PROFILE OF CARDIAC PATIENTS WHO DELIVERED AT UNIVERSITAS ACADEMIC HOSPITAL (UAH) IN BLOEMFONTEIN SOUTH AFRICA: 2012 - 2017

RESEARCH DISSERTATION

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Principal researcher: Dr C M Makgato

Supervisor: Prof S M Baloyi

Co-Supervisor: Dr T Nondabula

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Declaration of Authorship

I Calvin Mongamola Makgato hereby declare that the work submitted in this document is my original and independent work. I further declare that this work is submitted for the first time at the University of the Free State (UFS) toward a Master's Degree in Obstetrics and Gynaecology and that it has never been submitted for a qualification at any other institution of higher learning. I hereby cede copyright of this work in favour of UFS.

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Calvin Makgato

Date: 12/11/19

Acknowledgement and Dedication

My sincere gratitude goes to Prof Baloyi and Dr Nondabula for their contribution and guidance throughout this research project.

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ABSTRACT

INTRODUCTION

Maternal deaths related to cardiac disease in pregnancy is rising globally. Cardiac disease remains the leading cause of mortality and morbidity in women with medical and surgical conditions in South Africa. Prevalence of cardiac disease in pregnancy ranges between 0.1-0.9% in South Africa. Pre-existing cardiac disease also contributes to significant perinatal morbidity and mortality.

OBJECTIVES

To assess the profile of women with cardiac disease who delivered at UAH, taking into account maternal and perinatal outcomes, and to identify underlying risks.

METHODS

A retrospective analysis of 148 files of pregnant women with cardiac disease who delivered at UAH between January 2012 and December 2017 was carried out. Frequencies and percentages were used to summarise categorical data. Medians and percentiles were used to summarise numerical data. The data analysis was generated using the SAS statistical software.

RESULTS

There were 3 154 deliveries at UAH during the study period. The prevalence of cardiac disease in pregnancy was 4.7% (n=148), with black women most affected (89.7%). The average age was 27.0 years. The youngest parturient was 16 years old and the oldest 43 years old. The majority of the patients (71.6%) booked antenatal care in the second trimester, with average gestational age at 19.5 weeks. One hundred and six women (71.6%) tested negative for HIV. The study population had an average BMI of 27. The average gestational age at delivery was 36.7 weeks, with 27.3% of the babies born preterm. Twenty-one (15.3%) of these neonates were admitted to the neonatal intensive care unit. There were eight stillborn deliveries with no neonatal deaths reported. The Caesarean section rate was 67.6%. Vaginal deliveries were 32.4% of all deliveries, and 31.9%(15) of these were assisted deliveries.

Of the patients with cardiac disease, 85% were New York Heart Association class (NYHA) I and II. Rheumatic heart disease (RHD), congenital heart disease (CHD) and cardiomyopathy was diagnosed in 48.6% (n=72), 24.3% (n=36) and 18.9% (n=28) of cases respectively. Cardiac failure and pulmonary oedema contributed 56% of maternal morbidity. Cardiac failure was indication for 43.8% of intensive care unit admissions. Six deaths were reported, with a case fatality rate of 4.05%.

Peripartum cardiomyopathy was the cause of death in five deaths and valve thrombosis in one death respectively. All deaths were NYHA functional class III and IV

CONCLUSION

The prevalence of cardiac disease among pregnant women is increasing, with rheumatic heart disease (RHD) being the leading aetiology. The most significant increase was that of congenital heart lesions. Pregnancies complicated by underlying cardiac disease are associated with maternal and perinatal morbidity.

Keywords: maternal, perinatal, mortality, morbidity, cardiac disease, pregnancy.

