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A description of management and outcomes of pregnant patients with cardiac disease attending Charlotte Maxeke Johannesburg Academic Hospital in 2015

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2019
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A DESCRIPTION OF MANAGEMENT AND OUTCOMES OF PREGNANT PATIENTS WITH CARDIAC DISEASE ATTENDING CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL IN 2015.



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A research report submitted to the Faculty of Health Sciences, University of Witswaterstrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology.

Johannesburg 2019

DECLARATION

I, Pooja Nair, declare that this research report is my own, unaided work. It is being submitted in partial fulfilment for the degree of Master of Medicine (MMed) in the branch of Obstetrics and Gynaecology, Faculty of Health Sciences, at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at any other University.

_____

(Signature of candidate)

_____day of_____20_____

ABSTRACT:

Background:

Cardiac disease remains one of the leading causes of maternal morbidity and mortality in both developed and developing countries. There is a paucity of research work into the profile of cardiac disease in pregnancy. This study aims to describe the management and outcomes of pregnant women with cardiac conditions in pregnancy.

Methods:

This is a cross-sectional study with a retrospective analysis of all pregnant patients with cardiac disease presenting to Charlotte Maxeke Johannesburg Hospital. This study included all pregnant patients with cardiac disease that presented from 1st Jan 2015- 31st Dec 2015 to Charlotte Maxeke Johannesburg Academic Hospital.

Results:

The study included a total of 55 pregnant patients who had underlying cardiac disease. One patient was referred for medical termination of pregnancy and there was one miscarriage before 20 weeks of gestation. There were two maternal deaths with a case fatality rate of 3.6%. The distribution of cardiac disease was as follows: Rheumatic heart disease 23.6%, congenital heart disease 29.1%, prosthetic valves 12.7%, cardiomyopathies 20%, Cor pulmonale 3.6%, cardiac arrhythmias 5.5%, hypertensive heart disease 3.6%, and previous cardiac device implants 1.8%. The average gestational age was 37.8 weeks and caesarean section rate was 52.7%. The average birth weight was 2708 grams.

Conclusion:

Cardiac disease in pregnancy still poses one of the biggest challenges to peripartum morbidity and mortality. The profile of heart disease in these patients show that congenital disease and rheumatic heart disease are the top two causes of cardiac disease in pregnancy. The prevalence of rheumatic heart disease in pregnancy is in keeping with the high prevalence of rheumatic heart disease in developing countries. The rise of congenital heart disease in pregnancy is a reflection of better care for patients born with congenital heart disease allowing them to reach the reproductive age.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr Haroun Rhemtula for his support and patience as my supervisor for this MMed.

DEDICATIONS

I would like to dedicate this to my husband, Dr Anil Kurian, for his unwavering support.

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ABBREVIATIONS

ACE	Angiotensin converting enzyme
ANC	Antenatal Clinic
ARBS	Angiotensin receptor blockers
AS	Aortic Stenosis
ASD	Atrial Septal Defect
CARPREG	Cardiac disease in pregnancy
CMJAH	Charlotte Maxeke Johannesburg Hospital
ECG	Electrocardiogram
HOCM	Hypertrophic Obstructive Cardiomyopathy
ICU	Intensive care unit
LMWH	Low molecular weight heparin
MS	Mitral Stenosis
NICU	Neonatal intensive care unit
NYHA	New York Heart Association
PPCMO	Peripartum cardiomyopathy
SGA	Small for gestational age
TEE	Transoesophageal echo cardiography
UFH	Unfractionated heparin
VSD	Ventricular septal defect
WHO	World Health Organisation
ZAHARA	Zwangerschap bij vrouwen met een Aangeboren HARtAfwijking (Pregnancy in women with congenital heart disease)

1. Introduction

Cardiac disease remains one of the leading causes of maternal morbidity and mortality in both developed and developing countries.[1,2,3,4,5] There is a paucity of research work into the profile of cardiac disease in pregnancy.[3] The Sixth Confidential Enquiry into Maternal Deaths in South Africa attributes medical and surgical causes as the 4th most common cause of maternal deaths.[3,4] The most common medical causes of death were cardiac disease (34.3%, n=169), respiratory disease (14.4%, n=71) and disorders of the central nervous system (10.1%, n=50).[4]

2. Literature Review

The spectrum of cardiac disease in pregnancy differs between the developed and developing worlds. In the developed world, successful surgical correction of congenital heart disease and the increased incidence of diabetes, hypertension, obesity and advanced maternal age at their first pregnancy, have all resulted in the increased risk of cardiac disease.[2,5] While, there is dramatic improvement in survival of patients undergoing corrective cardiac surgery, who reach adult hood and conceive in the developed world, in developing countries, rheumatic and uncorrected congenital heart disease dominate the spectrum, making up 56- 89% of all cardiovascular disease seen in pregnancy.[2] Intensive care unit (ICU) admissions related to maternal cardiac disease comprises approximately 15% of obstetric ICU admissions and these could account for 50% of all maternal deaths that occur in an ICU setting in the USA.[7]

Serious complications such as congestive cardiac failure, arrhythmias, and stroke can occur in 12-20% of patients presenting with cardiac disease in pregnancy.[7] Mortality rates of 30% have been quoted.[7] Complication rates depend on several factors such as cardiac function, functional status of the valves, history of prior arrhythmias or other cardiac events.[2] In a meta-analysis from three different South African studies conducted over three years, the

maternal morbidity followed global patterns where pulmonary oedema and congestive cardiac failure were the greatest causes of maternal mortality and morbidity.[8] Despite serious complications, most patients with cardiac disease can have a satisfactory outcome provided a carefully planned perinatal, antenatal, intrapartum and post-partum management protocols and guidelines are reviewed and adhered to. [9]A multi-disciplinary team approach involving anaesthetists, cardiologists, haematologists and obstetricians are required for the optimal management of such high risk pregnancies.[19] Neonatal complications are more likely to occur in patients with New York Heart Association classification (NYHA) III and IV, use of anticoagulants during pregnancy, smoking, multiple gestations and left heart obstruction.[2] These complications include small for gestational age (SGA) infants, congenital abnormalities and neonatal death.[2] Infants born to patients with congenital cardiac anomalies have a 2%-18% risk of acquiring a congenital cardiac defect.[2]

In the South African setting, there are no country wide protocols for the management of cardiac diseases in pregnancy[26,31]. The European guidelines are followed and certain hospitals use their own version of these guidelines.[2,26] The prevalence of cardiac disease in pregnant patients in the local setting is important so as to distribute resources accordingly and to develop protocols in the future. The differences in the profile of pregnant patients in the developing world compared to the developed world was alluded to in the first paragraph. It is therefore important to look at our own settings as well as to collect and validate data that would reflect disease burden in our local clinical environment.

