Post caesarean section outcomes of obstetric valvular heart disease patients at Charlotte Maxeke Johannesburg Academic Hospital

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A research report submitted to the faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

Johannesburg, 2022

DECLARATION

I, Ntombizabanguni Glory Mfeka, declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

On this 16th day of March 2022

DEDICATION

This project is dedicated to Senate Likhoeli

ABSTRACT

Background

Valvular heart disease presents a unique set of conditions during pregnancy and delivery with the potential of adverse outcomes complicated by prior interventions and anticoagulation. The aim of this study was to describe the profile and outcomes of obstetric valvular heart disease patients who delivered via caesarean section at Charlotte Maxeke Johannesburg Academic Hospital.

Methods

A retrospective study was done using patient record files, anaesthetics forms and echocardiogram reports. The study period was a 5-year review from January 2016 to December 2020.

Results

Sixty-nine patients were included. The mean age ± SD of the patients in this study was 30.1 ± 5.6 years. A total of 83% had gravidity of 1-3 and 90% parity of 0-2. Majority of patients (57%) had elective caesarean section. General anaesthesia was the most common mode used and majority of patients had fixed interval analgesia (FIA) mode of analgesia postoperatively. 40.5% of the patients were on anticoagulants. A significantly higher percentage of those who needed anticoagulation (46%) had poorer outcomes when compared to those who did not (7%), (P<0.001). The was a univariable association between adverse maternal outcome and NYHA class and lack of use of anticoagulants [aOR 3.77, 95%CI 1.45 – 9.79, P=0.006 and aOR 0.11, 95%CI 0.018 – 0.67, P=0.017, respectively]. Low ejection fraction was univariably associated with adverse foetal outcome, uOR 0.94, 95%CI 0.90 – 0.99, P=0.032. One (1%) foetus demised.

Conclusion

Patients were younger and in relatively good functional status. They carried the pregnancies to term. Patients did experience adverse outcome related to bleeding and arrythmias predominantly, but none demised. One neonate was lost. A structured care plan for these patients, based on a multidisciplinary approach, to afford prehabilitation is necessary.

Keywords: obstetric valvular heart disease, caesarean section, adverse outcomes

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I would like to thank my supervisors for all the input they had the entire duration of the study. I would also like to thank my family for the support, especially Nqobile, thank you so much for all your hard-work and endless support.

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LIST OF ABBREVIATIONS

FIA-	Fixed interval analgesia
NYHA-	New York Heart Association
EF-	Ejection fraction
CMJAH-	Charlotte Maxeke Johannesburg Academic Hospital
GA-	General anaesthesia
M.O-	Medical officer
ICU-	Intensive care unit
SD-	Standard deviation
IQR-	Inter-quartile range

DRAFT ARTICLE

Introduction

The incidence of cardiac disease in pregnancy is estimated to be in the range of 1-1.5% (1, 2). Cardiac disease still represents a significant cause of poor maternal and foetal outcomes in pregnancy (2, 3). Valvular heart disease related to rheumatic fever has declined in high-income countries but remains a significant health problem in low-income countries (2, 4).

Valvular heart disease impacts the heart and the body's ability to cope with the normal physiological changes of pregnancy (5, 6). It also often exacerbates the physiological changes of pregnancy, with most patients being diagnosed for the first time with valvular heart disease during the pregnancy (7-9).

Many complications have been associated with the disease in pregnancy such as: thrombo-embolism, cardiac arrhythmias, pulmonary oedema, and bleeding post caesarean section due to the use of anticoagulation (2, 10, 11). Valvular heart disease has considerable effects on foetal outcomes and can result in preterm birth, respiratory distress, low birth weight even at term, increased resuscitation rates in severely preterm babies, and foetal demise (11, 12).

The role of a multidisciplinary team in these often challenging patients is not only to ensure that the patient can tolerate the challenges of pregnancy and delivery, but also to ensure survival in the postoperative period and beyond (4, 15).

Data on perioperative outcomes of valvular heart disease in pregnancy in Sub-Saharan Africa is sparse. Knowledge is required on the perioperative course of valvular heart disease patients for management protocols to be developed to assist with the management in our resource limited settings. This study is aimed at evaluating the perioperative outcomes in obstetric valvular heart disease patients post caesarean section in the Department of Anaesthesia at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methods

This study was a descriptive retrospective study. The data in this study was collected from CMJAH (single centre). The study population consisted of obstetric patients with valvular heart disease who delivered by caesarean section over a period of 5 years from January 2016 - December 2020. The patient information utilised in this study was obtained from anaesthetic charts, patient record files and echocardiographic reports.

A total of 69 patients were included. No patients were excluded from this study for the study period. Permission to perform the study was obtained from CMJAH and the Human Research Ethics Committee (HREC) of the University of the Witwatersrand, research number M200751. Data were collected by the primary investigator. Patient information was de-identified and confidentiality maintained. The patient data is currently stored securely in a locked cabinet in a secure building.

Statistical analysis

Data were collected on a Microsoft excel spreadsheet. Frequency and percentages were used to describe demographic data. Clinical and outcome data were reported as mean (SD) if normally distributed and median (IQR) if not normally distributed. Associations between patient characteristics and outcomes were determined using Fisher's Exact test, and the Wilcoxon-Ranksum test depending on the data distribution. A regression analysis was conducted to determine univariable associations with maternal and foetal outcomes. Those factors with $P<0.1$ were included into a multivariable regression analysis model. P values of <0.05 were accepted as significant.

Results

The total number of records analysed were 69. The valve lesions ranged from isolated mitral, tricuspid, pulmonary and aortic valves, to mixed valve lesions (Figure 1). Patients had a caesarean section under regional anaesthesia (spinal/epidural), general anaesthesia or a combined

technique. The mean age ± SD of the patients was 30.1 ± 5.6 with a range of 18- 41yrs (Table 1). Ninety percent (n= 62) of patients were of the Black race. A total of 83% had gravidity of 1-3 and 90% parity of 0-2. Most neonates were born at term (75%) with a median (IQR) gestation of 37 (36-38) weeks. Majority of patients (57%) had elective caesarean section whilst 43% had emergency caesarean section. General anaesthesia was the most used mode and majority of patients had fixed interval analgesia (FIA) postoperatively. Approximately half of the patients (40.5%) were on anticoagulants.