LIST OF ABBREVIATIONS

AO:	Aorta
AR:	Aortic regurgitation
ARV:	Anti-retroviral drugs
AS:	Aortic stenosis
ASD:	Atrial septal defect
AVSD:	Atrioventricular septal defect
BMI:	Body mass index
CARPREG:	Cardiac disease in pregnancy
CEMACH:	Confidential enquiries into maternal and child health
CFR:	Case fatality rate
CHD:	Congenital heart disease
CPD:	Cephalo-pelvic disproportion
EF:	Ejection fraction
FD:	Fezile Dabi
HB:	Haemoglobin
HIV:	Human immunodeficiency virus
HR:	Heart rate
HSREC:	Health Sciences Research and Ethics Committee
HT:	Hypertension
ICU:	Intensive care unit
IQR:	Interquartile range
LL:	Lejweleputswa

LMIC: Low and medium income countries

MAX: Maximum

MBRRACE-UK: Mother and Babies: Reducing Risk through Audits and Confidential Enquiries across the United Kingdom

MIN: Minimum

MS: Mitral stenosis

MP: Mitral prolapse

NC: Northern Cape

NICU: Neonatal intensive care unit

NYHA: New York Heart Association

PHT: Pulmonary hypertension

PPCM: Peripartum cardiomyopathy

PPH: Postpartum haemorrhage

RHD: Rheumatic heart disease

TB: Tuberculosis

TM: Thabo Mofutsanyana

TOF: Tetralogy of Fallot

TOP: Termination of pregnancy

TR: Tricuspid regurgitation

UAH: Universitas Academic Hospital

UFS: University of the Free State

VSD: Ventricular septal defect

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CHAPTER 1

1.1 INTRODUCTION AND BACKGROUND

Maternal mortality related to cardiac disease in pregnancy is rising globally, despite the coordination of specialists' services and international guidelines[1]. Both congenital and acquired cardiac disease may present for the first time in pregnancy and postpartum, for example peripartum cardiomyopathy (PPCM). In South Africa, cardiac disease remains the leading cause of mortality and morbidity in women with medical and surgical conditions. Pre-existing cardiac disease also contributes to significant perinatal morbidity and mortality[2]. Socio-economic factors have been described to partly explain the differences regarding pregnancy outcomes in women with cardiac disease, but the main denominator was the condition of the individual, at least in medium to high human development index (HDI) countries[3]. There is a lack of data describing cardiovascular disease presentation and patterns in developing countries. This study is the most recent and longest audit of pregnant women with cardiac disease in South Africa.

1.2 LITERATURE REVIEW

CARDIOVASCULAR PHYSIOLOGICAL ADAPTATIONS IN PREGNANCY

Knowledge of normal cardiovascular adaptations in pregnancy is important in understanding how they affect the natural course of cardiac disease and their management during this state. Pregnancy and the puerperium is a marked period of significant circulatory and heart physiological changes. Changes in cardiac function become marked by the 8thweek of pregnancy. By the 5thweek, cardiac output is increased. This is a reflection of reduced vascular resistance and increased heart rate, rising to 20% above pre-pregnancy values[4,5,6,7,8].

There is an increased hemodynamic load between the 10th and 20th week as plasma expands by 50% and increases circulatory preload. Structurally there is substantial ventricular remodeling characterised by eccentric mass expansion of approximately 30 - 35% near term. These changes are due to increase plasma volume, which is reflected by enlarged cardiac end systolic and end diastolic dimensions. The ejection fraction remains the same, which represents ventricular function[8].

Because of this decrease in mean arterial pressure and vascular resistance, together with an increase in blood volume and metabolic rate, cardiac output increases continuously throughout pregnancy. A diseased state in a non-pregnant patient may represent a normal adaptation in pregnancy, and conversely failure of these adaptations may represent pathology[6].

Symptoms and signs normally associated with cardiac disease may be found in normal pregnancies. It is crucial for health care workers to differentiate normal from suspicious symptoms and signs that may warrant further probing. Breathlessness is common in normal pregnancy in up to 75% of women by week 31 of gestation. Breathlessness leading to severe restriction in activities of daily living is abnormal. Lower limb oedema and varicose veins are normal in pregnancy. Cardiac disease and preeclampsia should be suspected with the presence of generalised oedema and proteinuria[6].

