitral position and double valves (29). First generation valves are uncommon because of their thrombogenic potential as compared to the newer generation valves. Recent guidelines continue to support the preferential use of VKA in women at increased risk of valve thrombosis (26). We, however, observed no valve thrombosis, thrombo-embolic complications or maternal deaths in pregnancies with double valves on LMWH with therapeutic anti-Xa levels.

The use of LMWH for anticoagulation in pregnant women with MPHV has been a topic of much controversy and discussion. Since the first publication from CMJAH by Chitsike et al., in 2011, this institution has used enoxaparin as the preferred anticoagulant of choice for patients with MPHV after extensive patient counselling (31). This is one of the three most commonly used and recommended strategies in contemporary practice. The European Society of Cardiology and American Heart Association guidelines suggest the use of LMWH if the warfarin dose is >5 milligrams/day. However when considering the use of LMWH, other patient specific factors such should be guided by multidisciplinary discussions (27, 28). The South African guidelines recommend subcutaneous LMWH in preference to unfractionated heparin as it has more predictable pharmacokinetics and less risk of allergic reactions, heparin-induced thrombocytopenia and osteoporosis (32). Enoxaparin can be administered safely during pregnancy to women with MPHV provided there is dosage adjustments throughout pregnancy to maintain a peak anti- Xa of >1 to 1.2 U/mL resulting in a high degree of anticoagulation. Chitsike et al., reported no valve thrombosis, bleeding episodes were minimal and no maternal deaths were reported (31). Extensive experience with LMWH has been gained at this institution over the last 13 years. Similarly, in the current study, we observed no valve

thrombosis, thrombo-embolic complications or maternal deaths in pregnancies on LMWH with therapeutic anti-Xa levels.

A significant increase in the second and third trimester enoxaparin doses, as compared to first trimester doses was required to achieve a therapeutic anti-Xa level. Chitsike et al., have also described that the highest rate of change in enoxaparin dose occurred just prior to and during the third trimester (after 27 weeks' gestation). (31). In pregnancy the increases in volume of distribution, renal blood flow with resultant increase in glomerular filtration rate alter the renal excretion of enoxaparin. Peak anti-Xa monitoring was done 3-4 hours after the morning dose of enoxaparin. Trough levels were not measured. Goland et al., however, advise doing both trough and peak levels. Their analysis of 187 paired (trough and peak) anti-Xa levels in patients receiving LMWH twice daily showed sub-therapeutic trough levels in 40% of patients when the peak anti-Xa level was between 1.0 and 1.2 U/mL (36). Currently, however, there is insufficient evidence to recommend the routine use of trough levels (22).

The reason for valve replacements in this cohort was predominantly secondary to RHD. RHD in the REMEDY (Global Rheumatic Heart Disease registry) study in low-middle income countries was complicated by congestive cardiac failure, pulmonary hypertension, AF, stroke, infective endocarditis and major bleeding (37). The highest risk period for valve thrombosis is in the first trimester during the transition from VKA to LMWH (10). In this study, at the first antenatal visit, the median INR measured was sub-therapeutic (INR 1.9 [1.2]) owing to maternal concerns for warfarin embryopathy in the first trimester. Additionally, there were three pregnancies who defaulted warfarin prior to conception. This resulted in a mitral valve

thrombosis in one and a stuck valve in another. Low dose aspirin in addition to anticoagulation has been recommended to reduce the risk of valve thrombosis (10, 38). In this group, low dose aspirin was prescribed in 4% as anti-platelet therapy but not as adjuvant therapy, however this is not the practice in our institution. Another important risk factor during pregnancy for valve thrombosis is poor compliance with LMWH owing to the burden of twice-daily subcutaneous injections (24). This necessitates a discussion of the advantages and disadvantages associated with the different anticoagulation options as well as maternal preference to ensure adherence. Lastly, there were 2 paravalvular leaks and these were both managed conservatively with no adverse clinical concerns.

In this cohort, the live birth rate was 53% which is comparable to the Registry of Pregnancy and Cardiac disease European registry (10). Of the live births, 1 was on warfarin and 27 were on enoxaparin (6). At conception, there was no significant difference in the weekly warfarin dosage. A dose dependent relationship has been inconsistently reported (10). Anti-Xa adjusted enoxaparin was commenced at a mean of 11 weeks' gestation in 48 of the 53 pregnancies. Women with MPHV attending the Anticoagulation Clinic Services at CMJAH, receive conception advice including frequent pregnancy tests and warfarin substitution in the first trimester. The current recommendation is to bridge to enoxaparin at 6-12 weeks' gestation to avoid warfarin embryopathy (26). Warfarin is also associated with an increased risk of miscarriage and stillbirths (13, 15, 39). The fetal complication rates in this study included 12 (23%) miscarriages at a mean gestation of 11 weeks. Additionally, in pregnancies on warfarin there were four (8%) intra-uterine fetal deaths and embryopathy/fetopathy in two (4%). Over-anticoagulation with warfarin in the first trimester in one pregnancy caused intrauterine

haemorrhage and fetopathy (34). This highlights the importance of close anticoagulant therapy monitoring.