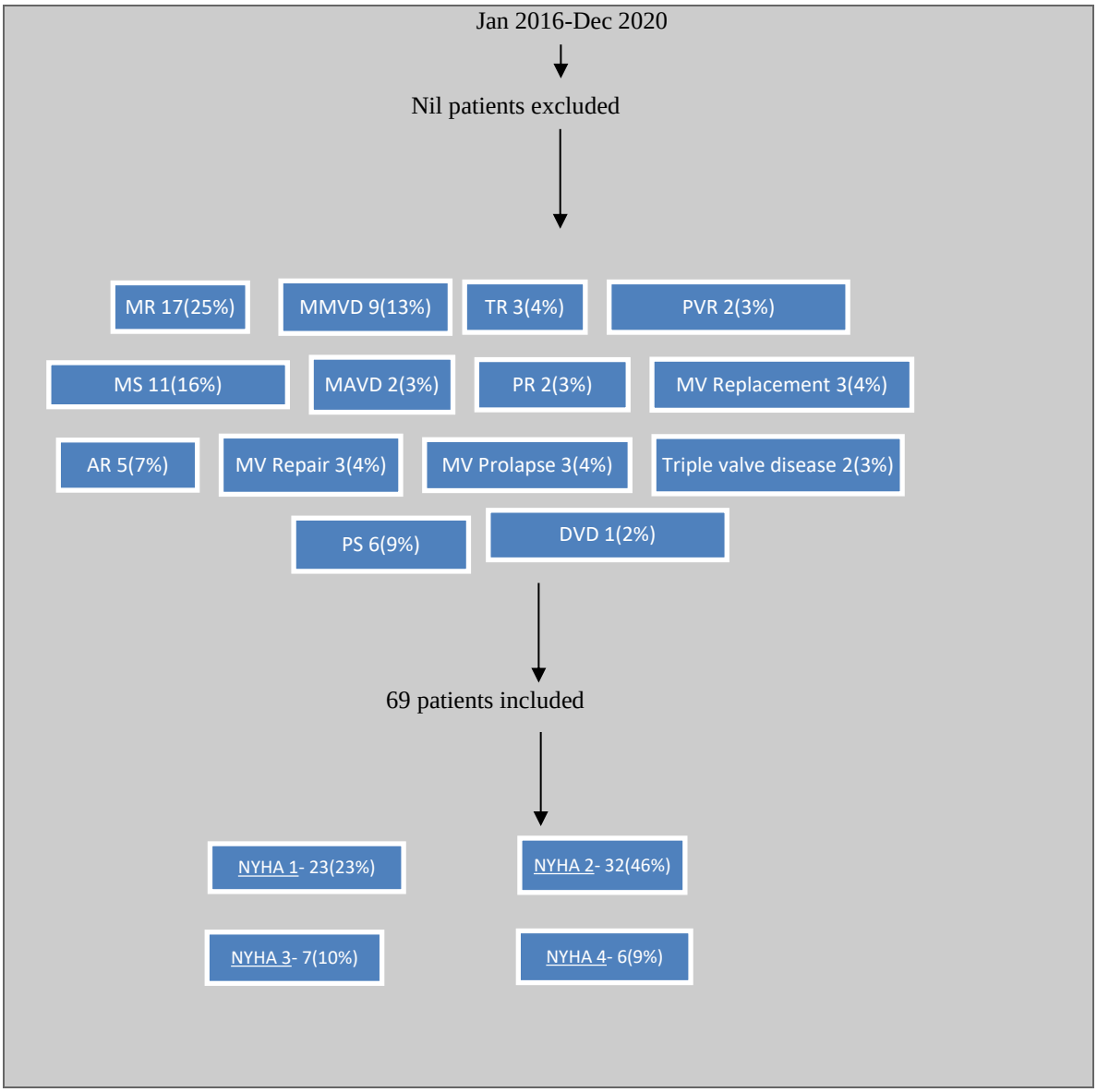

Figure 1 Flow diagram of the study data

A predominantly larger proportion of patients had mild to moderate valvular disease 62%, whereas 26% presented with severe disease (Table 2). The cause of the valvular heart disease was predominantly rheumatic in nature as opposed to congenital pathology, 75% vs 25% respectively.

Table 1 Patients characteristics

Parameters		N (%)
Age (Years)	16 – 25	18 (26)
	26 – 35	36 (52)
	36 – 45	15 (22)
Ethnicity	Black	62 (90)
	Coloured	2 (3)
	Caucasian	3 (4)
	Asian	2 (3)
Gravidity	1 – 3	57 (83)
	4 – 6	9 (13)
	7 – 9	3 (4)
Parity	0 – 2	62 (90)
	3 – 5	6 (9)
	6 – 8	1 (1)
Gestational age	28 – 32 weeks	5 (7)
	33 – 36 weeks	12 (17)
	37 – 42 weeks	52 (75)
Elective/Emergency	Elective	39 (57)
	Emergency	30 (43)
Mode of anaesthesia	Spinal	23 (33)
	Epidural	8 (12)
	General Anaesthesia	34 (49)
	Unknown	1 (1)
	Spinal + GA	2 (3)
	Epidural + GA	1 (1)
Post-op analgesia	Epidural	4 (6)
	Spinal	2 (3)
	FIA	36 (52)
	Unknown	1 (1)
	Spinal + Fixed	22 (32)
	Epidural + Fixed	4 (6)
Surgeon level of experience	MO	3 (4)
	Registrar	33 (48)
	Consultant	29 (42)
	Unknown	4 (6)
Anti-coagulant	On Anti-coagulation	28 (41)

*FIA – Fixed interval analgesia, MO – medical officer, GA – General anaesthesia.

The data in table 2 shows that NYHA classes 1 and 2 represented 79% of patients and also shows that 84% of patients had not had any surgical intervention for their cardiac pathology prior to the caesarean section.

Table 2 Presenting Cardiac Pathology

Parameters		N (%)
Lesion Severity	Mild	29 (42)
	Moderate	14 (20)
	Severe	18 (26)
	Severity unknown	8 (12)
Congenital/Acquired	Congenital	17 (25)
	Acquired	52 (75)
NYHA Class	1	23 (33)
	2	32 (46)
	3	7 (10)
	4	6 (9)
	Unknown	1 (2)
Prosthetic/Native valve	Tissue	3 (4)
	Mechanical	4 (6)
	Valvuloplasty	2 (3)
	Native valve	58 (84)
	Unknown cardiac intervention	2 (3)

*NYHA- New York Heart Association

Table 3 details the different predominant valvular lesions reported. Mitral valve disease accounted for most of the predominant lesions and tricuspid valve disease was the least reported. A total of 42% of patients with MS presented with a mitral valve area (MVA) of less than 1.5cm² (Table 3).