2.1. Physiological changes in pregnancy

Normal physiological changes that occur in pregnancy can mimic cardiac disease, therefore meticulous attention to the diagnosis, treatment and follow up of these patients is pertinent.[2,3] Realistic and accurate risk assessments for potential maternal and fetal complications are vital for the success and safety of the pregnancy and the postpartum period.[3] Regarding the circulatory system, the primary physiological events of importance are the increase in blood volume, increase in cardiac output and the decrease in both peripheral vascular resistance and blood pressure.[2,3] Systemic blood volume increases by 50% antenatally and a further 50% at delivery when a massive auto transfusion of blood from the involuting uterus enters the general circulation.[2,10] Pregnancy also brings haemostatic changes which promotes hypercoagulability and this is secondary to an increase in coagulation factors, fibrinogen and platelet adhesiveness.[2]

The respiratory changes in pregnancy induces a higher pO2 and lower pCO2 which results in a compensated respiratory alkalosis.[33] The lower pCO2 contributes to a diffusion gradient enhancing the fetus' ability to eliminate waste during aerobic metabolism.[33] Other respiratory changes include an elevated diaphragm, decreased functional residual capacity as well as an increased ventilation and respiratory drive.[33]

In the post- partum period, most of the changes are rapidly reversed in the first couple of weeks and further normalisation can take from 3-12 months.[11] However, some structural changes are never completely reversed.[11]

The physiological changes described are well adapted to, provided all essential bodily systems are healthy before pregnancy.[3,11] With underlying cardiac disease, the essential circulatory changes which occur may adversely affect maternal and fetal morbidity and perinatal outcome.[3,11]

Congenital as well as acquired cardiac lesions may present for the first time in pregnancy.[3] Conditions such as peri-partum cardiomyopathy can present for the first time in pregnancy or post-partum.[2,3]

2.2. General patient presentation

In all cases, a detailed history including family history especially of congenital cardiac disease is important. A New York heart association (NYHA) classification of the patient can be a good prognostic indicator with regards to the assessment of dyspnoea, the prognosis of valvular heart lesions as well as cardiac failure.[2 ,3 ,11]

Clinical evaluation of the symptoms described in history will assist in distinguishing pathology from normal physiological adaptations. Signs of cardiac failure with concomitant murmurs warrants further evaluation and investigations.[2]

The majority of patients have normal electrocardiograms (ECG)[2,27]. Changes can be related to a gradual change in the position of the heart and may mimic left ventricular hypertrophy.[2] Echocardiographic assessment is the gold standard in the evaluation of cardiac disease and is the preferred screening tool to asses cardiac function due to its availability and no exposure to radiation.[2] It is easy to perform and can be done on multiple occasions.[2] Transoesophageal echo cardiography (TEE) is more difficult to perform and is used when transthoracic echo cardiography yields poor results or is inconclusive.[2]

Chest X-rays should be used when other methods fail to clarify the cause of dyspnoea, cough or other respiratory symptoms.[2,28] The fetal dose from a single x-ray is 0.01mGy .[2,28] There is no evidence of an increased fetal risk of congenital malformations, intellectual disability, growth restriction, or pregnancy loss at doses of radiation to the pregnant woman of 0.50mGy.[2,28] Patients with known underlying cardiac disease should receive thorough

counselling and evaluation prior to conception. This counselling should include future life expectancy, ethical aspects of parenthood, genetic and inheritance patterns of certain congenital heart disease (Marfan syndrome, hypertrophic cardiomyopathy(HOCM)), contraception and the use of drugs which are lifesaving but could pose a teratogenic risk.[2,11]

Once the diagnosis is confirmed, an assessment of the potential effect of the pregnancy on the cardiac disease as well as the effect of the disease on the pregnancy should be evaluated.[3] Several risk scores have been evaluated and used and these assessments are population dependent and in general, the risk increases as the complexity of the disease rises.[2] The CARPREG (Cardiac disease in Pregnancy) score is widely known but others such as WHO (World Health Organisation), ZAHARA (Zwangerschap bij vrouwen met een Aangeboren HARtAfwijking- Pregnancy in women with congenital heart disease) and NYHA (New York Heart Association) risk assessments are also valuable.

CARPREG allocates a point for each of the following: prior cardiac conditions e.g. (congestive cardiac failure, arrhythmias); NYHA of greater than II or cyanosis, left ventricular dysfunction (ejection fraction of less than 40%); left heart obstruction (mitral stenosis less than $2cm^2$, aortic valve area less than $1.5cm^2$). Using this scoring system, 0 points equates to 5 % risk of maternal complications, 1 point for 27% of maternal complications, and greater than 1 point to a 75% of risk of maternal complications.[2,3]

The WHO scoring system takes into consideration maternal characteristics like age, number of children, time since last delivery, medical history and maternal education.[29] This is then used to classify patients into low, intermediate and high risk.[29]

ZAHARA allocates points for the following: history of cardiac arrhythmias, cardiac medications before pregnancy, NYHA functional class prior to pregnancy ≥II, left heart obstruction, systemic atrioventricular valve regurgitation pulmonary atrioventricular valve

regurgitation, mechanical valve prosthesis and cyanotic heart disease.[30] For each ZAHARA predictor that is present, a specific score is assigned. The maternal complication rate is 2.9% if the score is < 0.5, 7.5% if the score is between 0.5 to 1.5, 17.5% if the score is between 1.51 and 2.50, 43% if the score is between 2.51 and 3.50 and 70% if the score is > 3.5.[30]

