Haemorrhage and Other Complications in Pregnant Women on Anticoagulation for Mechanical Heart Valves; a Prospective Observational Cohort Study

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KRVSAR001

Submitted to the University of Cape Town in fulfilment of the degree

Master of Medicine (MMed) in Medicine

Faculty of Health Sciences

University of Cape Town

Supervisor: Professor Karen Sliwa

Date of submission: October 2018

Word count: 12 120

Contents

Declaration

The research is based on my own independent work done under supervision. Neither the whole work, nor any part of it, is being, or will be submitted for another degree to any other university. The work was not reported or published prior to registration for the abovementioned degree.

Signed by candidate

Acknowledgements and contributions

I am grateful for the direction and supervision generously supplied by Professor Karen Sliwa who instructed me at every step of the research process. Feriel Azibani provided essential input to the manuscript as well as help with the statistics. Professor John Anthony, Professor Priya Soma-Pillay and Dr Ayesha Osman provided insight and advice regarding obstetric aspects of the work. Dr Johan Baard assisted with data collection for the project.

The work is based on data originally collected for the Cardiac Disease in Maternity registry by Professor Sliwa and colleagues at the Hatter Institute for Cardiovascular Research in Africa and would not have been possible without the existing registry.

Abstract

Haemorrhage and other complications in pregnant women on anticoagulation for mechanical heart valves: a prospective observational cohort study

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Objective: To document maternal and foetal morbidity and mortality in anticoagulated, pregnant patients with mechanical heart valves until 42 days postpartum.
Methods: In a tertiary single-centre, prospective cohort, 178 consecutive patients at the cardiac-obstetric clinic were screened for warfarin use between 1 July 2010 and 31 December 2015. Of 33 pregnancies identified, 29 were included. Patients received intravenous unfractionated heparin from six to 12 weeks' gestation and peripartum, and warfarin from 12 to 36 weeks. Maternal outcomes including death, major haemorrhage and thrombosis, and foetal outcomes were documented.
Results: There were two maternal deaths, five returns to theatre post-delivery, eight patients transfused, six major haemorrhages, one case of infective endocarditis and three ischaemic strokes. Ten pregnancies had poor foetal outcomes (six miscarriages, three terminations, one early neonatal death). Twenty patients required more than 30 days' hospitalisation, and 15 required three or more admissions. HIV positivity was associated with surgical delivery (p = 0.0017).
Conclusions: Complication rates were high despite centralized care.
Keywords: warfarin, heparin, pregnancy, anticoagulation, mechanical heart valves, Africa

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Abbreviations

aPTT: Activated Partial Thromboplastin Time

BPM: beats per minute

CDM: Cardiac Disease in Maternity

C/S: Caesarean Section

CT: Computed Tomography

DBP: Diastolic Blood Pressure

dL: Decilitre

ECG: Electrocardiogram

Echo: Echocardiogram

EF: Ejection Fraction

ENND: Early Neonatal Death

FFPs: Fresh Frozen Plasma

g/dL: grams per decilitre

GA: Gestational Age

Hb: Haemoglobin

HIV: Human Immunodeficiency Virus

ICU: Intensive Care Unit

INR: International Normalised Ratio

Kg: Kilogram

LMWH: Low Molecular Weight Heparin

LVEDD: Left Ventricular End Diastolic Diameter

LVESD: Left Ventricular End Systolic Diameter

MHV: Mechanical Heart Valve(s)

NYHA: New York Heart Association

NYHA FC: New York Heart Association Functional Class

PPH: Post-partum Haemorrhage

RBBB: Right Bundle Branch Block

RBCs: Red Blood Cells

RHD: Rheumatic Heart Disease

RPOC: Retained Products of Conception

SBP: Systolic Blood Pressure

SD: Standard Deviation

SROM: Spontaneous Rupture of Membranes

T1: First Trimester

TAH and BSO: Total Abdominal Hysterectomy and Bilateral Salpingo-oophorectomy

UFH: Unfractionated Heparin

UKOSS: United Kingdom Obstetric Surveillance System

WHO: World Health Organisation

ZAR: South African Rand(s)

Chapter 1: Introduction

Pregnancies in patients with mechanical heart valves are relatively rare in the developed world with the UKOSS, a recent population based study in the United Kingdom, estimating an incidence of 3.7 per 100 000 maternities[1]. However, in the developing world, the incidence of pregnancies with mechanical heart valves is thought be much greater due to the prevalence of rheumatic heart disease.

Rheumatic heart disease affects between 15.6 and 19.6 million people worldwide and 79% of these are estimated to be in developing countries[2] while another study estimated that 42% of all children affected by rheumatic heart disease are in Subsaharan Africa[3]. Marijon et. al. has demonstrated that echocardiographic population screening detects subclinical rheumatic heart disease in approximately ten-fold greater numbers of patients than clinical examination alone[4] suggesting that numbers affected are significantly higher than previously thought.

Rheumatic heart disease is a complication of rheumatic fever, itself a complication of streptococcal pharyngitis. Rheumatic fever usually occurs in childhood and presents with carditis, chorea, arthritis, subcutaneous nodules and erythema marginatum. It is diagnosed by the Jones criteria, most recently updated in 2015[5], which now also incorporate echocardiographic criteria. Valvular damage develops with each successive episode of rheumatic fever leading to the development of rheumatic heart disease.

In more severely affected cases, valve replacement with a mechanical valve may be required. In these cases, lifelong anticoagulation is standard of care[6] in order to reduce risk of a valve thrombosis. Because rheumatic heart disease develops in childhood and, if a mechanical valve is inserted, requires lifelong anticoagulation with no treatment interruption, female patients will often desire one or more pregnancies while simultaneously needing anticoagulation.

It has been reported that only 58% of women with mechanical heart valves survive pregnancy without any serious adverse effects[7]and that without anticoagulation, thrombosis occurs in up to 25% of pregnant patients with mechanical heart valves[8]. Therefore, pregnancy in women with mechanical heart valves, for which they require anticoagulation, is known to be high risk. Risks to the mother include haemorrhage and thrombosis while risks to the foetus include miscarriage, stillbirth and warfarin embryopathy.

Management of these patients is challenging and must incorporate management of the pregnancy, the underlying cardiac disease as well as the choice of anticoagulation in pregnancy. Both guidelines for managing these patients as well as clinical practice vary[1]. There is thus a need for further study of this group.

Anticoagulation decisions in particular require attention. Warfarin is most effective in preventing thrombotic complications[6,8]. However, in pregnancy it causes warfarin embryopthy if given between 6 and 12 weeks gestation[8,9], foetal loss and stillbirth[10,11] and through crossing the placenta has the potential to cause foetal haemorrhage[6]. Heparin avoids the complications of warfarin but may be associated with a higher risk of thrombosis[6,12]. Complicating matters,

pregnancy is a dynamic state with changes in cardiovascular[13] physiology as well as a hypercoagulable state which increases risk of mechanical valve thrombosis[14].

Epidemiological differences between local and other cohorts may limit applicability of some developed world studies to local practice. Several South African studies document outcomes in pregnant women with mechanical heart valves[10,15,16] however more data is needed.

This study aims to characterize morbidity and mortality in pregnant women with mechanical heart valves receiving antenatal care at Groote Schuur Hospital.

Chapter 2: Article in publication ready format

Haemorrhage and other complications in pregnant women on anticoagulation for mechanical heart valves; a prospective observational cohort study

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Shortened title: Mechanical valves, anticoagulation and pregnancy complications

Word count: 3 392 (excluding abstract, references and tables)

ABSTRACT

Objective To document maternal and foetal mortality and morbidity in anticoagulated, pregnant patients with mechanical heart valves until 42 days postpartum.

Methods In a tertiary single-centre, prospective cohort; 178 consecutive patients at the cardiac-obstetric clinic between 1/7/2010 and 31/12/2015, were screened for warfarin use. Of 33 pregnancies identified, 29 were included. Patients received intravenous unfractionated heparin from 6-12 weeks gestation and peripartum; warfarin from 12-36 weeks. Maternal outcomes including deaths, major haemorrhage, and thrombosis and foetal outcomes were documented.

Results There were 2 maternal deaths, 5 returns to theatre post-delivery, 8 patients transfused, 6 major haemorrhages, 1 case of infective endocarditis and 3 ischaemic strokes. Ten pregnancies had poor foetal outcomes (6 miscarriages, 3 terminations, 1 early neonatal death). Twenty patients required >30 days hospitalization. Fifteen required ≥three admissions. HIV positivity was associated with surgical delivery (p=0.0017).

Conclusions: Complication rates were high despite centralized care.

Keywords Warfarin, heparin, pregnancy, anticoagulation, mechanical heart valves, Africa

TWEETABLE ABSTRACT

High rates of haemorrhage, other serious complications in anticoagulated pregnant patients with mechanical heart valves

INTRODUCTION

Rheumatic heart disease (RHD) is common in urban Africans, with an estimated yearly incidence of 23.5 cases per 100 000 population, aged over 14 years[17]. Mechanical prosthetic heart valves (MHVs) require lifelong uninterrupted anticoagulation treatment. Therefore, many female patients require anticoagulation during childbearing years. This anticoagulation is essential during pregnancy as without it, up to 25% of pregnant women will experience a thrombotic event[8].

Cardiac disease is the most important non-obstetric cause of maternal deaths[18] and RHD is an important contributor [19]. Mortality and serious morbidity are higher in patients with MHVs than in those with tissue valves, or those who have cardiac disease without prosthetic valves. It has been reported that only 58% of women with MHVs survive pregnancy without any serious adverse events[7].

Although warfarin is the most effective anticoagulant in preventing thrombotic complications[6,8,20], its use in pregnancy remains problematic. It is associated with warfarin embryopathy if administered between six and twelve weeks gestation[8,9] and with foetal loss and stillbirth later in pregnancy[10,11,20]. Warfarin crosses the placenta, placing the vitamin K deficient foetus at risk of haemorrhage[6]. Some findings suggest that certain foetal complications of warfarin may be dose-dependent[21,22], but not all studies have replicated these findings[16]. In some patients low doses may also result in subtherapeutic anticoagulation. Heparin, an alternative to warfarin, does not cross the placenta[23] but results in higher rates of thromboembolic complications[6].

The challenge of administering anticoagulation to pregnant women with valve replacements includes management of the underlying cardiac condition and its complications, as well as the obstetric risks of the anticoagulant regimen. A low-resource setting (such as South Africa) may further exacerbate these difficulties, although there are limited data available to inform local practice.

The objective of this study was to characterize the clinical course of patients with MHVs needing anticoagulation in pregnancy, and to document antenatal, intra-partum and postpartum morbidity and mortality as well as foetal outcomes.