Cardiac arrhythmias and bleeding were the leading complications at rates of 9% each (Table 4). Nineteen patients (27%) were cared for in ICU postoperatively, 35 (51%) were in high care, and 15 (22%) at the general ward. None of the patients died in hospital. Majority of the neonates were born at term (75%), at normal birth weight of ≥ 2500 gram (68%) (Table 6). Respiratory distress at birth occurred in 14 (20%) neonates and 1 (1%) foetus demised.

Table 3. Predominant cardiac lesions and echocardiography parameters

Parameter		N (%)
Cardiac Lesion		
Mitral regurgitation		20 (29)
Mitral stenosis		11 (16)
Mixed mitral valve disease		9 (13)
Mitral valve replacement previous		3 (4)
Mitral valve repair previous		3 (4)
Pulmonary stenosis		6 (9)
Pulmonary valve replacement		2 (3)
Pulmonary regurgitation		2 (3)
Aortic regurgitation		5 (7)
Mixed aortic valve disease		3 (4)
Tricuspid regurgitation		3 (4)
Triple valve disease		2 (3)
Echocardiography		
Ejection fraction (%)	<50	7 (10)
	50 – 55	7 (10)
	56 – 65	31 (46)
	66 – 75	18 (27)
	76 – 85	5 (7)
MVA (cm^2)	0.5 – 1.5	10 (42)
	1.6 – 2.5	10 (42)
	2.6 – 4	4 (16)
Pulmonary arterial pressure (mmHg)	25 – 30	4 (20)
	31 – 40	5 (25)
	41 – 50	7 (35)
	51 – 60	4 (20)

*MVA – Mitral valve area

There was a significant univariable association between NYHA and those not on anticoagulation with adverse maternal outcome [UOR 3.22, 95%CI 1.56 – 6.66, P= 0.002] [UOR 0.075, 95%CI 0.026 – 0.42, P= 0.002], respectively. Both factors remained significant in an adjusted model (Table 5). EF was the only factor univariably associated with adverse foetal outcome [UOR 0.94, 95%CI 0.90 – 0.99, P= 0.032] (Figure 2).

Table 4 Maternal and foetal outcomes

Parameters		N (%)
Maternal		
Bleeding		6 (9)
Thrombo-embolism		0 (0)
Cardiac-arrythmias		6 (9)
Cardiac failure		5 (7)
Pulmonary oedema		1 (1)
In-hospital mortality		0 (0)
Post-operative stay	ICU	19 (27)
	High care	35 (51)
	Ward	15 (22)
Neonatal		
Birth weight	< 1 500g	2 (3)
	1 500g – 2 499g	19 (28)
	≥ 2 500g	47 (68)
	Unknown	1 (1)
Maturity at delivery	28 – 32 weeks	5 (7)
	33 – 36 weeks	12 (17)
	≥ 37 weeks	52 (75)
Respiratory distress		14 (20)
Foetal demise		1 (1)

*ICU ─ Intensive care unit

The most used method of post-operative analgesia was fixed interval analgesia (FIA) 52%. Majority of patients 49% had a general anaesthetic, however, there was an insignificant relationship between the mode of anaesthesia with poor maternal outcomes (>0.1).

Table 5 Factors associated with maternal and foetal outcomes

Parameter		UOR (95% CI)	p-value	AOR (95% CI)	p-value
Maternal outcomes					
Age in years		1.09 (0.97 – 1.21)	0.14		
Gravidity		1.01 (0.70 – 1.49)	0.93		
Parity		0.98 (0.60 – 1.60)	0.95		
Acquired or congenital	Rheumatic	1 (reference)		1 (reference)	
	Congenital	0.17 (0.02 – 1.40)	0.10	0.26 (0.019 – 0.35)	0.31
NYHA class		3.22 (1.56 – 6.66)	0.002	3.77 (1.45 – 9.79)	0.006
EF %		0.98 (0.93 – 1.04)	0.55		
Anticoagulant	Yes	1 (reference)		1 (reference)	
	No	0.075 (0.026 – 0.42)	0.002	0.11 (0.018 – 0.67)	0.017
Elective/ Emergency	Elective	1 (reference)			
	Emergency	0.39 (0.11 – 1.38)	0.15		
Neonatal outcomes					
Age in years		1.02 (0.94 – 1.11)	0.64		
Gravidity		1.09 (0.79 – 1.50)	0.60		
Parity		0.89 (0.59 – 1.34)	0.58		
Acquired or congenital	Rheumatic	1 (reference)			
	Congenital	0.82 (0.26 – 2.48)	0.72		
NYHA class		1.15 (0.67 – 1.96)	0.62		
EF %		0.94 (0.90 – 0.99)	0.032	0.96 (0.90 – 1.01)	0.12
Anticoagulant	Yes	1 (reference)		1 (reference)	
	No	0.43 (0.16 – 1.16)	0.094	0.55 (0.17 – 1.77)	0.32
Elective/ Emergency	Elective	1 (reference)			
	Emergency	1.13 (0.44 – 2.95)	0.82		

*NYHA – New York Heart Association

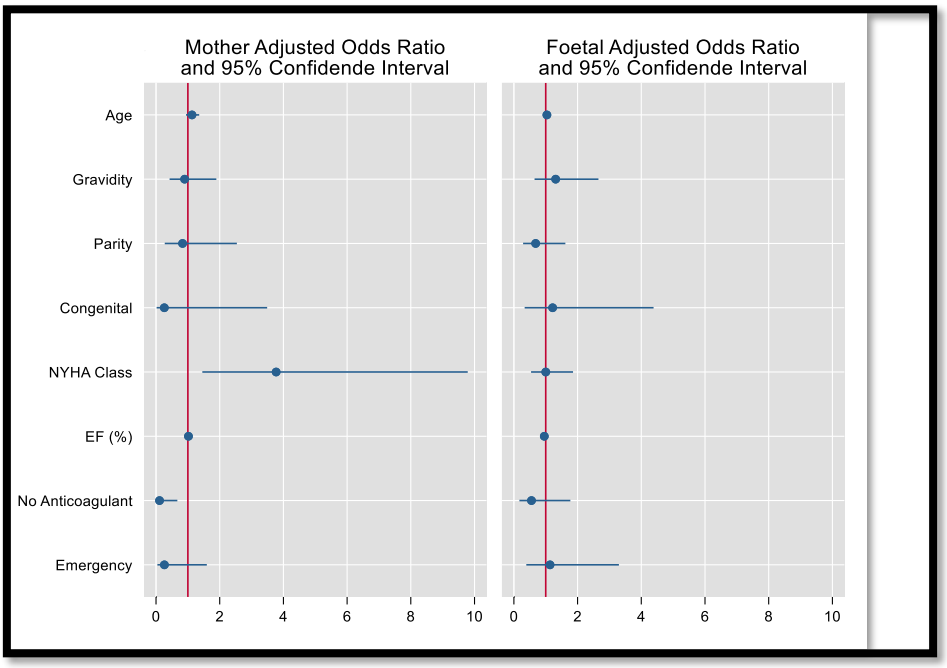

Figure 2 Forest plot of factors predictive of adverse foeto-maternal outcome.