2.3. Complications

Complications that could arise during pregnancy are dependent upon the cardiac pathology. Heart failure and arrhythmias are the most frequent.[2] Patients diagnosed with heart failure in pregnancy should be admitted to hospital for workup and bed rest.[2] Medical treatments should include strict fluid input and output monitoring with appropriate diuresis and where antihypertensive medications are used, these should be aimed at afterload reduction. Certain drugs such as angiotensin converting enzyme (ACE) inhibitors should be used only where benefits outweigh the risks as it can induce fetal anuria, pulmonary hypoplasia and skull deformation if used during the 2nd or 3rd trimester.[2,11] The incidence of arrhythmias increases during pregnancy.[2,13] When this occurs, beta blockers and digoxin are the drugs of choice.[2] The dosage of drugs would need to be modified to reach target therapeutic levels as both the pharmacokinetics and dynamics of the various agents are altered in the normal gravid state.[2] Electrical cardioversion, which is defined as the use of electricity to resynchronise the heart, is safe in pregnancy and should be done in all drug-refractory maternal arrhythmias.[2] Ectopic beats are mostly benign and can present in one third of healthy pregnant individuals.[2,13]

2.4. Timing and mode of delivery

The timing and mode of delivery should be discussed and planned by a multidisciplinary team.[2,11] A written record should be available at all times for all care givers involved and should include plans to manage unforeseeable complications.[2,11]

The cardiac status of the gravid patient influences the timing of delivery.[2,11]Awaiting spontaneous labour is ideal for patients with normal cardiac function and induction is preferred in patients who do not proceed into spontaneous labour.[2] Patients with more complex lesions such as severe cardiac dysfunction, mechanical valves, aortic dilation and heart failure, a planned delivery is more appropriate.[2,11,27,31,32] Maternal and fetal conditions may warrant a planned delivery prior to 37wks. [2,11]

Obstetric indication and maternal hemodynamic condition determines the mode of delivery.[2,11,27] If the Bishops score is favourable, induction of labour is indicated but prolonged induction should be avoided.[2] Mechanical induction is preferred to medical, particularly in patients where it is detrimental to drop their systemic vascular resistance.[2] There is however, no absolute contraindication to the use of either Misoprostol and Dinoprostone, although there is theoretically an increased risk of arrhythmias and coronary vasospasm[2,11]

Vaginal delivery is preferred and advised in patients with adequate cardiac function.[2,11] If this route is advised, patient management should be individualized and information containing the timing, mode of induction and type of anaesthesia should be indicated.[2] Vaginal delivery is associated with decreased blood loss, however this increases the patients risk of a venous thrombosis and thromboembolism.[2] Assisted vaginal delivery (vacuum/ forceps extraction) is recommended in patients where excessive maternal effort and prolonged labour is contraindicated.[11] A caesarean section is advised in patients with heart failure, preterm

labour, patients on anticoagulants, aortic root dissection, Marfan syndrome and an aortic diameter of greater than 45mm, or any stenotic valvular conditions with pulmonary hypertension, [2,14]

A caesarean section permits more appropriate invasive and non-invasive monitoring, however it is associated with an increased risk of post-partum haemorrhage, infection and thromboembolism.[2]

Once in established labour, the parturient should be nursed in a lateral decubitus position to attenuate the hemodynamic impact of uterine contractions.[2,11] With uterine contractions, the fetal head should descend to the perineum. The fetal heart rate should be monitored continuously and delivery should be assisted. The use of prophylactic antibiotics is controversial.[2] Adequate pain relief with an epidural is recommended but contraindicated in patients on anticoagulation and should be used with caution in patients with obstructive valve lesions. Such patients should be prescribed intravenous analgesia.[2,11,19]

2.5. Anticoagulation

Patients who are on oral anticoagulants should be switched to low molecular weight heparin (LMWH) or unfractionated heparin (UFH) by 36 weeks.[2] Those who are already on LMWH, should be switched to intravenous UFH 36 hours prior to induction of labour or caesarean section.[2] UFH should be discontinued 4-6 hrs prior to the planned delivery and reinitiated 4-6 hours post-surgery.[2] There has been some controversy with the use of LMWH with higher valve thrombosis than UFH but a study done by Saeed et al showed that if the peak anti-Xa level is monitored and kept between 1.0 to 1.2 U/ml then this thrombosis rate is lower.[19, 32, 34, 35]

The peak anti-Xa level is monitored 3 to 4 hours after administration of LMWH.[19] The target in mechanical valves is 1.0 to 1.2 U/ml for mitral valves and 0.8 to 1.0 U/ml in aortic valves. The initial dosing is started at 1 mg/kg twice a day and then adjusted according to peak anti-Xa levels.[19, 35]

When the delivery is elective, the last dose of LMWH dose should be given 24 hours prior to planned induction of labour or caesarean section.[34, 35] Unfractionated heparin is then commenced 12 hours prior to induction of labour or caesarean section at 1000 to 1250 units per hour to titrate to an aPTT of two times the control. The unfractionated heparin should be stopped four to six hours before initiation of neuraxial anaesthesia or analgesia or before delivery.[34, 35]

Intermittent LMWH can be used as another mode of bridging with Enoxaparin daily dose of 40 mg but the neuraxial anaesthesia or analgesia should be delayed 12 hours after the LMWH dose and the caesarean section should be performed 24 hours after LMWH dose.[34, 35]

In our setting, delivery is planned at 38 weeks and LMWH is used during pregnancy which is then stopped 24 hours prior to delivery. Peak anti-Xa levels are meticulously monitored and this guides the dosing of the LMWH antenatally and the timing of delivery.[19]

Induction of labour should commence 24 hours after the last LMWH dose with early insertion of epidural catheter.[35] A prophylactic dose of LMWH is recommended until patient is in active labour.[35] However, this is not routinely practiced in our setting.[19]

Cases where an emergent delivery is encountered, antidotes such as protamine sulphate, vitamin K and fresh frozen plasma should be used. Protamine sulphate however, only has limited reversal of LMWH.[2] Paediatricians should be informed of fully anticoagulant mothers, as they should administer fresh frozen plasma and vitamin K to the neonate. [2,11]

2.6. Third stage of labour

During the third stage of labour, administration of a low dose oxytocin infusion is preferred to a bolus dose.[18] This will avoid systemic hypotension and prevent postpartum haemorrhage.[2] If the latter is encountered, the use of Prostoglandin F2 alpha is recommended unless there is evidence of raised pulmonary artery pressure, which is a contraindication.[2]