METHODS

Study design

The ongoing,single-centre, prospective Cardiac Disease in Maternity (CDM) Cohort study collected data on all women with heart disease (WHO Risk group Class II-IV) presenting at the dedicated cardiac-obstetric clinic between 1/7/2010 and 31/12/2015. Clinical data such as blood pressure, pulse, presence of heart failure, medications, cardiac history, comorbidities, obstetric history and HIV status was collected. Echocardiographic parameters were measured with echocardiography being performed by a cardiologist. Data collected pertaining to the peripartum period included maternal and neonatal outcomes. Data was collected at each visit including postpartum. Socioeconomic information including the patient's home language and income level were also recorded.

From this registry, 178 consecutive women were screened for warfarin use. Of the 33 pregnancies in which warfarin had been used 29 (in 23 patients) were included, with 4 excluded due to incomplete data. Additional information, particularly maternal post-partum bleeding, ischaemic and thrombotic events and time hospitalised were collected retrospectively from maternity folders stored at Groote Schuur Hospital.

Pre-conception counselling in patients attending tertiary care included advice to conceive on warfarin and to attend a maternity clinic as soon as a period was missed or pregnancy was suspected. Echocardiography was not routinely performed pre-conception.

Management of the pregnancies was as per protocols currently in use at Groote Schuur Hospital for patients under the care of the combined cardiac obstetric clinic. This management was as follows:

Antenatal anticoagulation comprised warfarin up until 6 weeks gestation, unfractionated, intravenous heparin (Heparin Sodium-Fresenius) from 6 to 12 weeks gestation; warfarin from 12 to 36 weeks gestation and unfractionated heparin from 36 weeks gestation. During periods of heparin infusions, the activated partial thromboplastin time (aPTT) target was 2.5 – 3.5 times the control value for all patients, achieved through regular monitoring and adjustment of the infusion rate. International Normalised Ratio (INR) levels were used to monitor and adjust the warfarin dose to achieve an INR value between 2.5 and 3.5. Patients found to be sub therapeutic while on warfarin were admitted for heparin infusion concurrent with warfarin until INR levels were again therapeutic.

Peripartum anticoagulation involved stopping warfarin at 36 weeks gestation and admitting for heparinization. Heparin was omitted from onset of labour and reinitiated six hours postpartum in absence of clinical concern of haemorrhage. Warfarin was restarted at consultant discretion, usually the day after delivery with concurrent heparin until warfarin was therapeutic.

Induction of labour and caesarean sections were performed only for obstetric indications.

Clinical data

Parameters collected included baseline characteristics such as age, gravidity, HIV status and warfarin dosage, as well as occurrence of bleeding, thrombotic and ischaemic complications.

Gestational age was calculated by the obstetrician and measured either from last normal menstrual period if the date was certain, or by early foetal ultrasound dating. Failing either of these methods, a late ultrasound was used.

In patients who had more than one pregnancy, all pregnancies occurring during the study period were included.

Major haemorrhage was defined as bleeding necessitating return to theatre or bleeding associated with both transfusion as well as a drop in haemoglobin of greater than or equal to 2.0g/dL. Minor bleeding was defined as all other bleeding including gum bleeding, epistaxis or troublesome bleeding from drip sites.

Table 1 (supplementary) outlines parameters recorded.

Data Analysis

Data were analysed using GraphPad Prism version 5.00 for Windows (GraphPad Software, La Jolla California, USA). Results are expressed as mean ± SD and percentages. Unpaired t-tests with Welch correction were used to establish if differences in maternal outcome according to the HIV status were statistically significant.

RESULTS

Demographic data for the 23 patients are shown in Table 1. The majority of patients were black (78%) and spoke isiXhosa (61%). Most (78%) had reached high-school but none had tertiary education. Sixty-five percent of patients declared a monthly income of <ZAR 300 and none had a monthly income >ZAR 10 000.

Table 2 shows baseline maternal characteristics. All patients had baseline effort tolerance of NYHA I or II. The mean heart rate was 90 bpm, mean systolic blood pressure (SBP) 111 mmHg and mean diastolic blood pressure (DBP) 72 mmHg. The left ventricular mean ejection fraction was 54.4%. Seven patients had abnormal cardiac rhythms. Twenty eight of 29 patients had rheumatic valve disease, while just one patient had a valve replacement for Takayasu's disease. Nine patients (10 pregnancies) were HIV infected. Other comorbidities included syphilis, psoriasis and hearing impairment. Just two patients presented prior to 6 weeks gestation and five patients presented after 24 weeks gestation. No patient was known to have had a thrombotic event (deep vein thrombosis, pulmonary embolus, stroke) prior to her pregnancy.

Deaths

In this cohort there were two deaths, both occurring postpartum. The first was an 18 year old, HIV negative patient with a double valve replacement (mitral and aortic). In the third trimester, she required treatment for infective endocarditis complicated by acute kidney injury and disseminated intravascular coagulation. She was discharged after this episode and readmitted a week later at 36 weeks as per protocol. Normal vaginal delivery followed and she was discharged six days later in a satisfactory condition. She returned to casualty forty-one days post-delivery and complained to the pre-hospital crew that she was unable to hear her valve clicks. Her INR was 3.73 (supratherapeutic). She then suffered a cardiorespiratory arrest and could not be resuscitated. The cause of death was unclear however suspected to be a valve thrombosis on the basis of absent valve clicks. She had had no INR monitoring between discharge post-partum and this presentation.

The second death occurred in a 36 year old patient with a double valve replacement (mitral and aortic) necessitated by Takayasu's disease. She had tight aortic stenosis with pulmonary hypertension using standard criteria and was assessed as high-risk for surgical revision, although this was considered "semi-urgent". There was extensive vascular involvement including total occlusion of the left carotid and of both subclavian vessels as well as severe stenosis of other head and neck vessels. She was also HIV infected (CD4 count was 321 cells per mm^3) and had defaulted antiretroviral therapy. This was restarted late in pregnancy. Additionally, she was rhesus negative. There was also a history of previous tuberculosis which had been fully treated. Due to the very high-risk nature of the pregnancy, the patient was offered a termination of pregnancy which she declined. At 31 weeks gestation, she had spontaneous rupture of membranes and two days thereafter required a Caesarean section. She was discharged seven days postpartum but represented two days later requiring intubation for pneumonia and ICU admission. Her clinical course was complicated by acute kidney injury, supraventricular

tachycardia requiring cardioversion, pneumonia and a brainstem infarct. Intensive care was subsequently withdrawn and the patient demised.

Thrombotic and ischaemic complications

There were three cases of stroke and one patient with a clot on a prosthetic valve

One (HIV negative) patient developed a left middle cerebral artery infarct while on a heparin infusion at nine weeks gestation, presumably after a thrombotic event. At the time, her aPTT was 2.4 times that of the control. Despite the risks of warfarin in the first trimester, she was changed to warfarin-based anticoagulation after this event.

A second patient developed a brainstem infarct postpartum while intubated. On the four days preceding confirmation of the infarct on CT brain scan, her INR measurements ranged between 2.8 and 6.04. This patient who died following her infarct and is described in more detail above, had multiple risk factors for stroke, including Takayasu's arteritis and HIV.

A third patient developed an ischaemic stroke in the first trimester, prior to diagnosis of pregnancy. At the time, her INR was 1.35. The stroke resulted in right hemiplegia and aphasia. This patient was also HIV positive and attended the maternity clinic for the first time in the third trimester. The aetiology of the stroke remains unclear and may not have been embolic or thrombotic in nature, but rather an ischaemic stroke due to HIV.

A fourth (HIV negative) patient was noted to have a "small clot on her valve" at routine echocardiography while receiving a subtherapeutic dose of heparin. This resulted in no adverse sequelae.

The first death described above may have been due to a valve thrombosis but this is unproven. No deep vein thromboses or pulmonary emboli were detected.

Haemorrhage

Major haemorrhage occurred in six pregnancies (Table 3). These included four major haemorrhages in term deliveries and two major haemorrhages in pregnancies terminating at 11 and 19 weeks respectively.

Of the four term deliveries, there were two episodes of haemorrhage related to sepsis and two wound haematomas requiring return to theatre.

Sepsis contributed to two major haemorrhages. One patient with puerperal sepsis who delivered by caesarean section, needed total abdominal hysterectomy and bilateral salpingo-oophorectomy as well as massive transfusion for post-operative bleeding. Another patient with puerperal sepsis required evacuation of retained products of conception six days post normal vaginal delivery. This procedure led to postpartum haemorrhage (PPH) of two litres, massive blood transfusion, bilateral uterine artery embolization and vaginal packing to control bleeding.

There were two cases of wound haematomas requiring evacuation in theatre.

In patients delivering before 20 weeks gestation, two major haemorrhages occurred.

The first patient underwent a hysterotomy at 19 weeks. She required a second laparotomy for post-operative intraperitoneal bleeding of more than one litre. The lowest documented haemoglobin was 3.9 g/dL and she received a massive transfusion.

One episode of serious haemorrhage occurred following a first trimester termination of pregnancy performed as the patient did not wish to continue with a high risk pregnancy. Following evacuation of products of conception, this patient bled to a haemoglobin of 3g/dL and required fluid resuscitation.

Eight patients received blood transfusions. In five cases, blood products were given after bleeding. In three cases blood and/or fresh frozen plasma was given to increase a low haemoglobin or to avoid bleeding prior to a procedure.

Minor bleeding was common. One episode of haematemesis following assault occurred, eight patients experienced epistaxis on one or more occasion, four patients experienced gum bleeding, one patient had a drip site haematoma and another had problematic bleeding at a drip site.

Caesarean delivery

Nine (45%) of twenty term pregnancies were delivered by Caesarean section. There was an additional hysterotomy carried out to deliver a previable infant. The hysterotomy was performed as the mother had had two previous caesarean sections. HIV infection was more likely to be associated with surgical delivery (p=0.0017).

Arrhythmias and cardiac failure

Eleven pregnancies had episodes of arrhythmia, most commonly atrial fibrillation. However, in seven cases the arrhythmia had been documented prior to pregnancy.

Nine pregnancies were associated with worsening of New York Heart Association functional class with three patients developing pulmonary oedema.

Time in hospital

The average hospital stay was 41.0 days. Five (17.2%) patients spent 60 or more nights in hospital. The average number of admissions per patient was 3.0. Fourteen (48%) patients had four or more admissions.

There were 57 admissions between weeks 12 and 36, the period in which admissions were not mandatory. This equates to approximately two additional admissions per patient, most commonly for a subtherapeutic INR requiring “heparin cover”.

Four patients refused hospital treatment. In one case this occurred on five separate occasions, when the patient was repeatedly found to be subtherapeutic on warfarin at antenatal visits and offered in-patient intravenous heparin. Additionally, two patients absconded.