Normal pregnancy is associated with an increased heart rate, but a rate above 100 bpm may require further probing for an underlying trigger. Due to reduced systemic vascular resistance and an increase in cardiac output, the pulse is often of a bounding character. Loud heart sounds and the presence of a third heart sound is a normal finding in pregnancy. A soft ejection systolic murmur is heard in over 90% of pregnant women, but a very loud or palpable thrill points to an underlying pathology[6,7].

Normal adaptations found on a 12 lead electrocardiogram (ECG) in pregnant patients show left axis deviation of the heart (the heart is rotated to the left in normal pregnancy), transient ST-segment and T wave change (inverted T wave), atrial and ventricular ectopic beats[8,9].

The peripartum period represents another high-risk period in patients with cardiac disease. Dynamic changes occur in labour with each contraction contributing to auto-transfusion of about 300 - 500mls of blood back to systemic circulation. Blood pressure and heart rate increase due to sympathetic response to pain, and this increases cardiac output by up to 34% during contractions and by 12% between contractions[6]. This so-called Valsalva manoeuvre produces a wide swing in both venous and arterial pressures, leading to possible acute cardiac decompensation[10]. Effective labour analgesia with epidural together with assisted delivery to shorten the second stage of labour have proven to reduce this risk[11,12].

Re-distribution of blood volume and relief of venocaval compression following delivery result in an up to 60 - 80% increase in cardiac output, followed by a rapid decline to pre-labour values by one hour after delivery. These women are thus at high risk of pulmonary oedema during the second stage of labour and the immediate postpartum period. This is demonstrated by a four-year audit done at the Pretoria Academic Hospital, with most maternal deaths occurring after birth and pulmonary oedema being the main contributing factor occurring in 57% of the cases[13]. Cardiac output returns to pre-pregnancy values within two weeks postpartum[6].

RISK ASSESSMENT AND MANAGEMENT OF CARDIAC DISEASE IN PREGNACY

Pregnancy increases the risk of mortality and morbidity in women with heart disease, but data on the magnitude of the risks are limited[14]. The risk for both the mother and the fetus increases exponentially with the extent and complexity of the underlying disease[9]. It is vital to conduct a systematic, accurate and realistic risk assessment for potential maternal and fetal adverse events both during pregnancy and postpartum, as this will influence the success and safety of the index pregnancy. Risk stratification helps with counselling in pre-conception clinics[9].

All women with heart disease should be assessed at least once before pregnancy, and continually during pregnancy[8, 20]. Current risk stratification models described in the literature include the Cardiac Disease in Pregnancy score (CAPREG), the ZAHARA risk score (exclusively for mothers with congenital heart disease (CHD)), and the modified WHO classification based on expect consensus[7, 8,9,13].

The CARPREG score has been validated in several studies and is the most widely used. The score uses predictors, with each predictor given a score of one. Scores are then added to give an overall view of maternal complications. The predictors are as follows:

Prior cardiac event, baseline NYHA >II or cyanosis, left heart obstruction: MS <2cm, AO <1.5cm, LV outflow gradient of >30mmHg and left ventricular dysfunction (EF <40%). The total score is interpreted as follows: 0 point = 5% risk of maternal complication, 1 point = 27% risk of maternal complication and >1 point = 75% risk of maternal complication [7,8,9,29.] The ZAHARA risk score is used exclusively for populations with congenital heart disease. Predictors from this risk assessment score have not been validated by other studies. These predictors include the following: History of arrhythmia event, baseline NYHA functional class > II, left heart obstruction: Aortic valve peak gradient > 50mmHg, Mechanical valve prosthesis, moderate to severe systemic atrio-ventricular valve regurgitation, use of cardiac medication pre-pregnancy and repaired/unrepaired cyanotic heart disease[7,8,9].

Maternal risk assessment can also be carried out according to the modified WHO risk classification (mWHO). This integrates all known maternal cardiovascular risk factors, including the underlying heart disease and any co-morbidities. The mWHO risk classification is divided into four classes. Class I represents very low risk, class II low to moderate risk. In these two classes, follow-up during each trimester by a cardiology team is recommended mWHO class III includes women at high risk of complications while those in class IV are advised against falling pregnant. See summarised table below.