Volume shifts caused by auto-transfusion post-delivery can have detrimental effects on patients with diminished left ventricle function.[2,11] Close monitoring for signs of heart failure is essential.[2,11] Prophylactic use of diuretics and ACE inhibitors may be indicated in high risk patients with severe left ventricular dysfunction.[11]

2.7. Valvular lesions in pregnancy

The most common causes of cardiac disease in pregnancy in South Africa, are regurgitant lesions of the mitral and aortic valves.[2] These pathologies are well tolerated in pregnancy provided there is no significant left ventricular dysfunction.[15] A common cause of these lesions during child bearing age is rheumatic heart disease, congenital cardiac condition and degenerative disorders.[2,3] A rare cause for acute valvular regurgitation can be the antiphospholipid syndrome.[2] Women who are at great risk of heart failure include those with severe symptomatic regurgitant heart valves and those who have compromised left ventricular function.[2,3,6] Ideally such patients should be referred for pre-pregnancy surgery favouring valve repair.[2] These patients should be followed up frequently with the aim to optimising their medical condition and current symptomatology.[2,3,15,18] Anti-failure therapy can be instituted when fluid over load states occur, however with severe regurgitation with therapy refractory heart failure, surgery is unavoidable.[2] Vaginal delivery is preferred with an epidural and assisted delivery[2,15]

Stenotic valve lesions are less tolerated in pregnancy.[2,16] The increase in cardiac output causes an increase in transvalvular gradient with resultant upstream pressures which lead to an increase risk of fetal and maternal complications. [2,16] The most common cause of mitral stenosis is rheumatic heart disease.[2] Congenital stenotic conditions are rare.[2] The diagnosis is confirmed on an echocardiogram.[2] Mitral stenosis (MS) is responsible for most of the morbidity and mortality of rheumatic heart disease during pregnancy.[2] The maternal cardiac complications include functional deterioration, pulmonary oedema, atrial arrhythmias and transient ischemic attacks or even strokes.[2,16] Pulmonary hypertension is complication of mitral stenosis and this is related to persistently elevated pulmonary venous pressures.

Patients with significant pulmonary hypertension often have more severe mitral valve disease and worse outcomes.[37] The risk of decompensation depends on the severity of the lesion.[2] All patients with moderate or severe mitral stenosis (MS) should be counselled and advised against pregnancy.[2, 36] If interventions are required for management, it should be performed prior to conception.[2] Medical therapy should be aimed at a reduction of a maternal heart rate and thereby lengthening diastolic filling.[16] Factors that increase the heart rate should be aggressively corrected such as anaemia and infection.[16] Therapeutic anticoagulation should be considered in patients with atrial fibrillation.[2] Delivery should be by a caesarean section.[2,16] The surgical management of mitral stenosis includes percutaneous balloon mitral valvulotomy or mitral valve replacement.[38] Percutaneous mitral valvulotomy is reserved for patients who have a pliable valve as demonstrated by an echocardiogram, in the absence of any left atrial appendage clot or significant mitral regurgitation.[38] Patients who do not qualify for a valvulotomy needs a mitral valve replacement and lifelong anticoagulation.[38]

Aortic valve stenosis (AS) unlike mitral stenosis is mostly due to a congenital bicuspid valve.[16] Severe AS can be asymptomatic and can present for the first time with symptoms in pregnancy.[16] Mortality is rare, if careful management is planned.[16] Heart failure occurs in 10% of patients with AS in pregnancy.[2,16] Medical therapy and restricted activities are recommended in patients who show signs and symptoms of heart failure in pregnancy.[2] Surgical intervention such as a valvuloplasty is considered when medical therapy fails.[2] Caesarean section delivery is the preferred mode under general anaesthesia in patients with moderate or severe AS.[2,16] Vaginal delivery is tolerated in non-severe cases.[2]

2.8. Pregnancy and thrombosis

Pregnancy is considered a hypercoagulable state, and places the patient at an increased risk of thrombo embolic events.[2,17] Anticoagulation is essential for patients with mechanical prosthetic heart valves.[2,17] Patients with mechanical prosthetic heart valves have a higher risk of maternal and fetal mortality owing to the use of anticoagulants.[2,3,13] Mechanical valves have excellent hemodynamic performance and long term durability unlike bio prosthetic valves.[2,3] However, bio prosthetic valves not only offer a good hemodynamic performance but are associated with less thrombogenic complications.[2] There is conflicting evidence suggesting pregnancy accelerates bio prosthetic heart valve degeneration.[2] Factors such as the type, position and the functioning of the prosthetic heart valve including a history of arrhythmias contribute to thromboembolic risk but the main determinant is the type of anticoagulation used.[16] Haemodynamically, women with functioning mechanical prosthetic heart valves tolerate pregnancy well.[16] Guidelines suggest that various anticoagulants regimes can be used and these include the use of warfarin, low molecular weight heparin and unfractionated heparin.[19] A study done at CMJAH recommends the use of adjusted dose low molecular weight heparin (LMWH) twice a day, throughout pregnancy with therapeutic values being monitored by peak anti factor Xa levels.[31] Another option is to use LMWH until 13 weeks and then substituting it with warfarin until 36 weeks when Unfractionated Heparin or LMWH is resumed.[19] In addition the use of aspirin is recommended in women with prosthetic valves with an increased risk of thromboembolic event.[2,19] However, the evidence for this is not convincing and is not recommended routinely in our practice.[19, 39] Experience with LMWH has gained momentum and is the regimen of choice at our institution, provided peak anti factor Xa levels are closely monitored.[2,16,32]

2.9. Congenital heart disease and pregnancy

Congenital heart disease, such as atrial septal defects are well tolerated in pregnancy unless it is complicated by pulmonary hypertension or the Eisenmenger syndrome.[2] If the defect is not corrected then it should be done prior to pregnancy.[2]

Corrected ventricular septal defects also have a good prognosis in pregnancy provided left ventricle function is preserved.[2] Women with a residual shunt, have a higher risk of paradoxical embolism.[2] Use of compression stockings, prolonged bed rest and the supine position should be avoided.[2] The use of anticoagulation can be considered.[2] Spontaneous vaginal delivery is appropriate.[2]