Foetal outcomes and congenital abnormalities including warfarin embryopathy

Three spontaneous first trimester miscarriages and three second trimester miscarriages occurred (Table 4).

Three pregnancies were terminated; one in the first trimester because the patient did not wish to continue a high risk pregnancy. There were two terminations for foetal malformations not attributed to warfarin (Table 2: supplementary). One of these had confirmed Dandy-Walker syndrome and was delivered by hysterotomy at 19 weeks. The other delivered vaginally at 22 weeks because of suspected anomalies based upon the presence of echogenic bowel.

One infant was born alive with multiple anomalies including features consistent with warfarin embryopathy, together with other abnormalities. This patient had been taking 5 mg of warfarin daily. Antenatal ultrasound showed an absent nose and abnormal faces with close-set eyes, low set ears and a bossed forehead. Brain abnormalities were also noted and included dilated anterior horns of the lateral ventricle fusing in the midline and a dilated 4th ventricle. This patient refused early termination of pregnancy and the baby, born alive by Caesarean section, demised on day 5 of life.

DISCUSSION

Main findings

In this study, a high rate of serious adverse events was observed in maternal and foetal outcomes (Table 4). Maternal morbidity included major haemorrhage, cardiac failure and sepsis, as well as ischaemic stroke. There were three instances of pulmonary oedema, an approximately 20% risk of major haemorrhage, three ischaemic strokes and one case of infective endocarditis. Both deaths occurred post-partum. One was in a patient with significant vascular disease caused by Takayasu's arteritis, further complicated by HIV infection.

Adverse perinatal outcome was evident as a high rate of miscarriage in first and second trimesters, two cases of suspected unrelated foetal anomalies and a third case of a complex foetal anomaly probably attributable to warfarin. Only 20 pregnancies (69%) had a normal neonatal outcome.

The women in this cohort had lengthy hospitalisations with twenty patients (69%) requiring more than 30 days in hospital and 15 (52%) requiring three or more admissions demonstrating the resources required to manage the pregnancies described. The expected minimum number of admissions was two admissions per patient, one in the first trimester and from 36 weeks until after delivery. However, 13 patients presented at or after 12 weeks and were not admitted in the first trimester. Approximately two admissions per patient were required between 12 and 36 weeks gestation.

Interpretation

The mortality rate (6.9%) in our cohort is higher than similar local cohorts[15, 16, 10] and higher than in a large meta-analysis showing a 2.9% mortality rate[8] however it is lower than that in UKOSS, a recent United Kingdom population based study[1] which found a 9% mortality rate in women with mechanical heart valves. Both mortalities in our study occurred post-partum after discharge and in patients with double valve replacements, which have been associated with worse maternal outcomes[1].

Inducing an anticoagulated state opposes the pro-thrombotic milieu of normal pregnancy[12]. Obstetric haemorrhage is known to be a major contributor to maternal deaths[24]. Haemorrhage rates were significantly high with 21% of patients having major haemorrhagic complications. This rate is comparable with other cohorts of women with mechanical prosthetic heart valves[1, 7]. Another study [15] reported post-partum haemorrhage in only 5.8% of patients. These variable rates may reflect differing practice in the timing of anticoagulation reintroduction.

The anticoagulation protocol used prescribes heparin rather than warfarin from 36 weeks gestation allowing rapid reversal of anticoagulation if required during delivery. Delivery takes place during an anticoagulation-free "window" to minimise risk of PPH. There is a need to identify the optimal duration of this "window" to balance the risks of haemorrhage and thrombosis. Heparin is usually reinstated six hours after delivery unless there is clinical concern of haemorrhage.

Of the 19 pregnancies delivered after viability, and consistent with other literature[25, 26, 27], post-operative haemorrhage (3/9 Caesarean sections, 33%) was more frequent than major haemorrhage post-vaginal delivery (1/10 normal vaginal deliveries, 10%) indicating that a longer anticoagulation window may be appropriate after operative delivery. The data suggest that caesarean sections should be performed only when clearly indicated, with meticulous haemostasis, and in anticipation of possible haemorrhage.

Despite the risk of major bleeding, no death occurred as a direct result of bleeding. However, cases of major haemorrhage would have resulted in deaths had resuscitation including transfusion not been available.

Only one patient had a suspected thrombo-embolic event. Two further patients had ischaemic strokes in the setting of HIV positivity. As HIV itself is known to be a risk factor for ischaemic stroke[28,29], these strokes may have been either thromboembolic events related to mechanical valves or associated with HIV.

Protocols used called for intravenous unfractionated heparin from six to twelve weeks gestation and peri-partum, according to relevant guidelines[23]. However, more recent guidelines[30] recommend subcutaneous LMWH (enoxaparin, Clexane) in preference to UFH, dose-adjusted according to peak anti-Xa levels. LMWH has more predictable pharmacokinetics and less risk of allergic reactions, heparin-induced thrombocytopenia and osteoporosis compared to UFH[30,31]. However, there is concern that use of subcutaneous UFH may lead to unacceptably high rates of treatment failure and valve thrombosis[32]. Consequently intravenous UFH is generally recommended and may remain the only alternative to warfarin where access to anti-Xa monitoring is limited, such as in our setting.

Intravenous heparin infusions are, however, resource-intensive, requiring frequent monitoring and prolonged hospitalization. The single suspected thrombotic event occurred in a patient receiving UFH while in a sub-therapeutic range. However, thrombotic events may occur even when anticoagulation has achieved the target therapeutic level[11].

In general, heparin use avoids the pregnancy loss and embryopathy associated with warfarin but carries a higher risk of valve thrombosis [33]. Women at particularly high thrombosis risk may be offered warfarin throughout pregnancy, except peri-partum. Factors conferring higher risk of thrombosis include older generation mechanical heart valves, valves in the mitral position, and previous history of thrombosis on heparin. Improvements in prosthetic valve thrombogenicity over time have reduced thrombosis risk [22].

Among live births in the cohort, the rate of caesarean section was 45%. While above the national average rate of 23.1%[34], it did not differ from the background rate for all high-risk pregnancies receiving care at the tertiary hospital. HIV positive patients were more likely to have caesarean delivery (p=0.0017), perhaps reflecting the local policy of offering caesarean section to infected mothers with persistent viraemia.

Eleven (38%) patients had episodes of arrhythmia, of which seven (24%) had been documented prior to pregnancy, most commonly atrial fibrillation. This rate is high relative to both the developed[7] and developing[10] world.

Nine (31%) pregnancies were complicated by worsening New York Heart Association functional class, and three patients developed pulmonary oedema. This compares unfavourably with the cohort described by van Hagen et al [7] where 7.5% of pregnancies were complicated by heart failure, and may reflect more advanced disease or the effects of co-morbidities present in a low resource setting.

Long hospital stays are costly and contribute negatively to patient quality of life. Outpatient regimens such as self-administered subcutaneous heparin as per newer guidelines [30,35] would reduce length of admissions.

Pregnancy loss occurred in 9 pregnancies (31%) - comparable with similar South African cohorts[10,16]. Congenital abnormalities were seen in 3 pregnancies (10%). However, only one (3.4%) was considered to be due to warfarin embryopathy, a rate lower than reported elsewhere [8,10,16].

Warfarin embryopathy is caused by foetal exposure to warfarin between six and twelve weeks gestation and is avoided by using heparin during this period. Only two patients presented prior to six weeks gestation, enabling timeous switching from warfarin to heparin. Eleven patients presented between 6 and 12 weeks and received heparin from presentation to 12 weeks. The patient whose foetus may have been affected by warfarin embryopathy presented at 24 weeks gestation and therefore was on warfarin throughout the vulnerable period.

Stengths and limitations

Comparison of this cohort with previously published literature shows some differences in mortality and perinatal outcome which is likely spurious owing to small sample size and further skewed by the death related to complicated Takayasu's arteritis. The study is a single centre study. Certain data was collected retrospectively. For example, data pertaining to haemorrhage volume was collected retrospectively which could have led to measurement errors.

CONCLUSION

Pregnancies in patients on anticoagulation carry additional risks due to both the underlying condition for which the patient is anticoagulated and to the anticoagulation itself.

In this small study, ischaemic events occurred intra-partum while haemorrhagic events occurred peri- or postpartum. Avoidance of post-partum haemorrhage, particularly post-operatively, may be achieved by a longer anticoagulation-free "window" peripartum. More studies are needed to identify the optimal window to balance haemorrhagic and thrombotic risk but it is likely to be longer than six hours. Heightened vigilance is required postpartum.

Contraception should be offered routinely at out-patient cardiac clinics. Preconception counselling should emphasise the importance of early presentation.

Prolonged intravenous heparin is likely to be a risk factor for infective endocarditis. Subcutaneous, outpatient LMWH should be considered.

DECLARATION OF CONFLICT OF INTEREST

There is no conflict of interest to declare.

CONTRIBUTION TO AUTHORSHIP

KS conceived the project, provided intellectual input into the first and final draft of the manuscript. SK collected retrospective data, wrote the protocol, prepared the first draft of the manuscript and synthesized journal reviewer comments into the manuscript all with supervision from KS. . FA did statistical analysis of data, assisted with data collection and preparation of tables and manuscript. PS and JA provided intellectual input into the first draft of the manuscript and data interpretation. JB and AO contributed to data collection, manuscript preparation. All authors approved the final manuscript.

ETHICS APPROVAL

The research was approved by the University of Cape Town Human Research Ethics Committee (261/2015).

DECLARATION OF FUNDING

The Hatter Institute for Cardiovascular Research is supported by the National Research Foundation South Africa, The Medical Research Foundation South Africa, the Maurice Hatter Foundation and SERVIER.