Discussion

The patients in our study were young, mean age of 31 years (9). Majority were Black with low gravidity and parity. They seemed to carry the pregnancy to term successfully as a large proportion of patients were in NYHA 1-2, with mild to moderate disease. Symptoms of valvular heart disease are often unmasked during the pregnancy due to exacerbation of the physiological changes of pregnancy (7-9).

Higher classes of NYHA were associated with adverse maternal outcome, whereas low EF adversely affected foetal outcome. However, majority of our patients (90%) had normal EF, making the extrapolation difficult. Similar to our outcomes, it has been shown that severity of maternal disease affects foetal outcome (1). The presence of heart disease, more especially in those with a high NYHA class, have been shown to be associated with the highest risk of maternal and foetal morbidity and mortality (13, 14).

Of concern was that most were not on anticoagulants and this factor had a significant univariable association with adverse outcome. Despite this, the leading complication was haemorrhage

postoperatively. Patients were predominantly cared for in ICU or HCU. The nature of the cardiac lesions was predominantly acquired compared to congenital. This reflects an ongoing rheumatic heart disease state in our communities.

Majority of patients in this study had no cardiac surgical intervention prior to this pregnancy, possibly because many of them were only diagnosed with cardiac pathology during the pregnancy. This may be due to limitations in access to health care services in our country similar to that reported in low-income countries (1, 12). The predominant lesion in our study was mitral valve disease, which is patho-pneumonic of rheumatic heart disease as it known to predominantly affect the mitral valve (4). Of those with MS, 7 (64%) had critical stenosis. Within those with pulmonary hypertension, 2 (10%) had severe PHT.

In this currently study, complications such as postpartum haemorrhage (9%) and cardiac arrhythmias (9%), which have been reported in previous studies, were present in our patients (10,12). The type of anaesthetic, timing of surgery, level of qualification of surgeon, urgency of the procedure, parity or gravidity seemed to have no bearing on outcomes. The choice of regional or general anaesthetic, is often determined by the patient's haemodynamic stability and goals associated with each valve lesion (10, 16). Perhaps the reason why most had general anaesthesia.

Conclusion

However, it is evident that patients were younger and in relatively good functional status considering their valve lesions, affording them progress to term labour. Patients did experience adverse outcomes related to bleeding and arrythmias predominantly, but none demised. One neonate was lost. A structured care plan for these patients, based on a multidisciplinary approach, is necessary. Our cohort over 5 years was small. Data therefore cannot be extrapolated to the whole population

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APPENDICES

Proposal

Post caesarean section outcomes of obstetric valvular heart disease patients at Charlotte Maxeke Johannesburg Academic Hospital

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Table of Contents

1. Introduction

The declaration of the millennium development goals, aiming for a reduction in worldwide maternal deaths by 75%, has put maternal health as a priority subject (1). Cardiac disease in pregnancy has been highlighted as one of the leading causes of poor outcomes (1, 2). Cardiac disease remains as one of the leading causes of foetal and maternal morbidity and mortality especially in low income countries (2, 3). Management of these patients require a multidisciplinary approach consisting at the least, of a cardiologist, an obstetrician, and an anaesthesiologist, all with experience in managing high risk pregnancies in women with cardiac disease (1, 3).

The physiological haemodynamic changes of pregnancy may mimic cardiovascular disease, therefore careful examination of the cardiovascular system is imperative during pregnancy (1). Changes occurring in pregnancy at the beginning of the second trimester and peaking during the third trimester include: an increase in cardiac output, volume overload, decreased systemic vascular resistance, an increase in stroke volume, 15-20% increase in heart rate, and an increase in left ventricular end diastolic volume (1, 2).

The prevalence of cardiovascular disease in pregnancy has been reported to be 1-3% (2) in high income countries and higher (5.9%) in low income countries (4). It is reported to be accountable for more than 10-15% of maternal deaths (1, 2). Valvular heart disease in pregnancy was found mostly to be from congenital heart disease in high income countries whilst rheumatic heart disease was found to be responsible for more than 90% of the cases in low income countries (2, 3, 5). In a Cape Town study in South Africa by Anthony et al (5), it is reported that the high incidence of rheumatic valvular heart disease in sub-Saharan Africa is most likely due to socio-economic conditions, overcrowding and limited access to medical care.

Many women are diagnosed with cardiac disease during pregnancy (2, 6). This has been postulated to be due to the increased burden of haemodynamic changes in pregnancy that unmask or worsen the symptoms of pre-existing cardiac disease (2, 6).This has led to increased numbers of patients with no previous work-up with an index presentation during pregnancy (5).

Studies have reported a high mortality rate in patients with severe valvular heart disease in the postpartum period, mortality rates of 26% in South Africa(5), An American study reports the mortality rate to be 50% in Africa (2).

Cardiac disease is not the most common disease in pregnancy, it does however contribute significantly to maternal morbidity and mortality (2).In a study in Senegal (7) on maternal outcomes in sub-Saharan Africa, a number of predictive factors for adverse outcomes in women with rheumatic heart disease were found. Mitral stenosis, severe tricuspid regurgitation, NYHA functional class III or IV, and symptoms of heart failure, were the leading predictive factors associated with maternal mortality (7). This was correlated by Hameed et al (8) who found increased maternal morbidity and unfavourable foetal outcomes in women with moderate and severe mitral and aortic stenosis.