2.10. Peripartum cardiomyopathy

Peri-partum cardiomyopathy (PPCMO) is a diagnosis of exclusion.[20] It's aetiology remains an enigma.[20] It is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery.[20] The incidence of peri partum cardiomyopathy is 1: 3000- 1:4000 worldwide and in South Africa it is 1:1000.[2,16] Predisposing factors are multifactorial, however family history, ethnicity, multiparity and pre-eclampsia play a role.[2,16] Symptoms and signs are typical of heart failure but since this occurs in pregnancy, a broad spectrum of symptoms are reported.[20] Echocardiography is the gold standard for the diagnosis of this condition.[20] Echo findings should include left ventricular ejection fraction of less than 45%, fractional shortening of less than 30% and left ventricular end diastolic dimension of more than 2.7cm/m^2 body surface area.[20] Treatment should be targeted at managing heart failure.[2] Selective drugs should be used as most others such as ACE inhibitors and Angiotensin Receptor Blockers (ARBs) (Losartan) are teratogenic.[1,2] If pulmonary congestion is present, diuretics should be used however blood flow to the placenta could be compromised.[2] Vaginal delivery is almost always preferred if the patient is haemodynamically stable and there are no obstetric contraindications.[2,16,20]

The cardiac disease burden in obstetrics is significant. A look into the various types of cardiac diseases that affect patients presenting at our institution would therefore assist us in preparing targeted protocol regimens to deal with such diseases in pregnancy whilst also helping to understand the evolution of such pathologies in a developing country such as ours.

3. Problem statement and method

3.1. Aim of the study:

To evaluate and describe the profile of pregnant patients with cardiac diseases attending for antenatal care and delivery at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) including maternal and neonatal outcomes.

3.2. Study Objective:

Main Objective:

1. To evaluate and describe pregnant women with cardiac conditions in pregnancy presenting at CMJAH in 2015

Specific Objectives:

1. To describe the presentation of pregnant women with cardiac diseases.
2. To describe the types of cardiac disease.
3. To describe the short term maternal and neonatal outcomes.

3.3 Study design

- This will be a cross sectional study with retrospective analysis of all pregnant patients with cardiac diseases presenting to CMJAH from 1st Jan 2015- 31st Dec 2015

3.4. Study setting

- The study was conducted at Charlotte Maxeke Johannesburg Academic Hospital which is situated in the Johannesburg Metro District and serves the populations of Johannesburg Metro, Ekurhuleni and West Rand districts.
- This is a central referral hospital with an obstetric unit that has a combined cardiac clinic.

3.5. Study population and sampling:

- All pregnant patients with cardiac disease that delivered between 1 Jan to 31 December 2015 in Charlotte Maxeke Johannesburg Academic Hospital, were recruited into the study.
- Patients seen in the outpatient setting and those admitted with cardiac diseases in pregnancy were included if they delivered in the study period at Charlotte Maxeke Johannesburg Academic Hospital.

- Retrospective analysis was conducted using information from the patient records obtained through registers at ANC (antenatal clinic), wards and ICU (Intensive Care Unit).
- The pregnant patients who did not deliver at CMJAH in the time period 1 Jan to 31 December 2015, were excluded.
- Patient records in the given time frame were traced and information within neonatal intensive care unit (NICU) transferred on to a data sheet (see attached data sheet).

3.6 Data Management

- A data capture sheet was used for every patient recruited and the data will be transferred from the hospital file to the data capture sheet manually.
- The same researcher entered the data to ensure validity and reliability
- All the data was entered into an excel spreadsheet and datasets will be prepared and analysed.
- Prevalence of the cardiac diseases in pregnancy was calculated.
- Maternal outcomes in patients with cardiac diseases were described.
- Neonatal outcomes were also described.

3.7 Statistical analysis

- The data was grouped and analysed with descriptive statistics. The central tendency was measured as well as the dispersion. All results were presented with frequencies, means and percentages.

4. Ethics

All patients used in my research report will remain anonymous and the data was collected with a unique identifier. The study received approval from the University of Witwatersrand's Human Research Ethics Committee, approval number M161135.

5. Results

There were a total of 9209 deliveries between 1 January 2015 and 31 December 2015 at CMJAH. During this time period a total of 55 patients had underlying cardiac disease which translates to 0.6%. One patient was referred for medical termination of pregnancy and there was one miscarriage before 20 weeks of gestation. There were two maternal deaths with a case fatality rate of 3.6%.

Baseline characteristics

Table 5.1: Baseline characteristics of the study population N=54

Age of the patient (years)	
Mean (SD)	29.0 ± 6.3
Minimum (Youngest)	17 years
Maximum (Oldest)	41 years
Obstetric history (N (%))	
Primigravida	13 (23.6%)
Multigravida	42 (76.4%)
Advanced maternal age >35 years	8 (14.5%)
HIV positive	17 (30.9%)
Anticoagulation use – Enoxaparin	5 (9.1%)

The mean age for obstetric patients with cardiac diseases was 29 years with a wide distribution from 17 to 41 years of age as shown in Table 5.1. The majority of patients were multigravida (76.4%) with only 23.6% being primigravida. There were 17(30.9%) HIV positive patients and 8(14.5%) of patients were of advanced maternal age which was defined as age above 35 years. All patients who were previously diagnosed or newly diagnosed with HIV were included. Anticoagulation was used in 5 patients (9.1%) due to mechanical valves

and atrial fibrillation. There were 2 patients who had atrial fibrillation but they also had mechanical valves and therefore had multiple indications for anticoagulation.

Table 5.2: Distribution of cardiac diseases N=54

Cardiac lesion	**n (%)**
Rheumatic valvular heart disease	13 (23.6%)
Prosthetic valves	7 (12.7%)
Congenital heart disease	16 (29.1%)
Cardiomyopathies	11 (20.0 %)
Cor pulmonale	2 (3.6%)
Cardiac arrhythmias	3 (5.5%)
Other	2 (3.6%)

Table 5.2 illustrates that the two most prevalent cardiac diseases in pregnancy remain rheumatic and congenital heart disease. Cardiomyopathies also constituted a significant portion of patients with 20% of patients having this diagnosis. The diagnosis of rheumatic heart disease was based on echocardiographic criteria. The most common valvular lesion was mitral regurgitation (n=6), followed by mitral stenosis (n=2), aortic stenosis (n=2), aortic regurgitation (n=2) and tricuspid regurgitation (n=1). Patients with preserved left ventricular function but right ventricular dilatation and raised pulmonary pressures were included in the cor pulmonale group. The groups of patients with cardiac arrhythmias were all atrial arrhythmias.