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TABLES

Table 1: Demographic Data of 23 Patients

Ethnicity	**N (%)**
African or black	18 (78)
Mixed	4 (18)
White	0 (0)
Other (Arab, Indian, other)	1 (4)
Language	**N (%)**
isiXhosa	14 (61)
Afrikaans	4 (17)
English	3 (13)
Other	2 (9)
Education level	**N (%)**
Year 1-5	5 (22)
Year 6-10	18 (78)
Year >10	0 (0)
Income per month (ZAR)	**N (%)**
<300	15 (65)
300 – 999	3 (13)
1000 – 9999	5 (22)
>10 000	0 (0)

Table 2: Baseline maternal characteristics (n=29)

Age at delivery (years)	27.9±7.9
Weight in kg (N=26)	70.2±13.8
NYHA FC, n (%)	**N (%)**
I/II	29 (100)
III	0 (0)
Vital signs	
Heart rate in bpm	90 ± 18
SBP in mm Hg	111 ± 16
DBP in mm Hg	72 ± 11
Echocardiogram (N=25)	
LVEDD (mm)	50.1 ± 9
LVESD (mm)	35.8 ± 9.8
EF (%)	54.4 ± 13.7
ECG (N=27)	**N (%)**
Sinus rhythm	22 (81)
Atrial fibrillation	5 (19)
Atrial flutter	1 (4)
RBBB	1 (4)
Medical history	
HIV	10 (34)
Syphilis	2 (7)
Other (psoriasis, hearing impairment)	2 (7)
Reason for valve replacement	**N (%)**
Rheumatic Heart Disease	22 (97)
Takayasu's	1 (3)
Position of valves	**N (%)**
Mitral	18 (62)
Aortic	3 (10)
Mitral and aortic	8 (28)
Warfarin dose	**N (%)**
≤ 35 mg/week	10 (35)
> 35 mg/week	14 (48)
Undocumented	5 (17)
Obstetric history	**N (%)**
Primigravida	6 (21)
Multigravida	23 (79)
Gestation age at presentation	**N (%)**
< 6 weeks	2 (7)
< 12 weeks	14 (48)
12-24 weeks	8 (28)
≥ 24 weeks	5 (17)

Table 3: Details of Major Haemorrhage

Details of patients with major haemorrhage						
Patient	Time of bleeding	Delivery	Gestation (weeks)	Details	Transfusion	Drop in Hb pre- and post-delivery (g/dL)
1	Peripartum	C/S	37	1100ml lost during C/S. Wound continued to bleed. Day 5 post C/S had relook laparotomy but only required cauterization of fat	2 units RBCs	3.4
2	Peripartum	C/S	37	Required repeat laparotomy for evacuation of haematoma and TAH and BSO. Patient was septic.	2 RBCs, 4 FFPs	Not available
3	Peripartum	C/S	34	Wound haematoma, required return to theatre for evacuation.	No	1.6
4	Peripartum	NVD + forceps	35	On day 6 post delivery required evacuation of RPOC in theatre. Post evacuation found in shock requiring resuscitation and massive transfusion. Bilateral uterine artery embolization attempted. This failed and patient had further surgery to pack vaginal bleeders. Patient was septic.	3 units in pregnancy. Peripartum 11 RBCs + other products	6.6
5	Peripartum	Medical termination	11	Patient had termination of pregnancy. Later found in shock with Hb of 3g/dL.	2 units RBCs	7.0
6	Peripartum	Hystero-tomy	19	1 litre intraperitoneal bleed post hysterotomy. Lowest Hb 3.9. Required repeat laparotomy 2 days post hysterotomy.	Massive transfusion: 7 RBCs, 6 FFPs, cryo-precipitate and haemo-solvex	7.1

Table 4: Maternal and Foetal Outcomes

Maternal Outcomes	
NYHA FC (N=13)	
I/II	12
III	1
Deaths, n	2
Delivery	**N (%)**
Vaginal	19 (66)
Caesarean	9 (31)
Hysterotomy	1 (3)
Reasons for surgical delivery	**(N)**
Foetal distress	3
Previous Caesarian section	2
SROM	2
Other	3
Bleeding complications	**N (%)**
Major bleeding	7 (24)
Blood transfusion	8 (28)
Thrombotic complications	4 (14)
Arrhythmias	11 (38)
Time in hospital	
Hospital stay (days)	41 ± 28
Admissions (n)	3 ± 1.8
Foetal Outcomes	
Healthy, n(%)	19(66)
Birth weight (g) (n=19)	<2kg: 2 2-2.5kg: 4 2.5-4kg: 13 >4kg: 0
Apgar score at 5 min (n=18)	Apgars 9-10 : 17 Apgars 7 : 1 Born before arrival* : 1
ENND	1(3)
Pregnancy loss	6(21)
Termination	3(10)

*This infant was born before the mother reached hospital and therefore no APGARs were recorded. The infant was reported to have “cried at birth”.

Table 1 (supplementary): Maternal and Foetal outcomes recorded

Maternal, bleeding	Antepartum haemorrhage; postpartum haemorrhage, haemorrhagic stroke, need for transfusion, other bleeding complications
Maternal, thrombotic	Valve thrombosis, ischaemic or embolic stroke, other thrombotic complications
Maternal, other	Maternal mortality rates, maternal days in hospital, rates of caesarian section and indication (obstetric or medical), new onset atrial fibrillation, infective endocarditis, new onset or worsening heart failure
Foetal/infant	Warfarin embryopathy, analysed according to warfarin dosages; other congenital anomalies; rates of miscarriage; rates of stillbirth

Table 2 (supplementary): Congenital abnormalities including Warfarin Embryopathy

Patient no	Maternal age	GA at 1st antenatal visit	Parity	Anticoagulant and dose	Sonography	Foetal outcomes
1	25	24	1	Warfarin, 5mg	Polyhydramnios, abnormal facies, close-set eyes, absent nose, low set ears, bossed forehead, abnormal ventricles, short spine, fat puffy hands and feet	ENND
2	29	17’5	2	Warfarin, 5mg in T1 then defaulted	Dandy-Walker malformation	Termination at 19 weeks
3	38	19’1	4	Warfarin, 7.5mg daily	Echogenic bowel	Termination at 22 weeks

Appendices

Appendix 1: Protocol

Appendix 2: Questionnaire, data capture instruments, consent forms and any related participant information sheets

Appendix 3: Ethics approval letter

Appendix 4: Instructions to authors (Cardiovascular Journal of Africa)

Appendix 5: Published article

Appendix 6: Reviewer comments (Cardiovascular Journal of Africa)

Appendix 1: Research protocol

RESEARCH PROTOCOL

Anticoagulation in Pregnant Patients with Operated Rheumatic Heart Disease at Groote Schuur Hospital

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Co-investigator: Prof. Karen Sliwa (2,3)

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1. Background

Rheumatic heart disease (RHD), a type of valvular heart disease, is a common problem the world over. It leads to up to 1.4 million deaths annually (Zühlke, 2014) and is the most important cause of heart failure (Marijon, 2012) and of cardiovascular death (Chakravarty, 2014) in people younger than 50 years.

Developing countries, including South Africa, are disproportionately affected. One estimate is that between 15.6 and 19.6 million people worldwide suffer from RHD and that 79% of these are in developing countries (Carapetis, 2005). Nkomo estimates that 42% of all children affected by RHD are in sub-Saharan Africa (Nkomo, 2009). In industrialized countries however, valvular heart disease is predominately degenerative. For example, in Europe, RHD comprises only 22% of valvular heart disease (Iung, 2014).

RHD is a late complication of streptococcal pharyngitis. These infections give rise to host antibodies, which, via molecular mimicry, cross react with and cause damage to host tissues leading to acute rheumatic fever (Chakravarty, 2014). Rheumatic fever (RF) occurs predominantly in 5-15 year old children and usually develops two to three weeks after the initial streptococcal infection. It presents with carditis, chorea, arthritis, subcutaneous nodules and erythema marginatum. Diagnostic criteria for RF ("Jones criteria") were first published by Ducket Jones in 1944, and were most recently amended in 2015 by a subcommittee of the American Heart Association (Gewitz, 2015). In 60-65% of RF cases, valvular heart disease follows with progressive valve damage (RHD) occurring with each RF recurrence (Remenyi,

2013). RHD may lead to atrial fibrillation, infective endocarditis of the damaged valve, stroke, heart failure and complications in pregnancy (Remenyi, 2013).

Socioeconomic conditions, genetic differences amongst patient populations as well as the rheumatogenicity of local streptococcal strains may all be reasons for the disproportionately high rates of RHD in sub-Saharan Africa (Chakravarty, 2014). Marijon et al, conducting a study in Cambodia and Mozambique, have shown that echocardiographic population screening detects approximately ten-fold greater numbers of patients with subclinical RHD as compared with clinical examination (Marijon, 2007). This suggests that rates of RHD may be significantly higher than previously thought and has led to efforts to standardize criteria for echocardiographic diagnosis of subclinical disease (Remenyi, 2012).

RHD causes valve damage that evolves over time. In childhood, valve regurgitation is most common, but later in life mixed regurgitant-stenotic lesions frequently develop (Sliwa, 2015). The mitral valve is the most commonly affected valve, but the aortic valve and tricuspid valve are also commonly affected (Sliwa, 2015). Left-sided valve disease is predominant (Nkomo, 2009).

In the more severely affected cases, valve replacement with a prosthetic heart valve is required. The artificial valve may be a tissue valve or a mechanical valve. Tissue valves do not require ongoing anticoagulation but their use is limited by their tendency to undergo structural valve deterioration (Elkayam, 2005). Mechanical valves, which are more robust than tissue valves and less likely to require redo cardiac surgery, carry a risk of thrombosis – a catastrophic outcome requiring fibrinolysis or redo cardiac surgery. Therefore, lifelong anticoagulation in patients with mechanical prosthetic valves is standard of care (McLintock, 2011). Because rheumatic heart disease develops in childhood and, if a mechanical prosthetic heart valve is sited, requires lifelong anticoagulation with no treatment interruption, female patients will often desire one or more pregnancies while simultaneously requiring anticoagulation.

Although warfarin is the most effective anticoagulant in preventing thrombotic complications (McLintock, 2011; Chan, 2000), it is problematic in pregnancy. It is associated with warfarin embryopathy – nasal hypoplasia and epiphyseal stippling - if administered between six and twelve weeks gestation (Chan, 2000; Ginsberg, 2003). It is also known to cause foetal loss and stillbirth (Mazibuko, 2012; Basude 2012). In addition, warfarin crosses the placenta, placing the foetus at risk of haemorrhage (McLintock, 2011).

Some findings suggest that certain foetal complications of warfarin may be dose dependent. An Italian study showed a dose-related increase in foetal complications with significantly fewer complications when doses were below 5mg daily (Vitale, 1999). Another study found that in a small sample of patients with mechanical aortic valve prostheses, those patients in which therapeutic INRs were achieved with warfarin doses below 5mg daily, warfarin embryopathy did not occur (De Santo, 2012). Although these studies suggest safety when low dose warfarin is administered in pregnancy, not all studies have replicated these findings. For example, a South African study found stillbirth rates to be dose-dependent, but reported cases of warfarin embryopathy in patients on low dose warfarin (Soma-Pillay, 2011). Also, in some patients low doses may simply be inadequate to achieve therapeutic anticoagulation and avoid thrombo-embolic complications, either because of patient factors or because of the thrombogenicity of the prosthetic valve itself (Elkayam, 2012).

Due to the problems associated with warfarin use in pregnancy, alternative anticoagulation regimens are often used. Heparins, either unfractionated or low molecular weight have the advantage that they do not cross the placenta (Elkayam, 2004). Administering unfractionated heparin throughout pregnancy however, results in high rates of thromboembolic complications (McLintock, 2011). The American College of Chest Physicians recommends either (1) LMWH/UFH from 6-12 weeks gestation and close to term with warfarin at other times or (2) Heparins throughout pregnancy (either LMWH or unfractionated), with the proviso that these must be very closely monitored to keep anti-Xa levels in the therapeutic range (Goland, 2013). In women at very high risk of thrombotic complications, warfarin throughout the pregnancy may be considered (Goland, 2013).