There are increased complications associated with valvular heart disease in pregnancy that affect both mother and baby. The complications include maternal complications such as: pulmonary oedema; pulmonary hypertension; heart failure; arrhythmias; thromboembolism; stroke; and death (6). Foetal complications may also arise as consequence of maternal valvular heart disease and include: growth restriction; respiratory distress; preterm birth; low birth weight; and foetal or neonatal death (2, 6).

Studies have reported marked differences between epidemiology of valvular heart disease in African low income countries compared to high income countries (9). In a study in Senegal (7), 92% of hospitalisation due to heart disease were in women as a result of rheumatic heart valve disease. In addition to epidemiological differences, the mortality rate is also reported to be much higher in African low income centres at 50% compared to 3% in high income centres (9). These differences in mortality rate are reported to be due to early diagnosis and intervention before complications in high income countries (9).

The high mortality rate of pregnant patients with valvular heart disease has led to the development of risk stratification tools to identify patients at high risk of morbidity and mortality (10). The Cardiac Disease in Pregnancy I study (CARPREG 1) (1) described

ante-partum predictors such as cardiac events, arrythmias and prior New York Heart Association (NYHA) functional classes 3-4 as predictive.

The CARPREG II study (11) identified 10 predictors; prior cardiac events or arrhythmias; baseline NYHA III-IV or cyanoses; mechanical valve; ventricular dysfunction; high risk left-sided valve disease; pulmonary hypertension; coronary artery disease; high risk aortopathy; no prior cardiac intervention and; late pregnancy assessment.

“ZAHARA which is exclusively for adults with congenital heart disease, modelling risk for 8 conditions” (1). The validated World Health Organization (WHO) guidelines (12) which incorporated the European Society of Cardiology (ESC) guidelines in 2012 (12) are some such tools which have been developed to assist physicians to identify high risk patients (12).

In a South African study in Cape Town Joubert et al (13) used a modified table from Reimold and Rutherford (13) for classification of valvular heart lesions. This table included the following variables: maternal age, previous heart failure, previous stroke or transient ischaemic attack, multiple gestation, smoking during pregnancy, use of anticoagulant therapy throughout pregnancy and the different valvular heart lesions and their severity. This table assisted in classifying valvular heart lesions according to maternal, foetal, and neonatal risk.

Vaginal delivery remains the standard mode of delivery in patients where it is not contraindicated. For those patients who require operative delivery for obstetric or cardiac reasons, it has been found that elective caesarean section has better outcomes than emergency caesarean section (14). Emergency caesarean section is associated with higher post-operative complications. These are reported as increased fever rate, increased cases of urinary tract infection, poor wound healing and longer hospital stay (14).

The rate of post-partum haemorrhage was reportedly not significantly different in elective vs emergency caesarean section in patients with valvular heart disease (15).

On the contrary, Suwal et al (14) found that postpartum haemorrhage was more commonly seen in elective caesarean sections in their study in Nepal.

1.1 Mitral stenosis in pregnancy

Mitral stenosis is the most common valvular heart lesion in pregnancy resulting as a complication from rheumatic heart disease (16).

In the study by Wolfe et al (1) it is postulated to present in approximately 63% of women of childbearing age. Mitral stenosis is poorly tolerated in pregnancy (5). The symptoms of mitral stenosis are related to the degree of stenosis; those with severe disease experiencing the worst symptoms (5).

The spectrum of presentation can be asymptomatic in mild mitral stenosis to experiencing dyspnoea; orthopnoea; paroxysmal nocturnal dyspnoea and frank heart failure (5, 16). In the study by Saxena et al (17) in India it is reported that pregnancy results in a poorer NYHA functional class due to the increase in cardiac output.

The basic principles of management of patients with mitral stenosis outweighs the mode itself (18). Single shot neuraxial anaesthesia has not been advocated for in the literature because of its sudden sympathectomy which decreases systemic vascular resistance and leads to adverse outcomes in patients with mitral valve stenosis (18). Graded epidurals are favoured in some centres as this causes a less rapid decrease in systemic vascular resistance due to the gradual onset of the block (4, 18, 19). This is in contrast to spinal and general anaesthesia.

General anaesthesia is usually preferred for those patients with severe mitral stenosis (17). This mode of anaesthesia needs to be managed aggressively. Prevention or early correction of abnormal cardiac rhythms; prevention of increased ventricular rates due to pain; intubation and extubation responses; and prevention of rapid and sudden decreases in systemic vascular resistance from the effects of volatile agents when used are imperative (4). Prevention of sudden increase in blood volume post ventilation, hypoxia and hyperventilation resulting in increased pulmonary artery pressures, is also important (4). General anaesthesia may be performed in cases where patients have

known contraindications to neuraxial anaesthesia and cannot have neuraxial anaesthesia for obstetric reasons (6).

1.2 Aortic stenosis in pregnancy

Aortic valve disease is uncommon in obstetric patients. When present the condition is often due to congenital bicuspid valve (5). Unlike mitral stenosis, aortic stenosis is usually diagnosed pre-pregnancy giving room for optimization of the patient prior to pregnancy.

Patients with mild or asymptomatic disease during exercise testing have been noted to tolerate pregnancy better than those who have moderate to severe symptomatic disease (5).

Similar to mitral stenosis, the symptoms of aortic stenosis increase as the degree of stenosis increases. Symptoms are worst in patients with a total valve area less than 1 cm^2 (16).

The symptoms can range from dyspnoea, chest pain, syncope and a reduction or failure to increase transvalvular gradient (in pregnancy it should usually increase by 20%) (5). Patients with aortic valve disease often cannot tolerate tachycardia, decreased systemic vascular resistance and hypotension as these factors all have an effect on cardiac output (13).

The mode of anaesthesia is not as important as following the general principles of management of aortic valve stenosis (4). Most authors have advocated the use of epidural anaesthesia or a combined spinal epidural for these patients as these modes have been shown to have a favourable haemodynamic control (4). General anaesthesia is advised against except where there is an obstetric indication as the intubation and extubation responses increase heart rate and systemic vascular resistance affecting cardiac output and coronary perfusion negatively (4). As hypotension is an effect of almost all anaesthetic agents, phenylephrine has been recommended as the vasopressor of choice, as it causes peripheral vasoconstriction without a tachycardia which is a desired effect when dealing with aortic stenosis (13).

1.3 Tricuspid and pulmonary stenosis in pregnancy

The tricuspid and pulmonary valves are rarely affected alone in the pregnant patient but rather present as part of mixed valvular heart disease. The effects of these lesions if alone are well tolerated in pregnancy.