Table 5.3: Congenital heart disease in pregnancy n=16	
	N (%)
Congenital heart disease	16 (29.1%)
VSD	6 (10.9%)
ASD and VSD (Endocardial cushion defects)	3 (5.5%)
ASD	3 (5.5%)
TOF	2 (3.6%)
PDA	2 (3.6%)

This cohort of patients with grown up congenital heart disease accounted for 29.1% of patients. VSD was the most common congenital defect (10.9%) followed by ASD (5.5%). Endocardial cushion defects (5.5%) includes both ASD and VSD. The least common congenital heart condition in this pregnant cohort was TOF (3.6%) and PDA (3.6%). All the congenital diseases were corrected in the pregnant patient cohort, except for two patients with small VSDs which were not corrected surgically. See Table 5.3

Table 5.4: Maternal outcomes	
Outcomes N=54	**N (%)**
Mode of delivery	
Normal vaginal delivery	23 (41.8%)
Elective caesarean section	9 (16.4%)
Emergency caesarean section	20 (36.4%)
Miscarriage / TOP	2 (3.6%)
Gestational age at delivery	
Mean (SD)	37.8 (±3.1)
Minimum	20
Maximum	40
Maternal deaths	2 (3.6%)
ICU admissions post caesarean section	7 (12.7%)

The above table 5.4 demonstrates that 41.8% of deliveries were vaginal whilst 52.7% of deliveries were by caesarean section. The average gestational age at birth was 37.8 weeks with the earliest being at 20 weeks and the latest being at 40 weeks. There were two miscarriages of which one was a medical TOP that was also classified as a miscarriage. There were 2 maternal deaths, both were referred from Far East Rand Hospital and presented unbooked, requiring immediate resuscitation. There were 7 cases that were admitted to ICU post caesarean section. They were all admitted to ICU due to their pre-existing cardiac disease for anaesthetic reasons. The cases that were admitted to ICU had a spread of significant cardiac pathology including supraventricular tachycardia, peripartum cardiomyopathy, double valve replacement, severe hypertensive heart disease and VSD with pulmonary hypertension and isolated pulmonary hypertension. All of these patients survived to discharge.

Table 5.5: Maternal outcomes in rheumatic valvular heart disease n=13

Outcomes	**N (%)**
Mode of delivery	
Normal vaginal delivery	5 (38.5%)
Elective caesarean section	2 (15.4%)
Emergency caesarean section	5 (38.5%)
Miscarriage / TOP	1 (7.7%)
Gestational age at delivery	
Mean (SD)	38.1 (±1.0)
Minimum	38
Maximum	40
Maternal deaths	None
ICU admissions post caesarean section	None

Table 5.6: Maternal outcomes in prosthetic valves n=7	
Outcomes	**N (%)**
Mode of delivery	
Normal vaginal delivery	1 (14.3%)
Elective caesarean section	2 (28.6%)
Emergency caesarean section	4 (57.1%)
Miscarriage / TOP	None
Gestational age at delivery	
Mean (SD)	38 (±1.3)
Minimum	38
Maximum	38
Maternal deaths	None
ICU admissions post caesarean section	1 (14.3%)

Table 5.5 and 5.6 illustrates the maternal outcomes in rheumatic heart disease and prosthetic valvular patients. Patients with rheumatic heart disease had a vaginal delivery rate of 38.5% while 53.9% delivered by caesarean section. The average gestational age was 38.1 weeks.

Whilst patients with prosthetic valves had a 14.3% vaginal delivery rate and 85.7% caesarean section rate. There was one patient from the prosthetic valve cohort that was admitted to ICU for anaesthetic reasons.

Table 5.7: Maternal outcomes in congenital heart disease n=16	
Outcomes	**N (%)**
Mode of delivery	
Normal vaginal delivery	7 (43.8%)
Elective caesarean section	6 (37.4%)
Emergency caesarean section	3 (18.8%)
Miscarriage / TOP	None
Gestational age at delivery	
Mean (SD)	38.8 (±0.9)
Minimum	36
Maximum	40
Maternal deaths	None
ICU admissions post caesarean section	1 (6.3%)

The table above (Table 5,7) represents mothers with congenital heart disease reached on average a gestational period of 38.8 weeks. There were 43.8% of patients who delivered vaginally whilst 56.2% delivered by caesarean section. There was one patient who was admitted to ICU postoperatively.

Table 5.8: Maternal outcomes in cardiomyopathies n=11	
Outcomes	**N (%)**
Mode of delivery	
Normal vaginal delivery	5 (45.5%)
Elective caesarean section	3 (27.3%)
Emergency caesarean section	3 (27.3%)
Miscarriage / TOP	None
Gestational age at delivery	
Mean (SD)	38.3 (±1.0)
Minimum	38
Maximum	40
Maternal deaths	2 (18.2%)
ICU admissions post caesarean section	2 (18.2%)

Table 5.9: Maternal outcomes in cor pulmonale n=2	
Outcomes	**N (%)**
Mode of delivery	
Normal vaginal delivery	1 (50%)
Elective caesarean section	1 (50%)
Emergency caesarean section	None
Miscarriage / TOP	None
Gestational age at delivery	
Mean (SD)	39 (±1.4)
Minimum	38
Maximum	40
Maternal deaths	None
ICU admissions post caesarean section	1 (50%)

Table 5.10: Maternal outcomes in cardiac arrhythmias n=3	
Outcomes	**N (%)**
Mode of delivery	
Normal vaginal delivery	None
Elective caesarean section	2 (66.7%)
Emergency caesarean section	1 (33.3%)
Miscarriage / TOP	None
Gestational age at delivery	
Mean (SD)	36.3 (±1.3)
Minimum	33
Maximum	48
Maternal deaths	None
ICU admissions post caesarean section	1 (33.3%)

The cohort of patients with cardiomyopathies had a 45.5% vaginal delivery rate and a 54.6% caesarean section rate. There were two maternal deaths both of which were late referrals from level 1 hospitals that required resuscitation on arrival. There were two ICU admissions postoperatively in patients with peripartum cardiomyopathies.