Obstetric haemorrhage, both antepartum and postpartum is known to be a major contributor to maternal morbidity and mortality world-wide. In South Africa the institutional maternal mortality ratio for obstetric haemorrhage accounted for 23% of maternal deaths in 2017-2021 (2). A crucial question to ask is whether or not therapeutic LMWH during pregnancy increases bleeding risk? Regarding delivery of the parturient, delivery occurs during an anticoagulation-free "window." This is done to avoid maternal haemorrhage while balancing the risk of thrombosis. Therefore, it is important to identify the optimal duration of this window. LMWH is commenced after delivery within 6-12 hours provided there is no clinical concern for haemorrhage (40). In this study, the rate of primary postpartum bleeding was 6%. This can be attributed in part to a scheduled delivery in 93% with discontinuation of enoxaparin at a mean of 20 hours prior to delivery. After delivery, enoxaparin was restarted at a mean of 11 hours once haemostasis was adequate at a reduced median enoxaparin dose of 60mg. The antepartum/secondary postpartum bleeding rate was 29%, consistent with similar studies (10, 16, 23, 41, 42). In a Cape Town study, of 29 patients on intravenous unfractionated heparin from 6-12 weeks' gestation and peripartum, and warfarin from 12-36 weeks, major haemorrhage was a significant concern accounting for 21% (39). In the UK Obstetric Surveillance System study, antepartum and postpartum haemorrhagic complications occurred in 17% and 32% respectively (16). Caution, however, is required when interpreting these studies, because of the use of non-standardized definitions of bleeding. Likewise in this study population, the rate of caesarean section was high at 75 % (39, 41). A scheduled vaginal delivery, in most situations, is the preferred mode of delivery (43). Furthermore, warfarin

therapy was restarted at a mean of 3 days. More recently, British Society for Haematology Guidelines recommend delaying a VKA to 5–7 days post-delivery to reduce the risk of bleeding.

Outpatient regimens with the administration of subcutaneously administered LMWH reduces the need for hospital admissions and improves overall patient satisfaction. In a study from Cape Town, the mean hospital stay was 41 days owing to the use of intravenous unfractionated heparin from 6 to 12 weeks' gestation and peripartum (39). Admission to hospital is expensive. Moreover, long hospital stays contribute negatively to patient wellbeing and quality of life. Unfractionated heparin is not routinely used at CMJAH as it is difficult to administer and monitor intravenously and is associated with a higher rate of valve thrombosis (12). While the use of anti-Xa adjusted LMWH in a low-middle-income country such as SA is a cost-effective option, practically, anti-Xa monitoring has several limitations. In low-middle income settings, these chromogenic assays are expensive and are not routinely available (9). Furthermore, the timing of the assay is important for accurate interpretation.

Several limitations of this study warrant consideration. Firstly, the study population were heterogeneous and included pregnancies with bio-prosthetic valves. Secondly, bleeding was determined by visual estimation, which is increasingly recognized as an unreliable measure of bleeding. This may have resulted in underestimation of bleeding events. Thirdly, this study could not assess for predictors of bleeding, which merits further investigation. Lastly, the sample size was small as this is a rare condition. Moreover, during the study period services at CMJAH were interrupted because of a fire that broke out at the hospital on 16 April 2021.

Following this highly specialised clinical services including intensive care, neonatal and maternal care services only became available in 2023. The recent British Society for Haematology guideline comments on the limited evidence regarding optimal management of patients with MPHV (26). This study, although small, adds to the evidence that the use of anti-Xa adjusted LMWH throughout pregnancy was not associated with thrombo-embolic complications or maternal deaths.

CHAPTER 5

CONCLUSION

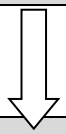
Patients with MPHV are at an increased risk of both maternal and fetal complications. The risks of haemorrhage, thrombosis and fetal concerns such as miscarriage and congenital abnormalities are an ever present threat. As in a previous study from the same institution, our data show that anti-Xa adjusted LMWH may be administered safely in pregnant women with MPHV. There were no thrombo-embolic complications or maternal deaths in pregnancies managed with anti-Xa adjusted LMWH throughout pregnancy. The rates of bleeding on LMWH were consistent with similar studies and can be used to inform pregnant women of the risks of potential bleeding. The monitoring of the anti-Xa is crucial with dosage adjustments throughout pregnancy to maintain a peak anti-Xa of >1.0-1.2 U/mL. Our recommendations remain the careful counselling of pregnant women with MPHV about the potential consequences of pregnancy and anticoagulation (risks associated with available options); and multidisciplinary cardio-obstetric care throughout pregnancy, delivery and in the postpartum period.