However in mixed valvular heart disease their effects are additive. The predominant symptoms that the patient will experience will be those of the dominant lesion (4, 5). Tricuspid and pulmonary stenosis will usually present with signs of right heart failure (2).

In severe tricuspid and pulmonary stenosis single shot spinal is not recommended as venous pooling may result in decreased venous return with resultant deleterious effects. A graded epidural anaesthesia is recommended with maintenance of preload, contractility and afterload. General anaesthesia may also be carried out however it carries a higher risk of unwanted side effects such as hypothermia, hypercarbia, acidosis and hypoxaemia (13).

1.4 Mitral regurgitation in pregnancy

Mitral regurgitation may occur as a consequence of valve prolapse, rheumatic fever, endocarditis and left ventricular dilatation within a structurally normal valve (16).Mitral regurgitation causes left ventricular damming and dilatation which ultimately leads to left heart failure and pulmonary oedema (5, 16).

Mitral regurgitation unlike stenosis is well tolerated in pregnancy as the physiological changes of pregnancy may actually assist to ameliorate symptoms of regurgitation (5, 13). The physiological changes of pregnancy most helpful in regurgitation include a substantial decrease in systemic vascular resistance which would encourage forward flow of blood, an increased heart rate that helps to decrease the regurgitant fraction, these effects help to increase the left ventricular end diastolic volume and improves overall hemodynamics (5). Of concern is the risk of a hypercoagulable state in pregnancy which, according to Chohan et al (16) lead to systemic embolism as a complication in up to 20% of patients with mitral regurgitation (16).

In general, as mitral regurgitation is well tolerated in pregnancy, the mode of anaesthesia is determined by physician experience as spinal, general anaesthesia or epidural may be carried out (16). There is a preference towards graded epidural in the literature (2).

The overall goals of management of mitral regurgitation should be to prevent bradycardia, decrease systemic vascular resistance, avoid pulmonary congestion and keep the patient in sinus rhythm (16).

1.5 Aortic regurgitation in pregnancy

Aortic regurgitation is often related to mitral regurgitation in incidence and cause; aortic regurgitation may be a consequence of endocarditis, structurally abnormal valve leaflets or may be due to a dilated aorta leading to functional regurgitation (2, 10). However it is reported that the leading cause is still rheumatic fever in approximately 75% of cases (16).

Aortic regurgitation is often accompanied by con-comitant mitral regurgitation (5). The effects of the regurgitation are a dysfunctional overloaded dilated left ventricle which leads to backflow of blood and pulmonary oedema (2). Surgical intervention for valve repair is rarely necessary during pregnancy (2, 5).

The general anaesthetic considerations are to prevent conditions that increase the regurgitant fraction and improve coronary perfusion (13). Bradycardia, increased systemic vascular resistance, decrease pain and avoidance of volume overload are some of the management principles (13). Neuraxial anaesthesia is favourable in these patients as it causes a decrease in systemic vascular resistance, and where a vasopressor is required, phenylephrine is best avoided as it is associated with bradycardia that is not well tolerated (13).

1.6 Tricuspid and pulmonary regurgitation in pregnancy

Tricuspid regurgitation, similar to aortic regurgitation, is rarely significant in the absence of ventricular dysfunction and is well tolerated in pregnancy (2). Extensive intervention

is not required and the lesion is rarely corrected during pregnancy with the exception of Ebstein's anomaly with associated decompensation (2).

Pulmonary regurgitation may be a sequel of previously repaired Tetralogy of Fallot or as a complication of stenosis treated by balloon valvuloplasty.

It is severe when combined with right ventricular dysfunction.

The normal physiology of pregnancy may aggravate right ventricular dilatation and precipitate right heart failure.(2)As previously mentioned isolated tricuspid or pulmonary regurgitation is rare and is not commonly due to rheumatic fever (5). When is does occur it is usually as part of a mixed valvular heart disease, the mode of anaesthesia here will be determined by the dominant lesion which is usually mitral stenosis or regurgitation and anaesthesia will be as mentioned for these valvular heart lesions above (2, 5).

1.7 Prosthetic valves in the pregnant patient

The definitive management of patients with valvular heart disease is often surgical replacement of the valve (20). This can be achieved by replacing the valve either with a mechanical, a bio prosthetic, or an autograft valve (20). The choice of valve best for the patient would depend on patient choice, child bearing age, severity of disease and the risk of thrombo-embolic events (2, 5).Prosthetic heart valves are prone to a set of complications including thrombosis, sepsis, endocarditis, regurgitation or stenosis despite surgical intervention (2, 5, 20).

Anticoagulation is extremely important for patients with prosthetic valves (13). The risk of prosthetic valve thrombosis increases from 0.1%-5.7% in the non-pregnant patient to 10% in pregnancy (2). Literature suggests that there are no optimal agents for pregnant patients with prosthetic valves (2, 13).

The risk of thromboembolic events differs from 3.9% when warfarin is used alone in the first trimester; to 9.2% when heparin is used in the first trimester followed thereafter by warfarin; 25% when heparin is used throughout pregnancy; and 10.3% when unfractionated heparin is used in the first trimester(2). Although warfarin may seem to

be the ideal agent, it is unsafe during foetal development as it can cause, foetal wastage, congenital foetal anomalies, increased risk of foetal intraventricular haemorrhage and embryopathy in 0.6% - 6% (2).

There are guidelines for the use of anti-thrombotic therapies in pregnancy from the American College of Chest Physicians and the European Society of Cardiology (ESC) that may assist physicians in making choices on anti-thrombotic agents in pregnancy (2).

The ESC uses a checklist for risk factors for venous thrombo-embolism modified according to the Royal College of Obstetricians and Gynaecologists (10). The 3 major categories are: pre-existing risk factors; obstetric risk factors and; transient risk factors (10).

According to the number of risk factors, the patient can be classified into high, intermediate, and low risk groups. The high risk group should receive low molecular weight heparin (LMWH) antenatally and post-partum, the intermediate risk group patients postpartum prophylaxis is recommended and antepartum prophylaxis with LMWH should be considered and in the low risk group early mobilization is recommended (10).

1.8 Congenital valvular lesions in pregnancy

Chohan, et al (16), in their 2006 study in Pakistan reported that congenital mitral valve prolapse was more common in pregnant women with an incidence of 10-17%. This condition in pregnancy is said to be benign and asymptomatic those that, do become symptomatic often complain of, chest pain, palpitations, dyspnoea and weakness (16).