Patients with cor pulmonale and cardiac arrhythmias had no maternal deaths and each group had one ICU admission postoperatively. This data is demonstrated in Tables 5.9 and 5.10

Table 5.11: Neonatal outcomes N=54

Outcomes	
Mean gestational age at delivery	37.8 weeks
Preterm (<37 weeks)	3 (5.6%)
Term (≥ 38 weeks)	51 (94.4%)
Apgar < 7/5	5(9.3%)
Apgar ≥ 7/5	49(90.7%)
Average weight	2708 g
Stillbirth rate	1 (1.8 %)

Table 5.12: Neonatal outcomes in specific cardiac diseases N=54

Cardiac diseases	**Mean gestational age (weeks)**	**Average birth weight (kilograms)**	**Maternal anticoagulation**
Rheumatic valvular heart disease (n=13)	38.2	2.56	30.8%
Prosthetic valvular disease (n=7)	38	2.49	85.7%
Congenital heart disease (n=16)	38.8	2.80	0
Cardiomyopathies (n=11)	38.3	2.86	9.1%
Cor pulmonale (n=2)	40	2.90	0
Cardiac arrhythmias (n=3)	36.3	2.73	0

Table 5.11 highlights the average weight of neonates born to patients with cardiac disease which is 2708 grams. There was 1 macerated stillbirth. The stillbirth rate was 18 per 1000 in this group of patients. There were 5.6% preterm births and 9.3% had Apgar scores below 7/5.

The breakdown of the specific cardiac diseases and their neonatal outcomes is displayed in the Table 5.12. The lowest birth weight was found in the prosthetic valvular heart disease group with an average birth weight of 2.46 kg, with the second lowest in the rheumatic valvular heart disease with an average birth weight of 2.56 kg. The prosthetic valvular heart disease group had the highest anticoagulation rate maternally at 85.7% as well.

6. Discussion

The prevalence of cardiac disease in pregnant patients at Charlotte Maxeke Johannesburg Academic hospital 0.6%. The patient profile resembles that of a developing country which is similar to other studies that were conducted in an African setting.[21] The predominant lesions remain that of rheumatic and congenital heart disease followed by cardiomyopathy.

Developed countries have a prevalence of rheumatic heart disease under 0.5/100 000 while developing countries have 100 – 200 times higher prevalence.[22] Local studies in Soweto have shown a prevalence of 6.5/1000 with a maximum prevalence of 20/1000 in the 7th and 8th grade which was the highest recorded at that time.[23] This is reflected in the prevalence of valvular pathologies secondary to rheumatic heart disease that manifest in pregnancy.

The results show that 23.6% of patients with cardiac disease in pregnancy have rheumatic heart disease at CMJAH. The disease burden of rheumatic heart disease is only second to congenital heart disease. However, there were 12.7% of patients with mechanical prosthetic valves whose most likely etiology was that of rheumatic heart disease. Rheumatic heart disease forms majority of these cases and if one is to combine the prevalence of cardiac disease due to rheumatic heart disease and prosthetic valves then the prevalence would be 36.3%. The primary care in rheumatic heart disease has improved resulting in earlier intervention and often correction or treatment of the underlying pathology, allowing more of these patients to reach reproductive age. The prevalence of rheumatic heart disease at CMJAH is much lower than the data from Steve Biko Academic Hospital which showed a 63.5% prevalence of rheumatic heart disease.[21] This can possibly be explained by differences in geographical location as well as better treatment due to increased awareness of rheumatic fever in the last 10 years, considering that the data from Steve Biko Academic Hospital is 10 years old.

Patients with valvular heart disease are managed in our institute with LMWH unlike other centres in the country. The maternal outcomes showed no deaths in this group of patients and only one ICU admission that was for pure anaesthetic reasons. The average gestational age was 38 weeks with an average birth weight of 2.53 kg which reflects good ante and peri – natal care. This group of patients also had the highest anticoagulation rate at 85.7% in the prosthetic valve group. Anti-Xa guided LMWH allows regular and close monitoring the anticoagulated patients and allows easier management with lower complication rate.

Congenital cardiac defect occurs with 1% of newborns having congenital cardiac disease. The most common defect was VSD, followed by a combination of ASD and VSD, then ASD. TOF and PDA were the other remaining congenital heart diseases. Except for two patients with VSDs, all the other congenital heart diseases were corrected. The mortality of complex congenital diseases was 90% prior to the 1940s but this has now changed with the advances in cardiology and cardiac surgery.[24] Presently 90% of these patients reach 18 years of age. Adults with congenital disease are therefore a rapidly growing part of the population.[24]

The proportion of pregnant patients with cardiac disease who had congenital heart disease was 29.1% which formed the largest group if taken individually even though rheumatic heart disease is still the largest etiology if combined with prosthetic valve disease. This reflects a change in prevalence from previous studies. This could be related to better cardiac care for patients with congenital heart disease allowing those with corrected congenital heart diseases to reach reproductive age.[24]

Cardiomyopathies have a high prevalence in Sub-Saharan Africa.[21] The study is consistent with other reports in South Africa.[21]

The maternal mortality of 3.6% is dramatically higher than the maternal mortality rate of 288.6 per 100 000 live births that is reported in CMJAH.[40] A higher mortality and morbidity in patients of cardiac disease is expected but the mortalities reported in the study were referrals from Level 1 hospitals which reflects a failure of primary health care services to identify high risk patients and early referral. The two maternal deaths were patients that were late referrals from level one hospitals who needed immediate resuscitation at our institution. One patient had confirmed etiology of peripartum cardiomyopathy whilst the second patient had clinical features suggestive of peripartum cardiomyopathy which could be confirmed on further investigations as the patient demised shortly after arrival.