Table 1.1 Modified World Health organisation (mWHO) risk classification.

Conditions in which pregnancy risk is WHO class I; risk no higher than general population
I. Uncomplicated, small or mild; • Pulmonary stenosis • Patent ductus arteriosus • Mitral valve prolapse II. Successfully repaired simple lesions (atrial or ventricular septal defect, ductus arteriosus, anomalous pulmonary venous drainage) III. Atrial or ventricular ectopic beats isolated.
Conditions in which pregnancy risk is WHO class II or III
WHO II; Small increased risk of maternal mortality or moderate increase in morbidity
I. Unoperated atrial or ventricular septal defect II. Repaired tetralogy of Fallot III. Most arrhythmias
WHO II–III (depending on individual)
I. Mild left ventricular impairment II. Hypertrophic cardiomyopathy III. Native or tissue valvular heart disease not considered WHO I or IV IV. Marfan syndrome without aortic dilatation V. Aorta <45mm in aortic disease associated with bicuspid aortic valve VI. Repaired coarctation
WHO III
I. Mechanical valve II. Systemic right ventricle III. Fontan circulation IV. Cyanotic heart disease (unrepaired) V. Other complex congenital heart diseases VI. Aortic dilatation 40 – 45mm in Marfan syndrome VII. Aortic dilatation 45 – 50mm in aortic disease associated with bicuspid aortic valve
WHO IV

I. Pulmonary arterial hypertension of any cause
II. Severe systemic ventricular dysfunction (LVEF <30%, NYHA III–IV)
III. Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
IV. Severe mitral stenosis, severe symptomatic aortic stenosis
V. Marfan syndrome with aorta dilated >45mm
VI. Aortic dilatation >50mm in aortic disease associated with bicuspid aortic valve
VII. Native severe coarctation

Adapted from ESC guidelines, 2011[8].

Once the diagnosis has been made and cardiac function has been assessed, the effect of pregnancy on the disease and vice versa must be evaluated and documented. Further arrangement in terms of referral, antenatal care, delivery and postpartum care should be made and discussed with the patient. The best time to discuss and implement a management strategy would actually be before conception, as this will allow for a baseline evaluation of cardiac function and provide an opportunity for individualised counselling. This will also allow interventions prior to pregnancy, which could avoid fetal exposure to ionising radiation and risk from medical procedures[9].

Neonatal complications have been reported in the region of 20 - 28% of patients with a cardiac condition, with a neonatal mortality of between 1 - 4%. Maternal and neonatal events are highly correlated. Maternal predictors of neonatal morbidity include, baseline NYHA > II or cyanosis, maternal left heart obstruction, smoking during pregnancy, multiple gestation, use of oral anticoagulants during pregnancy and mechanical valve prosthesis[8]

Elliot[9] and colleagues have developed a referral algorithm in Groote Schuur Hospital based on risk scores. It provides guidelines to help with the correct referral of pregnant patients to a multidisciplinary combined cardiology and obstetrics clinic. Tertiary hospitals such as Steve Biko Academic and Groote Schuur Hospitals provide a bi-weekly combined cardiac-obstetric clinic[9].

PATHOLOGY

Globally up to 25 0000 premature deaths due to rheumatic heart disease (RHD) are reported annually[15]. RHD can be regarded as a disease of the poor, and represent social inequality[16]. RHD remains a major public health challenge in LMIC[17,18]. Acute rheumatic fever is caused by an abnormal autoimmune response to group A streptococcal pharyngitis, which can present as arthritis of the large joints. It affects the skin and brain, and causes heart valvular inflammation. Functional and morphological valvular damage can clinically present with severe valve dysfunction and cardiac failure. Effective treatment strategies in LMIC involve secondary antibiotic

prophylaxis together with a reduction of other risk factors such as overcrowding, poor hygiene and limited access to health care. There is concerted efforts by the WHO to reduce RHD and other communicable diseases by 25% by the year 2025[16,19].