Even in healthy women, pregnancy causes protean changes in cardiovascular physiology. These changes, which largely reverse postpartum and are thought to be adaptive, were reviewed by Sanghavi (2014) in *Circulation*. They include changes in cardiac output, blood pressure and heart rate, as well as the size and volume of heart chambers. Peripheral vascular resistance decreases with trough levels occurring during the second trimester. Cardiac output increases by up to 45% at 24 weeks (Sanghavi, 2014) and further increases during labour due to auto-transfusion from the uterus into the systemic circulation. Blood pressures decrease, while heart rate increases. There are also important haematological changes, notably that pregnancy is a hypercoagulable state, causing an increase in mechanical valve thrombosis (Sliwa, 2015). Due to the extensive physiological adaptation that occurs during normal pregnancy, it is often a stressor that unmasks subclinical heart disease.

This clinical situation, in which a pregnant patient has underlying rheumatic heart disease as well as an artificial mechanical valve requiring adequate anticoagulation treatment; the foetus

requires protection against the teratogenic potential of the treatment; and the pregnancy itself causes changes in cardiac and haematological physiology gives rise to considerable management challenges.

2. Rationale for the study

A paucity of data exists documenting the maternal and foetal outcomes of anticoagulation in operated RHD in pregnancy in South Africa. American and European recommendations may or may not be appropriate in our setting. Therefore, we would like to document the outcomes observed in patients treated at Groote Schuur Hospital with various anticoagulation regimens in pregnancy.

3. Aims and Objectives

Aims

To document maternal and foetal outcomes during and after pregnancy in women with operated rheumatic heart disease (RHD) on anticoagulation treatment.

Objectives

To study the relationship between anticoagulation (warfarin, heparins or a combination thereof) and maternal and foetal outcomes in pregnancy in rheumatic heart disease patients with mechanical heart valves.

4. Methodology

Study design

The study is an observational, longitudinal analysis of a cohort of women with RHD seen at the cardiac maternity clinic between July 2010 and 2014. The Cardiac Disease in Maternity Cohort study (phase 1 and phase 2) will be used to collect the relevant information.

Characteristics of the study population

The study population will include women with operated rheumatic heart disease who have been attending the cardiac maternity clinic, E17, Groote Schuur Hospital.

Inclusion criteria

(i) Patients must have operated rheumatic heart disease with one or more mechanical heart valves requiring anticoagulation treatment during the course of one or more pregnancies, which occurred during the study period.
(ii) Patients over the age of 18 years at first contact with researchers.
(iii) Patients with valid, informed consent.

(iv) Patients whose first language is not English will be included, provided they have valid informed consent.

Exclusion criteria

Patients without valid informed consent will be excluded.

Sample size

The sample size is between 50 and 60 consecutive cases with sufficient maternal and foetal data set.

Recruitment and Enrollment

Patients will be recruited from the CDM-I and II registry.

Outcomes measured

Data will be documented and analysed under the following headings:

Maternal, bleeding	Antipartum haemorrhage; postpartum haemorrhage, haemorrhagic TIA/CVA, need for transfusion, other bleeding complications
Maternal, thrombotic	Valve thrombosis, embolic TIA/CVA, other thrombotic complications
Maternal, other	Maternal mortality rates, maternal days in hospital, maternal days in ICU, rates of caesarian section and indication (obstetric or medical), new onset atrial fibrillation, infective endocarditis, new onset or worsening heart failure
Foetal/infant, bleeding	Intra-cranial bleeding, other bleeding
Foetal/infant, other	Warfarin embryopathy, analysed according to warfarin dosages; other congenital anomalies; rates of miscarriage; rates of stillbirth

Interventions

There are no medical or surgical interventions in this study except for venesection already performed, for which informed consent was obtained.

5. Ethical considerations

Ethical approval and protection of human subjects

Ethical approval has been obtained from the University of Cape Town Human Research Ethics Committee – reference 173/2010. This protocol as well as the accompanying FHS013 form constitute an application to proceed with a further subanalysis of the data.

Participants have already given informed consent which includes future subanalyses of the data and are free to withdraw at any time. Withdrawal from the study has no impact whatsoever on care provided to the individual.

Risk to subjects

There is no risk to the subjects as a result of participation in this subanalysis. There is no invasive component to the analysis. There is also no direct patient contact.

Protection of confidentiality

Data will be anonymized. No identifying information will be published whatsoever.

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Appendices

1. FHS013 Cardiac Disease and Maternity Registry
2. FHS006: Protocol Amendment 20 November 2014
3. Patient information and informed consent form for Cardiac Disease in Maternity Registry
4. FHS013 form for this amendment

Appendix 2: Questionnaire, data capture instruments, consent forms and any related participant information sheets

Cardiac Disease in Maternity (CDM-II) Registry (CDM-II)

PATIENT INFORMATION AND CONSENT FORM

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Research nurse:	Mrs Unita September
Cell:	827387516

Cardiac Disease in Maternity (CDM-II) Registry (CDM-II)

Informed Consent Form

I agree to participate in a study of the clinical, biochemical, immunologic and electrocardiographic factors that may affect the outcome in women with heart problems complicating pregnancy.

We will document standard care as well as the mother and child's outcome.

I understand that I will be interviewed about my medical history, family history, social history, history of current and/or previous pregnancy/pregnancies and medication. I have also been told that I will be examined in detail, including an examination of my heart by an ECG and ultrasound scan. In addition, I will have a blood sample drawn consisting of 4 tubes of blood. This blood will be used to test for biochemical and immunologic factors that may increase the risk of heart muscle dysfunction.

I understand that the researchers are asking for permission to store some of my unused blood samples for future research. I have the right to decide about the future use of my blood. I understand that I am free to have my blood stored for future tests. The results of the tests conducted on the stored blood will be confidential, and my personal details will not be identifiable in any way. This research has been approved by the University of Cape Town Human Research Ethics Committee (HREC 173/2010). I understand that if I refuse to have my blood stored for future tests, this will not affect my participation in this study and it will not affect my care at this hospital. Some of the blood will be stored for tests to be conducted at a later stage, but all cellular material will be discarded at the end of the study. I also understand that no genetic tests will be done on this stored blood.

Participation in this study will take about 90 minutes at the first visit. Thereafter, I will be followed up at regular intervals, as necessary for the heart condition, for up to 2 years to assess the state of cardiovascular health through clinical, electrocardiographic and echocardiographic assessment. If abnormalities are detected during the course of this study, I will be informed of the findings and referred to the appropriate health care team for further treatment.

I understand that my participation in this study is entirely voluntary. All information gathered in this study is strictly confidential, and will only be used for research relating to the disease of heart failure complicating pregnancy-induced hypertension. The information collected for this study will not be used to generate any profit. I will not be identifiable in any published report.

I understand that I am free to refuse to participate or withdraw from the study at any time, without jeopardising my future care. If I have any questions, I understand that I may contact (Mrs Unita September and Prof. Karen Sliwa) at the telephone number and address printed at the top of this page.

I have read the information, or it has been read to me. I have had the chance to ask questions about it and I am satisfied with the answers I was given. I consent voluntarily and understand that I have the right to withdraw my consent without this affecting the research I am currently taking part in or my medical care.

☐ I agree to take part in this study.

☐ I am willing to be re-contacted by the researcher about possible future use of my tissue samples in future research.

If any of the blood I have provided for this research is unused or left over,

☐ I give permission for my blood sample to be stored indefinitely, if the research has been approved by the HREC.

☐ I want my blood sample destroyed immediately.

☐ I want my blood sample destroyed after ___ years

_____	_____	_____
Participant's name	Participant's signature	Date
_____	_____	_____
Witness's name (If necessary)	Witness's signature	Date
_____	_____	_____
Investigator's name	Investigator's signature	Date

Appendix 3: Ethics approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • **Facsimile** [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 April 2015

HREC/REF: 261/2015

Dr S Kariv
Internal Medicine
Department of Medicine
J-Floor
OMB

Dear Dr Kariv

Project Title: ANTICOAGULATION IN PREGNANT PATIENTS WITH OPERATED RHEUMATIC HEART DISEASE AT GROOTE SCHUUR HOSPITAL (linked to 173/2010)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 28 April 2016.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please update the protocol to Helsinki Declaration 2013.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:261/2015

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Hrec/ref:261/2015

Appendix 4: Instructions to authors (Cardiovascular Journal of Africa)

All categories of manuscripts for the Cardiovascular Journal of Africa must be submitted on-line to Editorial Manager. You will be assigned your own password and user name. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title; authors' surname and forename, address of each author and full address, telephone, fax and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (download off-line document). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to info@clinicscardive.com

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

Preferred Image Format	Alternative Image Format
Image Format	.tif
Image Width	Greater than or equal to intended display size
Colorspace	RGB
DPI	500+
Alpha Channels	None
Layers	Flattened
Image Format	.jpg
Image Width	Greater than or equal to intended display size
Colorspace	RGB
DPI	500+
Compression Quality	Maximum

References numbered in the order of appearance in the text, according to Vancouver style. For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183. For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher,

1999: 133 –139. DOI Numbers / PMID (Pubmed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

Original articles: Title page as above. Abstract (150 words) a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results and the main conclusion. Keywords: maximum of six keywords for indexing. Introduction: concise description of background, sufficient for the non-specialist to appreciate the context of the work. Clear statement of the purpose of the study. Methods: a brief description of study design, procedures, analytical techniques and statistical evaluation. Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures. Discussion: an interpretation of the study placed within the context of current knowledge, leading to specific conclusions where possible. Acknowledgements. References, figures and tables as above.

Reviews

Title page as above. Abstract (150 words) setting out the scope, key messages and conclusions of the review. Body of text liberally partitioned with headings and subheadings leading to a synopsis with conclusions at the end. Key messages in a separate box itemising two to five short principal statements. Acknowledgements, references, tables and figures as above.

Other articles should adopt a concise style consistent with similar articles previously published in the journal. Manuscripts should include a title page, and appropriate subheadings for text. Style of tables, figures and references as above.

Figures be sent to us in a high resolution JPEG format, but they MUST be sent separately from the Word document. If not in high resolution JPEG, then PowerPoint will do.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (download off-line document). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to info@clinicscardive.com

The status of progression of the peer-review system will be directly accessible by authors. The Editorial Manager system is particularly useful to authors and reviewers as there is a direct link to PubMed for viewing all related articles on the subject matter.