There is a wide array of operative procedures that may be carried out for congenital heart lesions and with the success of these operations, more women reach childbearing age and need special consideration during pregnancy (16). One such operation is a Fontan procedure for single ventricle physiology. The main concern in these pregnant

patients is that the Fontan circulation is passive and therefore adequate blood volume and pressure is needed to perfuse the pulmonary circulation (4).

Epidural anaesthesia is the anaesthetic of choice in a pregnant patient with congenital mitral valve prolapse (16). Other methods are however not contra-indicated. The basic principles are to avoid decreases in cardiac output, heart rate and left ventricular end diastolic volume as this may worsen the prolapse (16).

Since peripheral and systemic vascular resistance are vital to patients with Fontan procedure, general anaesthesia is not usually recommended. Anaesthetic drugs may affect peripheral vascular resistance by depressing the myocardium.

Positive pressure ventilation used during general anaesthesia may impede venous return and ultimately pulmonary blood flow. These patients are also prone to atrial fibrillation which is often difficult to treat (4).

1.9 Analgesia

Adequate post caesarean section analgesia has increasing importance as it decreases the development of chronic pain syndromes, facilitates mother and child bonding and decreases hospital stay. Most literature on this subject seems to be in support of multimodal analgesia. Patients who have had epidural anaesthesia are at an advantage post-operatively because this can be continued into the post anaesthesia period. Spinal anaesthesia also offers post-operative analgesia (21).

In patients who have had general anaesthesia, multimodal analgesia involving use of opioids, non-steroidal anti-inflammatory agents, paracetamol and various blocks including the transverse abdominis plane (TAP) block is recommended. Analgesia is extremely vital even in valvular heart disease as pain is known to have deleterious cardiac effects that may cause worsening of cardiac symptoms due to valvular heart disease post-operatively if not treated (21).

1.10 Outcomes of valvular heart disease in pregnancy

Cardiac disease is not the most common disease in pregnancy, it does however contribute significantly to maternal morbidity and mortality (2).The following parameters have been used to determine the risk of morbidity in patients with valvular heart disease: congestion and pulmonary oedema; cardiac arrhythmias and their associated sequelae from thrombus formation such as strokes and pulmonary emboli; and worsening symptoms with the need for correction of valvular heart lesion during pregnancy (20). Those with a higher NYHA functional class are at higher risk of morbidity and mortality (6, 20).

In a study in Senegal (7) on maternal outcomes in sub-Saharan Africa, a number of predictive factors for adverse outcomes in women with rheumatic heart disease were found.

Mitral stenosis; severe tricuspid regurgitation; NYHA functional class III or IV and; symptoms of heart failure, were the leading predictive factors associated with maternal mortality (7).

This was correlated by Hameed et al(8) who found increased maternal morbidity and unfavourable foetal outcomes in women with moderate and severe mitral and aortic stenosis.Correction of the valvular heart lesion by prosthetic valves does not exempt these patients from increased risk of morbidity and mortality.

Mechanical valve replacement carries a higher risk of maternal morbidity as compared to biological valves, particularly when they are placed in the mitral or aortic position (20). Their increased morbidity is also related to the associated anti-thrombotic therapy that is required after replacement (20).

2. Research assumptions

These following definitions are will be used in this study:

Anaesthesia: refers to the anaesthetic that the cardiac obstetric patient receives for delivery. This may be neuraxial, local or general anaesthesia. Neuraxial anaesthesia will be a spinal, an epidural, or a combination of both.

Anaesthetist: a qualified doctor who is currently working in the Department of Anaesthesiology, including medical officers, registrars, and consultants.

Records: will include the labour admission book, cardiac obstetric anaesthetic assessment form, and the intraoperative anaesthetic form, and patients file.

Maternal outcome: refers to the outcome of the cardiac obstetric patients post-delivery and includes: cardiac failure, pulmonary oedema, pulmonary embolism, fatal haemorrhage from anti thrombolytic agents, cardiogenic shock, atrial fibrillation, and mortality.

Foetal outcome: refers to the outcome of children born to mothers with valvular heart disease and includes: low birth weight, preterm birth, respiratory distress, and foetal demise.

Caesarean section: is the surgical delivery of a baby by an incision through the mother's abdomen and uterus. This procedure is done when it is determined to be a safer method than a vaginal delivery for the mother, baby, or both.

Adverse outcomes: An unintended and unwanted event or state occurring during or following medical care, that is so harmful to the patient's health that (adjustment of) treatment is required or that permanent damage results. The adverse outcome may be noted during treatment or in a predefined period after discharge or transfer to another department.

3. Problem statement

Cardiac disease is noted to have a significant impact on maternal and neonatal outcomes (1, 2, 22). There is a paucity of data on the prevalence of cardiac disease in low and middle income countries (22). There is no data from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) describing the profile, perioperative management and outcomes of these patients. This study may assist with development of standardised management protocols and may assist in improving outcomes. Additionally, if poor outcomes are found, it may assist management in determining the factors associated with poor outcomes.

4. Study aims

The aim of this study is to describe the profile and outcomes of obstetric valvular heart disease patients post caesarean section at CMJAH.

5. Study objectives

- To describe the profile of valvular cardiac patients presenting for caesarean section at CMJAH.
- To describe the perioperative management and outcomes of these patients
- To describe factors associated with poor/ adverse outcomes.

6. Study methodology

6.1 Study design

A retrospective study examining patient records with a special interest in outcomes pertaining to the following subheadings will be conducted:

- Demographics of the study population

- Elective or emergency caesarean section
- Mode of anaesthesia
- Post-operative analgesia
- Morbidity and Mortality
- Level of experience of the surgeon

6.2 Site of study

The study will be conducted at CMJAH. This hospital is a quaternary hospital with a total of over 1088 usable beds. It offers 24-hour obstetric services and employs interns, community service officers, medical officers, registrars, and consultants.

6.3 Study population and size

The study population will be records of obstetric valvular heart disease patients who delivered by caesarean section at CMJAH. The sample size will be determined by the collection and availability of records for a 2-year period from 1st January 2018 to 31st December 2019.

6.4 Inclusion criteria

- Patients with valvular heart disease in pregnancy who had a caesarean section as mode of delivery at CMJAH.