Peripartum cardiomyopathy (PPCM) is defined as heart failure that occurs towards the end of pregnancy, or in the months following delivery, where no other causes of heart failure are found[8]. Reported incidences vary across the globe. In the USA it is between 1:9 00 and 1:4 000, in Nigeria 1:100 and in Haiti 1:300[21,24]. The incidence in South Africa is 1:1 000, as reported by Desai[22] and colleagues. This condition maybe difficult to distinguish from other forms of cardiomyopathy, such as familial or pre-existing idiopathic dilated cardiomyopathy, which usually presents prior to pregnancy or in the second or third trimester[23,25]. The risk factors for PPCM include Black race, age above 30 years, hypertension, anaemia, multiple gestations and obesity[24]. Gilles[26] and colleagues concluded that patients with cardiomyopathy were at a higher risk of poor maternal and perinatal outcomes. They emphasised the importance of risk stratification of such patients, and reported the CARPREG score as the most appropriate predictor of maternal adverse events[26]. Patients who attended a combined multidisciplinary clinic early in the pregnancy had better outcomes[27].

The population of people with congenital heart disease (CHD) is increasing globally, owing to advances in childhood cardiac interventions[28]. Kramlon[30] reported a 5% annual increase in the USA since 2005. Hidano et al[31] concluded that despite low overall incidences in maternal and perinatal mortality in the pregnant CHD population, there is still significant morbidity. Maternal morbidity among CHD patients is 18 times that of the general population. VSD is associated with a higher prevalence of poor obstetric and maternal outcomes compared to other subgroups[30].

PREGNANCY OUTCOMES IN WOMEN WITH CARDIAC DISEASE

Globally, complications from heart disease during pregnancy account for a significant portion of maternal morbidity and mortality[32,33]. Heart disease is the leading cause of death among pregnant women in the United States of America[34].

There has been a 24.7% increase in women with heart disease presenting for delivery in the USA from 2003 to 2012[35]. Similarly, there was an almost 50% increase in pregnancies among women with congenital heart disease. On the one hand, this is due to improved survival rates of women with congenital heart disease. On the other, a lack of pregnancy risk stratification, a lack of knowledge by patients and health care providers, and poor transition of care from paediatric to adult health care providers, all seem to contribute to the growing number of pregnant women with cardiac disease[35]. Lima et al[35] found that the proportion of pregnant women with cardiac disease was 0.2%. Of these, congenital heart disease (CHD) formed a large proportion (41.8%), followed by valvular heart disease (30.9%). In 20.8% of the cases, cardiomyopathy was predominant, while pulmonary hypertension contributed only

6.5%. Major cardiac adverse effects were found in women with cardiomyopathy, and the lowest among CHD. Pulmonary hypertension had the most in-hospital deaths followed by cardiomyopathy[35]. Cardiovascular disease accounted for 15.5% of maternal deaths between the years 2011 and 2013[36] .

Women with cardiomyopathy were negatively affected by adverse cardiovascular adverse and poor perinatal outcomes[35]. Hink et al[32] found that even though the prevalence of heart disease in pregnancy is low, it is the most important cause of indirect maternal mortality in the Netherlands. In 2003 - 2005 the indirect maternal mortality rate due to cardiac disease was 9.2% (1.6/10 0000 pregnancies), and this is a significant increase compared to earlier studies[32]. This finding is also consistent with the United Kingdom's Confidential Enquiry into Maternal and Child Health (CEMACH) [37]. The Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries MBRRACE-UK report of 2015 recorded 33.79% of indirect deaths due to cardiac disease in 2011 - 2013[1]. The NORMANDY study by Vincent et al[38] concluded that the various cardiomyopathy types were associated with increased maternal, obstetric and fetal complication compared to the healthy pregnancy population in France. This is consistent with global trends.