Submitted manuscripts must be supplied with a covering letter with any additional information that may be helpful to the editor, such as the type or format of article that the manuscript represents. If the manuscript has been submitted previously to another

journal, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Copies of any permission to reproduce published material, to use illustrations or report information about identifiable people, or to name people for their contributions must accompany the manuscript.

Appendix 5: Published article

Cardiovascular Topics

Haemorrhage and other complications in pregnant women on anticoagulation for mechanical heart valves: a prospective observational cohort study

S Kariv, F Azibani, J Baard, A Osman, P Soma-Pillay, J Anthony, K Sliwa

Abstract

Objective: To document maternal and foetal morbidity and mortality in anticoagulated, pregnant patients with mechanical heart valves until 42 days postpartum.

Methods: In a tertiary single-centre, prospective cohort, 178 consecutive patients at the cardiac-obstetric clinic were screened for warfarin use between 1 July 2010 and 31 December 2015. Of 33 pregnancies identified, 29 were included. Patients received intravenous unfractionated heparin from six to 12 weeks' gestation and peripartum, and warfarin from 12 to 36 weeks. Maternal outcomes including death, major haemorrhage and thrombosis, and foetal outcomes were documented.

Results: There were two maternal deaths, five returns to theatre post-delivery, eight patients transfused, six major haemorrhages, one case of infective endocarditis and three ischaemic strokes. Ten pregnancies had poor foetal outcomes (six miscarriages, three terminations, one early neonatal death). Twenty patients required more than 30 days' hospitalisation, and 15 required three or more admissions. HIV positivity was associated with surgical delivery ($p = 0.0017$).

Conclusions: Complication rates were high despite centralised care.

Keywords: warfarin, heparin, pregnancy, anticoagulation, mechanical heart valves, Africa

Submitted 4/2/18, accepted 22/5/18

Cardiovasc J Afr 2018; **29**: online publication www.cvja.co.za

DOI: 10.5830/CVJA-2018-029

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Rheumatic heart disease (RHD) is common in urban Africans, with an estimated yearly incidence of 23.5 cases per 100 000 population aged over 14 years.[1] Mechanical prosthetic heart valves (MHVs) require lifelong, uninterrupted anticoagulation treatment, therefore, many female patients require anticoagulation during childbearing years. This anticoagulation is essential during pregnancy as without it, up to 25% of pregnant women will experience a thrombotic event.[2]

Cardiac disease is the most important non-obstetric cause of maternal deaths,[3] and RHD is an important contributor.[4] Mortality and serious morbidity are higher in patients with MHVs than in those with tissue valves, or those who have cardiac disease without prosthetic valves. It has been reported that only 58% of women with MHVs survive pregnancy without any serious adverse events.[5]

Although warfarin is the most effective anticoagulant in preventing thrombotic complications,[2,6,7] its use in pregnancy remains problematic. It is associated with warfarin embryopathy if administered between six and 12 weeks' gestation,[2,8] and with foetal loss and stillbirth later in pregnancy.[7,9,10] Warfarin crosses the placenta, placing the vitamin K-deficient foetus at risk of haemorrhage.[6] Some findings suggest that certain foetal complications of warfarin may be dose dependent,[11,12] but not all studies have replicated these findings.[13] In some patients, low doses may also result in sub-therapeutic anticoagulation. Heparin, an alternative to warfarin, does not cross the placenta[14] but results in higher rates of thromboembolic complications.[6]

The challenge of administering anticoagulation to pregnant women with valve replacements includes management of the

underlying cardiac condition and its complications, as well as the obstetric risks of the anticoagulant regimen. A low-resource setting (such as South Africa) may further exacerbate these difficulties, although there are limited data available to inform local practice.

The objective of this study was to characterise the clinical course of patients with MHVs needing anticoagulation in pregnancy, and to document antenatal, intra-partum and post-partum morbidity and mortality rates as well as foetal outcomes.

Methods

In the ongoing, single-centre, prospective Cardiac Disease in Maternity (CDM) cohort study, 178 women with heart disease (WHO risk group class II–IV) presenting at the dedicated cardiac-obstetric clinic between 1 July 2010 and 31 December 2015, were screened for warfarin use. The research was approved by the University of Cape Town Human Research Ethics Committee (261/2015).

Of the 33 pregnancies identified, 29 (in 23 patients) were included, with four excluded due to incomplete data. Additional information, particularly maternal post-partum bleeding, ischaemic and thrombotic events, and time hospitalised were collected retrospectively from maternity folders stored at Groote Schuur Hospital.

Preconception counselling in patients attending tertiary care included advice to conceive on warfarin and to attend a maternity clinic as soon as a period was missed or pregnancy was suspected. Echocardiography was not routinely performed pre-conception.

Antenatal anticoagulation comprised warfarin up to six weeks' gestation, unfractionated, intravenous heparin (heparin sodium–fresenius) from six to 12 weeks' gestation, warfarin from 12 to 36 weeks' gestation, and unfractionated heparin from 36 weeks' gestation. During periods of heparin infusion, the activated partial thromboplastin time (aPTT) target was 2.5 to 3.5 times the control value for all patients, achieved through regular monitoring and adjustment of the infusion rate. International normalised ratio (INR) levels were used to monitor and adjust the warfarin dose to achieve an INR value between 2.5 and 3.5. Patients found to be sub-therapeutic while on warfarin were admitted for heparin infusion concurrent with warfarin until INR levels were again therapeutic.

Peripartum anticoagulation involved stopping warfarin at 36 weeks' gestation and admitting for heparinisation. Heparin was omitted from the onset of labour and reinitiated six hours post-partum in the absence of clinical concern of haemorrhage. Warfarin was restarted at the consultant's discretion, usually the day after delivery, with concurrent heparin until warfarin was therapeutic. Induction of labour and caesarean sections were performed only for obstetric indications.

Parameters collected included baseline characteristics such as age, gravidity, HIV status and warfarin dosage, as well as occurrence of bleeding, thrombotic and ischaemic complications. Gestational age was calculated by the obstetrician and measured either from the last normal menstrual period if the date was certain, or by early foetal ultrasound dating. Failing either of these methods, a late ultrasound was used. In patients who had more than one pregnancy, all pregnancies occurring during the study period were included.

Major haemorrhage was defined as bleeding necessitating return to theatre or bleeding associated with both transfusion as well as a drop in haemoglobin of ≥ 2.0 g/dl. Minor bleeding was defined as all other bleeding including gum bleeding, epistaxis or troublesome bleeding from drip sites. Table 1 outlines the parameters recorded.

Table 1. Maternal and foetal outcomes recorded

Maternal, bleeding	Antepartum haemorrhage, postpartum haemorrhage, haemorrhagic stroke, need for transfusion, other bleeding complications
Maternal, thrombotic	Valve thrombosis, ischaemic or embolic stroke, other thrombotic complications
Maternal, other	Maternal mortality rates, maternal days in hospital, rates of caesarian section and indication (obstetric or medical), new-onset atrial fibrillation, infective endocarditis, new-onset or worsening heart failure
Foetal/ infant	Warfarin embryopathy, analysed according to warfarin dosages; other congenital anomalies; rates of miscarriage; rates of stillbirth

Statistical analysis

Data were analysed using GraphPad Prism version 5.00 for Windows (GraphPad Software, La Jolla California, USA). Results are expressed as mean ± SD and percentages. Unpaired *t*-tests with Welch correction were used to establish whether differences in maternal outcome according to the HIV status were statistically significant.

Results

Demographic data for the 23 patients are shown in Table 2. The majority of patients were black (78%) and spoke isiXhosa (61%). Most (78%) had reached high school but none had tertiary education. Sixty-five per cent of patients declared a monthly income of < ZAR 300 and none had a monthly income > ZAR 10 000.

Table 3 shows baseline maternal characteristics. All patients had baseline effort tolerance of NYHA I or II. The mean heart rate was 90 beats per min, mean systolic blood pressure (SBP)

Table 2. Demographic data of 23 patients

Demographics	*Number (%)*
Ethnicity	
African or black	18 (78)
Mixed	4 (18)
White	0 (0)
Other (Arab, Indian, other)	1 (4)
Language	
isiXhosa	14 (61)
Afrikaans	4 (17)
English	3 (13)
Other	2 (9)
Education level	
Year 1–5	5 (22)
Year 6–10	18 (78)
Year > 10	0 (0)
Income per month (ZAR)	
< 300	15 (65)
300–999	3 (13)
1 000–9 999	5 (22)
> 10 000	0 (0)

was 111 mmHg and mean diastolic blood pressure (DBP) was 72 mmHg. The left ventricular mean ejection fraction was 54.4%. Seven patients had abnormal cardiac rhythms. Twenty-eight of 29 patients had rheumatic valve disease, while just one patient had a valve replacement for Takayasu's disease. Nine patients (10 pregnancies) were HIV infected. Other co-morbidities included syphilis, psoriasis and hearing impairment. Just two patients presented prior to six weeks' gestation and five presented after 24 weeks' gestation. No patient was known to have had a thrombotic event (deep-vein thrombosis, pulmonary embolus, stroke) prior to her pregnancy.

In this cohort there were two deaths, both occurring post-partum. The first was an 18-year-old, HIV-negative patient with a double valve replacement (mitral and aortic). In the third trimester, she had required treatment for infective endocarditis, complicated by acute kidney injury and disseminated intravascular coagulation. She was discharged after this episode and readmitted a week later at 36 weeks, as per protocol. Normal vaginal delivery followed and she was discharged six days later in a satisfactory condition. She returned to casualty 41 days post-delivery and complained to the prehospital crew that she was unable to hear her valve clicks. Her INR was 3.73 (supra-therapeutic). She then suffered a cardiorespiratory arrest and could not be resuscitated.

The cause of death was unclear, however it was suspected to be a valve thrombosis on the basis that she complained that she was unable to hear her valve clicks. She had had no INR monitoring between discharge post-partum and her presentation in cardiac arrest.

The second death occurred in a 36-year-old patient with a double valve replacement (mitral and aortic) necessitated by Takayasu's disease. She had tight aortic stenosis with pulmonary hypertension using standard criteria and was assessed as high risk for surgical revision, although this was considered 'semi-urgent'. There was extensive vascular involvement, including total occlusion of the left carotid and of both subclavian vessels as well as severe stenosis of other head and neck vessels. She was also HIV infected (CD4 count was 321 cells per mm^3) and had defaulted on antiretroviral therapy. This was restarted late in pregnancy. Additionally, she was rhesus negative. There was also a history of previous tuberculosis, which had been fully treated.

Due to the very high-risk nature of the pregnancy, the patient was offered a termination of pregnancy, which she declined. At 31 weeks' gestation, she had spontaneous rupture of the membranes and two days thereafter required a caesarean section. She was discharged seven days postpartum but represented two days later requiring intubation for pneumonia and ICU admission. Her clinical course was complicated by acute kidney injury, supraventricular tachycardia requiring cardioversion, pneumonia and a brainstem infarct. Intensive care was subsequently withdrawn and the patient died.

