Cardiovascular Topics

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

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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 ($p = 0.0017$).

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Conclusions: Complication rates were high despite centralised care.

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

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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.

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

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.

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

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)

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) 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.

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.

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 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

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.

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.

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.[5,16] 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.

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