6.5 Exclusion criteria

- Patients with non-valvular cardiac diseases

7. Data collection and analysis

Data will be collected using a Microsoft ® excel spreadsheet (Appendix C). Continuous data will be described using the mean and standard deviation, or median and interquartile range based on the distribution of data collected. For categorical data frequency (percentage) tables will be used. The statistical test that will be used are the Mann-Whitney U test, and the single sample t-test for continuous data. The Chi-squared test will be used for categorical data. Data will be analysed with the assistance of a biostatistician.

8. Ethical considerations

Permission will be sought from the hospital board or CEO at CMJAH, the ethics committee, the head of the anaesthetic department, and the gatekeeper of records to access patient records at CMJAH. In the study only data pertaining to the patient's illness, management and outcome will be collected.

No patient identifying features or details will be collected. Separate list of patient hospital and study number will be kept and only be available to the primary researcher.

The list will be stored securely in a locked cupboard for a minimum period of 6 years after completion of the study. The study will be conducted according to the principles of the Declaration of Helsinki (2013) and the South African Guidelines for Good Clinical Practice.

9. Validity and reliability

Botma et al (23) refer to “validity as indicating whether the conclusions of the study are correct based on the study design and interpretation” and reliability refers to how consistent the measurements are.

Validity and reliability will be maintained by:

- Employing an appropriate study design
- Using appropriate data collection techniques
- All the data being collected by a single researcher
- Having an adequate sample size
- Strict adherence to the specified inclusion and exclusion criteria during data collection

10. Potential limitations

As this is a retrospective study looking at pre-collected data, the validity and reliability of the study may be affected by the completeness and quality of the records available. Additionally, a small patient sample may affect quality findings. This is a single centre study and therefore data may not be generalizable.

11. Project outline

	Nov 2019	Dec 2019	Jan 2020	Feb 2020	Mar 2020	Apr 2020	May 2020	Jun 2020	Jul 2020	Aug 2020	Sep 2020	Oct 2020
Literature review												
Preparing protocol												
Protocol assessment												
Ethics application												
Collecting data												
Data analysis												
Writing up- thesis												

12. Financial plan

The Wits Department of Anaesthesiology will incur the costs of paper and printing as follows:

Item	**Price**	**Number of pages**	**Copies**	**Total**
Proposal	R1.50	22	4	R132
Ethics form	R1.50	10	1	R15
Postgraduate cover page	R1.50	3	15	R22.50
Binding	R40		5	R200
TOTAL				R369.50

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2021/02/23

Dr NG Mfeka
School of Clinical Medicine
Department of Anaesthesiology
Medical School
University

Sent by e-mail to: ntombizabanguni@gmail.com

Dear Dr Mfeka

Re: **Protocol Ref No:** M200751
Protocol Title: *Post caesarean section outcomes of obstetric valvular heart disease patients at Charlotte Maxeke Johannesburg Academic Hospital*
Principal Investigator: Dr NG Mfeka

Thank you for your e-mail of 2021/02/12.

I confirm that your proposal to extend your data collection window to 2016/01/01 to 2020/12/31 has been noted and approved.

Thank you for keeping us informed.

Yours Sincerely

J. Burns

.....

Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny

.....

Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. X Dlamini
Office of the Clinical Director
Email: xolisane.dlamini2@gauteng.gov.za
Tel: (011) 488-3710
29 May 2020

Dear Dr. N Mfeka

STUDY TITLE: Post Caesarean section outcomes of Obstetric Valvular Heart Disease Patients at Charlotte Maxeke Johannesburg Academic Hospital

Permission to conduct the above-mentioned study is provisionally approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / not supported

Dr. PN Africa
Acting Clinical Director
DATE: 03/06/2020

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 05-06-2020

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr NG Mfeka
School of Clinical Medicine
Department of Anaesthesiology
Medical School
University

E-mail: ntombizabanguni@gmail.com

CC: Supervisor: Drs A Nkuna, P Motshabi and H Rhemutla
<palesa.motshabi@wits.ac.za>
and <HREC-Medical ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/11/12

REF: *R14/49*

PROTOCOL NO: **M200751** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Post caesarean section outcomes of obstetric valvular heart disease patients at Charlotte Maxeke Johannesburg Academic Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0307/Clearcan.wpa

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R14/49 Dr NG Mfeka

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200751

NAME: (Principal Investigator)	Dr NG Mfeka
DEPARTMENT:	School of Clinical Medicine Department of Anaesthesiology Medical School University
PROJECT TITLE:	Post caesarean section outcomes of obstetric valvular heart disease patients at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	2020/07/31
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs A Nkuna, P Motshabi and H Rhemutla
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/11/12

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore reports and re-certification will be due early in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL
Office of the Head of Department: Obstetrics and Gynaecology
Enquiries: Dr L. Chauke

Tel: 011 488-3179
Fax: 011 643-2522

29 May 2020

To whom it may concern

Re: Request to obtain permission to conduct research titled:

Post caesarean section outcomes of obstetric valvular heart disease patients at Charlotte Maxeke Johannesburg Academic Hospital

This letter is in support of the Post caesarean section outcomes of obstetric valvular heart disease patients at Charlotte Maxeke Johannesburg Academic Hospital research study application. The Department will also be fully participating in this study that can draw sustainable research in the outcomes of obstetric valvular heart disease patients at Charlotte Maxeke Johannesburg Academic Hospital

It is within the service and strategic point of view that your consideration will be greatly appreciated.

Yours sincerely,

Dr. H.L Chauke

Assistant Head of School, School of Clinical Medicine, University of the Witwatersrand

Clinical Head of Department, Obstetrics and Gynaecology, Charlotte Maxeke Johannesburg Academic Hospital, Parktown, Johannesburg

Example of data collection spreadsheet

Study number	
Demographics:	
Age	
Ethnicity	
Parity	
Cardiac valvular lesion present: date diagnosed	
Severity:	
Mild, moderate or severe	
Congenital or acquired	
NYHA class	
Gestational in weeks	
Elective or emergency caesarean	
Mode of anaesthesia	
Prosthetic valve (yes or no)	
Anticoagulation	
Level of surgeon experience	
Complications post-operatively:	
Bleeding	
Thrombo-embolic phenomena	
Cardiac arrhythmias	
Cardiac failure	
Pulmonary oedema	
Post-operative analgesia:	
Epidural	
Spinal	
Patient controlled analgesia	
Fixed interval analgesia	
Post-operative stay:	

ICU	
High care	
Ward	
Foetal outcomes:	
Low birth weight/ growth restriction	
Preterm birth	
Respiratory distress	
Foetal demise	
In hospital mortality:	

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- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
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Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

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This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

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This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

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All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
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