An audit in the Singapore General Hospital reported maternal and perinatal outcomes in 60 pregnant women with cardiac disease. Two thirds of patients had congenital heart disease, while a third suffered from acquired heart disease. Peripartum cardiomyopathy remained an important indication for longer hospital stay. The study reported good maternal and perinatal outcomes, and this was attributed to the availability of joint obstetric and cardiology services[39].

Studies in India found the prevalence of heart disease among pregnant women to be 4.3%. The greatest proportion of patients suffered from rheumatic heart disease (56.6%) compared to 13% with congenital heart disease. Maternal and perinatal outcomes were poor in women with NYHA class III and IV. The most common mode of delivery was reported to be caesarean section, and only 7% of vaginal deliveries were assisted. Four maternal deaths were reported with CFR of 4.44%[40].

In a prospective study in Uganda over 24 months, Beaton et al[41] reported a prevalence of cardiac disease in pregnancy of 1.7% with only 3.4% of patients knowing about their cardiac disease at presentation. RHD was reported in 88% of the study population. PPCM and CHD were reported in only 1.7% of the cases. More than half of the cases (51.8%) presented with complications, and 34% presented with heart failure. Maternal mortality of 1.5% and PNMR of 116/1 000 was reported. A caesarean section rate of 10.7% was reported.

Medical disorders in pregnancy are one of the top five causes of maternal mortality in South Africa. Cardiac disease is the main contributor[9]. Acquired heart diseases such as

rheumatic heart disease and cardiomyopathy significantly contribute to maternal morbidity in South Africa and other developing countries. According to the Saving Mothers Report 2015, maternal deaths due to medical and surgical conditions declined significantly between 2010 and 2015 (17.66% to 13.44%). The most significant decrease was from 2014 to 2015. In the same period, however, the cardiac disease category remained the same[2]. An audit of maternal deaths by Soma-Pillay et al[23] found that 33.7% of mothers with cardiac disease delivered vaginally, 26% by caesarean section while 39.8% were undelivered. That study also reported on perinatal morbidity, indicating that 71.8% of the babies were born preterm with an average gestational age of 32 weeks at delivery. The average birth weight of babies born alive was 2558g. Of the babies born alive 64% were low birth weight (<2.5kg)[23].

In 2015, 44% of maternal deaths due to medical and surgical conditions were due to cardiac disease. This is an increase of 34% between 2011 and 2013. These figures are higher than in developed countries, although the trends are similar.

In 2012, Watkins et al[33] reported that cardiac disease accounts for 41% of the indirect causes of maternal deaths in South Africa. Rheumatic heart disease is a huge proportion of cardiac disease in pregnancy, as seen from studies showing a high burden of RHD in poorer countries[33]. Demographic data in a study by Soma-Pillay[23] shows a high cardiac disease burden among African women, which comprised 88% of the study population. This correlates with other local studies.

Schoon et al[42] did a study at Pelonomi Hospital from 1990 to 1995 and found the prevalence of pregnancies complicated by cardiac disease to be 0.6%. Maternal mortality rates due to cardiac conditions in the Mangaung district was 3.7%, compared to 11% from all the referring districts combined. Rheumatic heart disease accounted for most of the cases[42]. In a 2012 South African systematic review, the Free State province was found to have the highest case fatality rate compared to the other provinces[33]. Late booking and a lack of insight into the implications of pregnancies complicated by cardiac disease were noted as major contributors to morbidity and mortality. The caesarean section rate among pregnant cardiac patients was higher that the institution average of 17.2%. Mothers had an average hospital stay of 12 days in obstetrics high care. Women with poor cardiac outcomes also had the highest perinatal mortality rate of 19.3%[43].

A four-year audit at the Pretoria Academic Hospital by Soma-Pillay[13] found a prevalence of cardiac disease among pregnant patients of 0.94%. RHD was the most frequently diagnosed condition, followed by congenital heart disease and cardiomyopathy with 63.5%, 9% and 5.8% respectively. Prosthetic heart valves were reported in almost 40% of the study population. They reported perinatal losses of 12%, with mean age at delivery of 35 weeks and average birth weight of 2500g. A

severe maternal morbidity rate of 11.6% and a case fatality rate of 3.3% was reported. Pulmonary oedema was found to be a contributing factor in 57% of maternal deaths.