The caesarean section rate was 52.7% in patients with cardiac disease which is very high. Soma-Pillay et al reported a caesarean section rate of 39.7% in Steve Biko Academic Hospital from 2002 to 2005 in pregnant patients with cardiac disease.[21] The higher figure in our setting could be explained by the different geographical location of the hospital in Gauteng, the difference it temporal relationship between the studies, with Soma-Pillay et al looking at this data 10 years ago. They also present in an advanced stage of cardiac disease which require operative intervention rather than vaginal delivery. The state sector caesarean section rate has been documented in South Africa as 12% for all patients but there is a large

disparity between state and private sector caesarean section rates with figures of 25% and above reported in the private sector.[25] Patients with cardiac disease form a high risk population group and this does warrant a higher caesarean section rate.

There were seven ICU admissions who all survived to discharge. This in the setting of high risk cardiac patients with late referrals reflects antenatal and perinatal care.

The neonatal outcomes reflect a mean gestational age of 37.8 weeks and an average of weight of 2708 g. The average weight is lower than what is expected for the average gestational age but low weight for gestational age can be explained by the maternal cardiac condition.

There was one stillbirth in this cohort. The stillbirth rate was 1.8% or 18 per 1000 births which is in keeping with other studies in the local setting. Stillbirth rate is a reflection of peripartum and antenatal care and it is therefore used to assess the health care system. A lower than average stillbirth rate would indicate better health care delivery provided the same risk groups are compared.

7. Conclusion

Cardiac disease in pregnancy still poses one of the biggest risk and is a large contributor to peripartum morbidity and mortality. The profile of heart disease in these patients confirm that rheumatic and congenital heart disease are the top two causes of cardiac disease in pregnancy. Rheumatic heart disease prevalence in pregnancy is in keeping with the high prevalence of this disease in developing countries. The rise in congenital heart disease in pregnancy is a reflection of better care for such patients, allowing them to reach reproductive age.

Despite the challenges of resource constrained setting, the outcomes in high risk patients are still comparable to other, more resourced settings. The data for LMWH showing comparable outcomes in patients needing anticoagulation is supported in this cohort with good maternal and neonatal outcomes. This reflects a respectable multidisciplinary team approach.

High risk patients who are identified early and referred appropriately seem to have a much better outcome. Those who were referred late with advanced disease had very poor outcomes as reflected in the discussion previously.

Cardiac disease in pregnancy is associated with a high morbidity and mortality for the mother and the child. Early identification of these diseases, appropriate risk stratification, close monitoring during pregnancy, during delivery are the steps needed to address this problem.

8. Limitations

Paper records are not easy to decipher or trace and this limits the amount of data that can be collected.

Quality of the records could also pose a concern as the information provided may be insufficient to complete the data sheet.

There will be an element of selection bias as this is held at a central hospital thus selected patients are referred – for example, mild cardiac diseases maybe missed as this is not often referred to a central hospital.

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Appendix 1: Data capture sheet

Case ID: ☐

Hospital Number: ☐

Age: ☐ Miscarriages: ☐ Parity: ☐ Gravidity: ☐

Race: ○ Black ○ White ○ Coloured ○ Asian

Booking bloods:	**RPR**	**Rh**	**HIV**	**Hb**
	○ Positive	○ Positive	○ Positive	☐
	○ Negative	○ Negative	○ Negative	
	○ Unknown	○ Unknown	○ Unknown	

Maternal Complications:

☐ PIH ☐ PET ☐ GDM

☐ Anaemia ☐ UTI ☐ Infections

☐ Others: Specify: _____

_____

Sonars: Fetal anomaly scan done ○ Yes ○ No

If yes: Anomaly found: ○ Yes ○ No

If yes: Specify: _____

_____

Cardiac diagnosis: Congenital ◯ Yes ◯ No

If yes: Specify: _____

_____

If no: ◯ Valvular ◯ Non-valvular

☐ MR ☐ TR ☐ HPT

☐ MS ☐ TS ☐ IHD

☐ AR ☐ PR

☐ AS ☐ PS

Others: Specify: _____

_____

ECHO findings:

LVEF ☐ LVIDd ☐ LVIDs ☐

RVSP ☐ LA ☐ RV fxn ☐

E/A ☐ E/E` ☐

Diastolic dysfunction: ◯ Yes ◯ No

Regional wall motion abnormalities: ◯ Yes ◯ No

If yes specify area:

Valve lesion: ◯ Yes ◯ No

If yes: Specify lesion: ◯ MR ◯ MS ◯ AR ◯ AS

Specify severity: _____

Other pertinent findings: _____

_____

_____

RV ☐ RV function(TAPSE) ☐ TR ☐

PASP ☐ RAP ☐

IVC ☐ Specify: _____

Pericardium: _____

Masses: _____

Shunts: _____

Congenital lesion: ◯ Yes ◯ No

Specify: _____

_____

_____

ECHO assessment: _____

_____

_____

NYHA: ◯ I ◯ II ◯ III ◯ IV

ECG findings: ◯SR ◯ AF Heart rate ☐

Other pertinent findings: _____

_____

_____

Anaesthetic review: ◯ Yes ◯ No

If Yes: Recommendations: _____

_____

_____

_____

Cardiology review: ◯ Yes ◯ No

If Yes: Recommendations: _____

_____

Management strategy:

_____

_____

_____

_____

Treatment:

_____
_____
_____
_____

Anticoagulants: ◯ Yes ◯ No

If yes: Type: _____

Mode of delivery: ◯ NVD ◯ C/S

If C/S: ◯ Emergency ◯ Elective

Maternal complications:

☐ PPH ☐ Heart failure

☐ Hysterectomy ☐ Pulmonary embolism

☐ Transfusion ☐ Others: _____

_____

_____

Maternal outcomes: ◯ ICU ◯ Discharged ◯ Demised

Neonatal outcomes:

Gestational age at birth: ☐

Stillbirth ◯ Yes ◯ No

If No: Apgar at 5 min ☐ Weight: ☐

Cardiac orange form: ◯ Yes ◯ No

Appendix 2: Turnitin

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Appendix 2: Turnitin

Appendix 3: HREC

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr P Nair

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M161135

NAME: (Principal Investigator)	Dr P Nair
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A description of management and outcomes of pregnant patients with cardiac disease attending Charlotte Maxeke Johannesburg Academic Hospital in 2015
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	Project title change noted on 28 February 2018
SUPERVISOR:	Dr HA Rhemtula
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/03/2017

This clearance certificate is valid for 5 years from 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 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/We fully understand the conditions under which I am/we are authorised 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 resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

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