Appendices

Appendix A: Recommended protocol for pregnancy with mechanical prosthetic heart valves

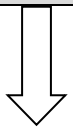
Antenatal

- Present early to a specialist antenatal clinic when menstruation is delayed
- A multidisciplinary team needs to be involved in the management of pregnancy, including an obstetrician, a cardiologist and a haematologist
- First visit - full history and examination, including cardiac and obstetric review with fetal ultrasound examination
- Switch to subcutaneous LMWH, e.g. enoxaparin 1 mg/kg 12-hourly
- Dose adjust to achieve a peak anti-Xa level >1.0 - 1.2 U/mL for valves in the mitral position and >0.8 - 1.0 U/mL) for valves in the aortic position, 3 - 4 hours post injection
- Thereafter anti-Xa levels should be monitored, ideally weekly
- Baseline investigations include FBC, U&E, Urine MC&S, 12-lead ECG and transthoracic echocardiography
- Counsel regarding alternative anticoagulant options from the 13th week including substitution with warfarin from 13 weeks until 36 weeks and associated fetal risks
- Follow-up antenatal visits- routine obstetric management, in addition to a history of bleeding, valve thrombosis, focal neurological signs and symptoms, haematological cardiac and neurological examination



Delivery

- Delivery at 38 weeks' gestation
- Warfarin: Discontinue 2 weeks prior to delivery and switch to LMWH
- LMWH: Admit and stop LMWH 24 hours prior to a scheduled delivery. Mode of delivery is determined according to obstetric indications
- If the patient has not delivered within 24 hours of the last dose of LMWH, consider administering a prophylactic dose of LMWH, in consultation with the haematologist and anaesthetist
- Neuraxial anaesthesia/analgesia, in consultation with the haematologist and anaesthetist
- should be delayed for at least 24 hours after the last treatment dose and 12 hours after the last prophylactic dose of LMWH
- Caesarean delivery can be safely performed at least 24 hours after the last treatment dose and 12 hours after the last prophylactic dose of LMWH
- If an emergency delivery is necessary and the patient is on therapeutic LMWH, protamine sulphate should be considered in consultation with the haematologist and anaesthetist. It will however only partially reverse the anticoagulant effect of LMWH.



Postpartum

- Neonate: Examination for warfarin embryopathy
- Maternal management: Restart heparin therapy 6 - 12 hours post-delivery, or later if there is any evidence of bleeding from the surgical site
- Neuraxial catheters may be removed no sooner than 24 hours after the last treatment dose and 12 hours after the last prophylactic dose of LMWH
- LMWH should be started at least 6 hours after removal of neuraxial catheters. LMWH should be delayed at least 24 hours if there is blood in the needle or neuraxial catheter during needle insertion.
- Neurological monitoring is mandatory for a minimum of 12 hours and ideally for 72 hours after neuraxial blockade
- LMWH: Restart at half the pre-delivery antepartum dose for the first 24 hours. Adjust dose to achieve an anti-Xa level of >0.8 - 1.0 U/mL
- Start warfarin at prior dose after day 3 of LMWH to reduce the risk of bleeding
- Stop LMWH once INR is therapeutic (2.5 - 3.5)
- Discharge to follow-up at an anticoagulation clinic (as per INR), obstetrics and cardiology at 6 weeks postpartum
- Discuss contraception and breastfeeding or formula feeding

Supplemental Fig. 1. Suggested regimen for anticoagulation in pregnant patients with mechanical heart valves at CMJAH.

Appendix B: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr H Rhemtula

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M231092

NAME: (Principal Investigator)	Dr H Rhemtula **DEGREE:** MSc (Med)
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital
TITLE:	*The use of low molecular weight heparin in pregnant women with mechanical and bio-prosthetic heart valves; an eight year experience at an academic hospital* Change of study title noted on 7 August 2024
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Renewal of M18/09/01 - expired on 2023/11/05
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office <Nicoleen.Potgieter@wits.ac.za>
SUPERVISORS:	Not applicable
APPROVED BY:	Professor P Ruff, Chairperson, HREC (Medical)

DATE OF APPROVAL: 7 November 2023 **EXPIRY DATE:** 6 November 2028

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report** in the format available at https://wits.ac.za/research/researcher-support/research-ethics/ethics-committees/. This report is due annually, for the duration of the Clearance Certificate, beginning on the first anniversary of Date of Approval above. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date

Appendix C: Similarity report

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by Haroun Rhemtula

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CHAPTER 6

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