Nqayana[44] and colleagues reviewed 95 pregnant women with cardiac disease in KwaZulu-Natal. RHD was reported in 81.1% of their cohort. CHD was reported in 9.5% of cases and 56% of the cases had VSD. PPCM was reported in only 3% of the study population. Poor obstetric outcomes were reported in 27% of cases. No maternal deaths were recorded. Almost 14% of complicated patients had heart failure. The overall caesarean section rate was 57.9%. The perinatal mortality rate was 76/1 000 births. Most stillbirths occurred in patients using oral anticoagulants.

A prospective study over two years among 225 pregnant women with cardiac disease in Groote Schuur Teaching Hospital, reported a case fatality rate of 5.92%. PPCM was reported as a cause of death in 77.8% of cases. A low perinatal mortality rate of 7/1 000 was reported, comparable to that in high-resource countries. This was attributed to intensive surveillance through multidisciplinary clinics. A large proportion of cases had RHD, similar to other South African studies. CHD diagnosis was made in 32% of the cases, and 27% of cases had cardiomyopathy[45].

1.3 PROBLEM STATEMENT AND AIMS

Despite reported increasing morbidity and mortality from cardiac disease in pregnancy, there is lack of local literature regarding the profile of cardiac patients in pregnancy, together with description of obstetric, maternal and perinatal outcomes. The available literature is old and does not reflect the current situation.

STUDY AIMS

To determine the profile of cardiac patients who delivered at UAH between 2012 and 2017 and assess maternal and perinatal outcomes associated with cardiac disease.

CHAPTER 2

METHODOLOGY

2.1 STUDY DESIGN

The study is a descriptive retrospective audit of clinical records of pregnant patients with cardiac disease who delivered at UAH between January 2012 to December 2017.

2.2 STUDY SETTING

The study was conducted at Universitas Academic Hospital, a tertiary hospital in Bloemfontein, Free State province. The Free State is located in central South Africa, and is bordered by five other provinces (Gauteng, Northwest, Northern Cape, Eastern Cape and Kwazulu Natal), and Lesotho. The hospital receives referrals from five districts (each with a secondary hospital), the Northern Cape and Lesotho. The hospital has an established obstetrics department with four high dependency care beds and twenty antenatal and postnatal beds. There is a neonatology department with a NICU, a paediatric and adult cardiology unit and a cardiothoracic unit. These departments work together to form multidisciplinary team caring for pregnant cardiac patients.

2.3 STUDY POPULATION

A retrospective audit of medical records of all pregnant women with cardiac disease who delivered at UAH was done. The delivery register for January 2012 to December 2017 was used to identify cardiac patients. Other registers used were of maternal deaths and medical TOP/congenital anomalies to identify cardiac patients.

OBSTETRIC, PERINATAL AND MATERNAL OUTCOMES

Obstetric outcomes included, single or multiple pregnancy, induction of labour, termination of pregnancy, mode of delivery, and antenatal admission

Maternal outcomes included, cardiac disease diagnosis, maternal complications including mortality, ICU admission and NYHA functional class.

Perinatal outcomes included, congenital anomalies, perinatal mortality, preterm deliveries, neonatal birth weight and NICU admission

2.4 STATISTICAL ANALYSIS

A biostatistician from the UFS Department of Biostatistics analysed the data. Frequencies and percentages were used to summarise categorical data. Medians and percentiles were used to summarise numerical data. The data analysis was generated using the SAS statistical software.

2.5 ETHICS

Ethical approval to conduct the study was granted by University of the Free State Health Sciences Research and Ethics committee HSREC. The ethics approval number is **UFS-HSD2018/0042/3107.** The Free State Department of Health Research Committee granted permission for the research. The head of the Department of Obstetrics and Gynaecology gave permission for the researcher to access patient files. Data from files were transferred to data collection forms, which were coded for confidentiality, and only the principal investigator had access to named files.