There were three cases of stroke and one patient with a clot on a prosthetic valve. One HIV-negative patient developed a left middle cerebral artery infarct while on a heparin infusion at nine weeks' gestation, presumably after a thrombotic event. At the time, her PTT was 2.4 times that of the control. Despite the risks of warfarin in the first trimester, she was changed to warfarin-based anticoagulation after this event.

A second patient developed a brainstem infarct post-partum while intubated. On the four days preceding confirmation of the infarct on CT brain scan, her INR measurements ranged between 2.8 and 6.04. This patient, who died following her infarct and is described in more detail above, had multiple risk factors for stroke, including Takayasu's arteritis and HIV.

A third patient developed an ischaemic stroke in the first trimester, prior to diagnosis of pregnancy. At the time, her INR was 1.35. The stroke resulted in right hemiplegia and aphasia. This patient was also HIV positive and attended the maternity clinic for the first time in the third trimester. The aetiology of the stroke remains unclear and may not have been embolic or thrombotic in nature, but rather an ischaemic stroke due to HIV infection.

A fourth, HIV-negative patient, was noted to have a 'small clot on her valve' at routine echo while receiving a sub-therapeutic dose of heparin. This resulted in no adverse sequelae. The first

Table 3. Baseline maternal characteristics ($n = 29$)

Characteristics	*Mean ± SD or* n *(%)*
Age at delivery (years)	27.9 ± 7.9
Weight (kg) ($n = 26$)	70.2 ± 13.8
NYHA FC, *n* (%)	
I/II	29 (100)
III	0 (0)
Vital signs	
Heart rate (bpm)	90 ± 18
SBP (mmHg)	111 ± 16
DBP (mmHg)	72 ± 11
Echocardiogram ($n = 25$)	
LVEDD (mm)	50.1 ± 9
LVESD (mm)	35.8 ± 9.8
EF (%)	54.4 ± 13.7
ECG ($n = 27$), *n* (%)	
Sinus rhythm	22 (81)
Atrial fibrillation	5 (19)
Atrial flutter	1 (4)
RBBB	1 (4)
Medical history	
HIV	10 (34)
Syphilis	2 (7)
Other (psoriasis, hearing impairment)	2 (7)
Reason for valve replacement, *n* (%)	
Rheumatic heart disease	22 (97)
Takayasu's	1 (3)
Position of valves, *n* (%)	
Mitral	18 (62)
Aortic	3 (10)
Mitral and aortic	8 (28)
Warfarin dose, *n* (%)	
≤ 35 mg/week	10 (35)
> 35 mg/week	14 (48)
Undocumented	5 (17)
Obstetric history, *n* (%)	
Primigravida	6 (21)
Multigravida	23 (79)
Gestation age at presentation, *n* (%)	
< 6 weeks	2 (7)
< 12 weeks	14 (48)
12–24 weeks	8 (28)
≥ 24 weeks	5 (17)

kg: kilogram, NYHA FC: New York Heart Association functional class, bpm: beats per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, LVESD: left ventricular end-systolic diameter, LVEDD: left ventricular end-diastolic diameter, EF: ejection fraction, ECG: echocardiogram, RBBB: right bundle branch block.

death, described above, may have been due to a valve thrombosis but this was unproven. No deep-vein thromboses or pulmonary emboli were detected.

Major haemorrhage occurred in six pregnancies (Table 4). These included four major haemorrhages in term deliveries and two major haemorrhages in pregnancies terminating at 11 and 19 weeks, respectively.

Of the four term deliveries, there were two episodes of haemorrhage related to sepsis and two wound haematomas requiring return to theatre. Sepsis contributed to two major haemorrhages. One patient with puerperal sepsis, who delivered by caesarean section, needed total abdominal hysterectomy and bilateral salpingo-oophorectomy as well as massive transfusion for post-operative bleeding. Another patient with puerperal sepsis required evacuation of retained products of conception six days post normal vaginal delivery. This procedure led to postpartum haemorrhage of two litres, massive blood transfusion, bilateral uterine artery embolisation and vaginal packing to control bleeding. There were two cases of wound haematomas requiring evacuation in theatre.

In patients delivering before 20 weeks' gestation, two major haemorrhages occurred. The first patient underwent a hysterotomy at 19 weeks. She required a second laparotomy for post-operative intraperitoneal bleeding of more than one litre. The lowest documented haemoglobin was 3.9 g/dl and she received a massive transfusion.

One episode of serious haemorrhage occurred following a first-trimester termination of pregnancy, performed as the patient did not wish to continue with a high-risk pregnancy. Following evacuation of the products of conception, this patient bled to a haemoglobin of 3g/dl and required fluid resuscitation.

Eight patients received blood transfusions. In five cases, blood products were given after bleeding. In three cases blood and/or fresh frozen plasma was given to increase a low haemoglobin level or to avoid bleeding prior to a procedure.

Minor bleeding was common. One episode of haematemesis following assault occurred, eight patients experienced epistaxis on one or more occasion, four patients experienced gum bleeding, one patient had a drip-site haematoma and another had problematic bleeding at a drip site.

Nine (45%) of 20 term pregnancies were delivered by caesarean section. There was an additional hysterotomy carried out to deliver a previable infant. The hysterotomy was performed as the mother had had two previous caesarean sections. HIV infection was more likely to be associated with surgical delivery ($p = 0.0017$).

Eleven pregnancies had episodes of arrhythmia, most commonly atrial fibrillation. However, in seven cases, the arrhythmia had been documented prior to pregnancy. Nine pregnancies were associated with worsening of New York Heart Association functional class, with three patients developing pulmonary oedema.

The average hospital stay was 41.0 days. Five (17.2%) patients spent 60 or more nights in hospital. The average number of admissions per patient was 3.0. Fourteen (48%) patients had four or more admissions.

Four or more admissions refused hospital treatment. There were 57 admissions between weeks 12 and 36, the period in which admission was not mandated, equating to an additional two admissions per patient, most commonly for sub-therapeutic INR requiring 'heparin cover'. In one case this occurred on five separate occasions, when the patient was repeatedly found to be sub-therapeutic on warfarin at antenatal visits and offered in-patient intravenous heparin. Additionally, two patients absconded.

Three spontaneous first-trimester miscarriages and three second-trimester miscarriages occurred (Table 5). Three pregnancies were terminated, one in the first trimester because the patient did not wish to continue a high-risk pregnancy. There were two terminations for foetal malformations not attributed to warfarin (Table 6). One of these had confirmed Dandy–Walker syndrome and was delivered by hysterotomy at 19 weeks. The other delivered vaginally at 22 weeks because of suspected anomalies based upon the presence of echogenic bowel.

One infant was born alive with multiple anomalies, including features consistent with warfarin embryopathy, together with other abnormalities. This patient had been taking 5 mg of warfarin daily. Antenatal ultrasound showed an absent nose and abnormal face with close-set eyes, low-set ears and a bossed forehead. Brain abnormalities were also noted and included dilated anterior horns of the lateral ventricle fusing in the midline and a dilated fourth ventricle. This patient refused early termination of pregnancy and the baby, born alive by caesarean section, died on day five of life.

Table 4. Details of major haemorrhage

Patient No.	*Timing of bleeding*	*Delivery*	*Gestation (weeks)*	*Details*	*Transfusion*	*Drop in Hb pre- and post-delivery (g/dl)*
1	Peripartum	C/S	37	1 100 ml lost during C/S. Wound continued to bleed. Day 5 post C/S had relook laparotomy but only required cauterisation of fat	2 units RBCs	3.4
2	Peripartum	C/S	37	Required repeat laparotomy for evacuation of haematoma and TAH and BSO. Patient was septic	2 RBCs, 4 FFPs	Not available
3	Peripartum	C/S	34	Wound haematoma, required return to theatre for evacuation	No	1.6
4	Peripartum	NVD + forceps	35	On day 6 post-delivery required evacuation of RPOC in theatre. Post evacuation found in shock requiring resuscitation and massive transfusion. Bilateral uterine artery embolisation attempted. This failed and patient had further surgery to pack vaginal bleeders. Patient was septic	3 units in pregnancy. Peripartum 11 RBCs + other products	6.6
5	Peripartum	Medical termination	11	Patient had termination of pregnancy. Later found in shock with Hb of 3 g/dl	2 units RBCs	7.0
6	Peripartum	Hysterotomy	19	1 litre intraperitoneal bleed post hysterotomy. Lowest Hb 3.9 g/dl. Required repeat laparotomy 2 days post hysterotomy.	Massive transfusion. 7 units RBCs, 6 units FFPs, cryoprecipitate and haemo-solvex	7.1

Hb: haemoglobin, RBCs: red blood cells, FFPs: fresh frozen plasma, C/S: caeserean section, TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy, RPOC: retained products of conception.

Table 5. Maternal and foetal outcomes

Outcomes	*Number (%)*
Maternal outcomes	
NYHA FC ($n = 13$)	
I/II	12
III	1
Deaths	2
Delivery	
Vaginal	19 (66)
Caesarean	9 (31)
Hysterotomy	1 (3)
Reasons for surgical delivery	
Foetal distress	3
Previous caesarian section	2
SROM	2
Other	3
Bleeding complications	
Major bleeding	7 (24)
Blood transfusion	8 (28)
Thrombotic complications	4 (14)
Arrhythmias	11 (38)
Time in hospital	
Hospital stay (days)	41 ± 28
Admissions	3 ± 1.8
Foetal outcomes	
Healthy	19 (66)
Birth weight (g) ($n = 19$)	< 2 kg: 2 2–2.5 kg: 4 2.5–4 kg: 13
Apgar score at 5 min ($n = 18$)	Apgars 9–10: 17 Apgars 7: 1 Born before arrival: 1
ENND	1 (3)
Pregnancy loss	6 (21)
Termination	3 (10)

NYHA FC: New York Heart Association functional class, SROM: spontaneous rupture of membranes, ENND: early neonatal death.

Table 6. Congenital abnormalities including warfarin embryopathy

Patient no	*Maternal age*	*GA at 1st antenatal visit*	*Parity*	*Anticoagulant and dose*	*Sonography*	*Foetal outcomes*
1	25	24	1	Warfarin, 5 mg	Polyhydramnios, abnormal facies, close-set eyes, absent nose, low-set ears, bossed forehead, abnormal ventricles, short spine, fat puffy hands and feet	ENND
2	29	17'5	2	Warfarin 5 mg in T1 then defaulted	Dandy–Walker malformation	Termination at 19 weeks
3	38	19'1	4	Warfarin 7.5 mg daily	Echogenic bowel	Termination at 22 weeks

GA: gestational age, ENND: early neonatal death, T1: first trimester.

Discussion

In this study, a high rate of serious adverse events was observed in maternal and foetal outcomes (Table 5). Maternal morbidity included major haemorrhage, cardiac failure and sepsis, as well as ischaemic stroke. There were three instances of pulmonary oedema, an approximately 20% risk of major haemorrhage, three ischaemic strokes and one case of infective endocarditis. Both deaths occurred post-partum. One was in a patient with significant vascular disease caused by Takaysu's arteritis, further complicated by HIV infection.

Adverse perinatal outcome was evident as a high rate of miscarriage in the first and second trimesters, two cases of suspected unrelated foetal anomalies and a third case of a complex foetal anomaly probably attributable to warfarin. Only 20 pregnancies (69%) had a normal neonatal outcome. The women in this cohort had lengthy hospitalisations, with 20 patients (69%) requiring more than 30 days in hospital and 15 (52%) requiring three or more admissions.

The mortality rate (6.9%) in our cohort compares unfavourably with similar local cohorts[9,13,15] and with a large meta-analysis showing a 2.9% rate,[2] but favourably with UKOSS, a recent United Kingdom population-based study.[16] Both mortalities occurred postpartum after discharge and in patients with double valve replacements, which have been associated with worse maternal outcomes.[16]

Inducing an anticoagulated state opposes the pro-thrombotic milieu of normal pregnancy.[17] Obstetric haemorrhage is known to be a major contributor to maternal deaths.[18] Haemorrhage rates were significantly high with 21% of patients having major haemorrhagic complications. This rate is comparable with other cohorts of women with mechanical prosthetic heart valves.[2,16] Another study[15] reported post-partum haemorrhage in only 5.8% of patients. These variable rates may reflect differing practice in the timing of anticoagulation reintroduction.

The anticoagulation protocol used prescribes heparin rather than warfarin from 36 weeks' gestation, allowing rapid reversal of anticoagulation if required during delivery. Delivery takes place during an anticoagulation-free 'window' to minimise risk of post-partum haemorrhage. There is a need to identify the optimal duration of this 'window' to balance the risks of haemorrhage and thrombosis. Heparin is usually reinstated six hours after delivery unless there is clinical concern of haemorrhage.

Of the 19 pregnancies delivered after viability, and consistent with other literature,[19-21] post-operative haemorrhage (3/9 caesarean sections, 33%) was more frequent than major haemorrhage post-vaginal delivery (1/10 normal vaginal deliveries, 10%), indicating that a longer anticoagulation window may be appropriate after operative delivery. The data suggest that caesarean sections should be performed only when clearly indicated, with meticulous haemostasis, and in anticipation of possible haemorrhage.

Despite the risk of major bleeding, neither death occurred as a direct result of bleeding. However, cases of major haemorrhage would have resulted in deaths had resuscitation, including transfusion not been available.

Only one patient had a suspected thrombo-embolic event. Two further patients had ischaemic strokes in the setting of HIV positivity.

Protocols used called for intravenous unfractionated heparin from six to 12 weeks' gestation and peripartum, according to relevant guidelines.[14] However, more recent guidelines[22] recommend subcutaneous low-molecular-weight heparin (LMWH) (enoxaparin, Clexane) in preference to unfractionated heparin (UFH), dose adjusted according to peak anti-Xa levels. LMWH has more predictable pharmacokinetics and less risk of allergic reactions, heparin-induced thrombocytopenia and osteoporosis compared to UFH.[22,23] However, there is concern

that the use of subcutaneous UFH may lead to unacceptably high rates of treatment failure and valve thrombosis.[24] Consequently, intravenous UFH is generally recommended and may remain the only alternative to warfarin where access to anti-Xa monitoring is limited, such as in our setting.

Intravenous heparin infusions are, however, resource intensive, requiring frequent monitoring and prolonged hospitalisation. The single suspected thrombotic event occurred in a patient receiving UFH while in a sub-therapeutic range. However, even ideal anticoagulation can lead to treatment failure.

In general, heparin use avoids the pregnancy loss and embryopathy associated with warfarin but carries a higher risk of valve thrombosis.[25] Women at particularly high thrombosis risk may be offered warfarin throughout pregnancy, except at peripartum. Factors conferring higher risk of thrombosis include older-generation mechanical heart valves, valves in the mitral position, and previous history of thrombosis on heparin. Improvements in prosthetic valve thrombogenicity over time have reduced the risk of thrombosis.[12]

Among live births in the cohort, the rate of caesarean section was 45%. While above the national average rate of 23.1%,[26] it did not differ from the background rate for all high-risk pregnancies receiving care at the tertiary hospital. HIV-positive patients were more likely to have caesarean delivery ($p = 0.0017$), perhaps reflecting the local policy of offering caesarean section to HIV-infected mothers with persistent viraemia.

Eleven (38%) patients had episodes of arrhythmia, of which seven (24%) had been documented prior to pregnancy, most commonly atrial fibrillation. This rate is high relative to both the developed[5] and developing[9] world.

Nine (31%) pregnancies were complicated by worsening New York Heart Association functional class, and three patients developed pulmonary oedema. This compares unfavourably with the cohort described by van Hagen *et al*.,[5] where 7.5% of pregnancies were complicated by heart failure, and may reflect more advanced disease or the effects of co-morbidities present in a low-resource setting.

Long hospital stays are costly and contribute negatively to patient quality of life. Out-patient regimens such as self-administered subcutaneous heparin as per newer guidelines[22,27] could reduce length of admissions.

Pregnancy loss occurred in nine pregnancies (31%), comparable with similar South African cohorts.[9,13] Congenital abnormalities were seen in three pregnancies (10%), however, only one (3.4%) was considered to be due to warfarin embryopathy, a rate lower than reported elsewhere.[2,9,13]

Warfarin embryopathy is caused by foetal exposure to warfarin between six and 12 weeks' gestation and is avoided by using heparin during this period. Only two patients presented prior to six weeks' gestation, enabling timeous switching from warfarin to heparin. Eleven patients presented between six and 12 weeks and received heparin from presentation to 12 weeks. The patient whose foetus may have been affected by warfarin embryopathy presented at 24 weeks' gestation and therefore was on warfarin throughout the vulnerable period.

Stengths and limitations

Comparison of this cohort with previously published literature shows some differences in mortality rate and perinatal outcome, which is likely spurious owing to the small sample size, and is further skewed by the death related to complicated Takayasu's arteritis.

Conclusion

Pregnancies in patients on anticoagulation carry additional risks due to both the underlying condition for which the patient is anticoagulated and the anticoagulation itself. In this small study, ischaemic events occurred intrapartum, while haemorrhagic events occurred peri- or post-partum. Avoidance of post-partum haemorrhage, particularly post-operatively, may be achieved by a longer anticoagulation-free 'window' peripartum. More studies are needed to identify the optimal window to balance haemorrhagic and thrombotic risk but it is likely to be longer than six hours. Heightened vigilance is required post-partum.

Contraception should be offered routinely at out-patient cardiac clinics. Preconception counselling should emphasise the importance of early presentation. Prolonged intravenous heparin is likely to be a risk factor for infective endocarditis. Subcutaneous out-patient LMWH should be considered.

The Hatter Institute for Cardiovascular Research is supported by the National Research Foundation South Africa, the Medical Research Foundation South Africa, the Maurice Hatter Foundation and SERVIER.

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Appendix 6: Reviewer comments

Ref.: Ms. No. CVJSA-D-18-00013
Haemorrhage and other complications in pregnant women on anticoagulation for mechanical heart valves; a prospective observational cohort study
CardioVascular Journal of Africa

Dear Dr Kariv,

We wish to inform you that your manuscript, Haemorrhage and other complications in pregnant women on anticoagulation for mechanical heart valves; a prospective observational cohort study, has been accepted for publication in CardioVascular Journal of Africa.

Unfortunately, we are unable to tell you which Volume and on what pages at present as we rely on our set-out design & publishers for that information.

You will be contacted by our Production Editor when your article is ready for final proof reading before publication.

It has become necessary for the Cardiovascular Journal of Africa to charge a manuscripts submission fees for all articles submitted for publication from 1 January 2017. On acceptance of a manuscript an additional Article Processing Fee will apply before publishing.

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Thank you for submitting your work to this journal.

With kind regards

Pat J Commerford, MBChb FCP(SA)
Editor-in-Chief
CardioVascular Journal of Africa

Comments from the Editors and Reviewers:

Reviewer #1: Good relevant study

Minor revision.

Line 141 - 145: She returned to casualty forty-one days post-delivery having suffered a cardiorespiratory arrest and could not be resuscitated. The cause of death was unclear however suspected to be a valve thrombosis on the basis that the patient complained to the pre-hospital crew that she was unable to hear her valve clicks. Her INR on the day of death was 3.73 (supratherapeutic). She had had no INR monitoring between discharge post-partum and her presentation in cardiac arrest.

Comment on above: I Struggle to make sense. Was patient dead on arrival at hospital? Was patients still alive when help arrived (the pre-hospital crew?). Where does INR information come from? Was blood taken from dead person?

Line 178 - 179: The death described above may have been due to a valve thrombosis, but this is unproven. No deep vein thromboses or pulmonary emboli were detected.

Comment on above: Death of Takayasu patient or the other one? It must be the latter, but not automatically evident.

Line 221 - 223: Comment: What was outcome in patients that refused treatment an absconded? Did they have complications?

"Time in hospital" and in "Discussion
In results

Line 218 - 220. The average hospital stay was 41.0 days. Five (17.2%) patients spent 60 or more nights in hospital. The average number of admissions per patient was 3.0. Fourteen (48%) patients had four or more admissions.

In Discussion

Line 250 - 251 The women in this cohort had lengthy hospitalisations with twenty patients (69%) requiring more than 30 days in hospital and 15 (52%) requiring three or more admissions
Comment on above: I do not quite follow the information and reporting of the length of hospital stay
(1) Question: Did all patients not have mandatory admission week 6 to 12 and from week 36 onwards for IV administration of Heparin? So is starting point not 2 admissions/patient and about 40 to 60 days of admissions?
(2) For the reader it may maybe one should bring what is said in discussion in line with results. The reader will not be able to derive some of this information from from table 4.

Line 279 - 286:

Comment: One was wondering why low molecular heparin was not used sub-cutaneously. The authors explain very well about the choice of UFH and why given IV (in the discussion, not the introduction)

Reviewer #2:
The authors should be congratulated for describing this series of cases which are relevant to understand the poor outcomes and multimorbidity found in similar settings.
The are few grammar errors that can be reviewed.
Table 1 - please include in the right column n(%)
I recommend that only the most important features of each case are described.

End