CHAPTER 3

RESULTS

There were 3 154 recorded deliveries at UAH during the six-year study period. The number of pregnant patients with cardiac disease was 190. Of these patients, 148 files could be retrieved for analysis, which is a retrieval rate of 77.9%. The retrieved files included that of maternal deaths, which are usually kept separately in the matron's office. This reduces the likelihood of one of the missing files containing a maternal death. For calculating maternal death and case fatality rates, 190 was used as a denominator as it represents the total number of women with cardiac disease that delivered at UAH. The rest of the data presented was based on the actual number of retrieved files.

UAH is a tertiary hospital situated in the greater Mangaung Metropolitan area. Its catchment area includes five Free State districts, each with a secondary hospital, the Northern Cape and Lesotho. Of the total number of 3 154 deliveries, 148 were women with cardiac disease. This is an institutional prevalence of 4.69%. The bulk of these patients (n=49) 33.6% were referred from the Mangaung District. See a summary of referrals in figure 3.1 below.

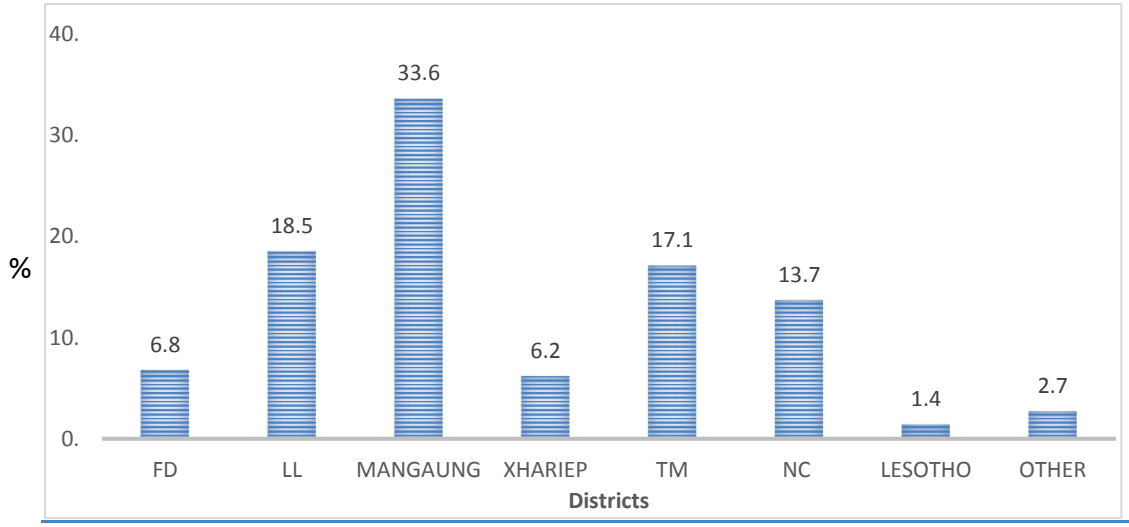

FIGURE 3.1 Free State Referral Districts

TABLE 3.1 Baseline characteristics table

CHARACTERISTICS	N (%)
RACE • African • Coloured • Caucasian • Indian	N=148 130 (89.7) 8 (5.5) 6 (4.1) 1 (0.7)
AGE • Median • Mean • IQR • Min/Max	 27 27.4 23 - 32 16/43
BMI • Median • Mean • IQR • Min/Max	 27 29.1 22.9 - 32.9 17.1/55

OBSTETRIC HISTORY	
• Primigravida	46 (31.1)
• Multigravida	102 (68.9)
HIV STATUS	
• Positive	40 (27)
• Negative	106 (71.6)
• Unknown	2(1.4)
CD4	
• Median	408.5
• Min/Max	50/1253
BOOKING HB	
• Median	11.5g/dl
• Mean	11.3g/dl
• Min/Max	6.4/14.8g/dl
	N=21
BOOKING HR	
• Median	89.0
• Mean	90.9
• Min/Max	72.0/116.0
BOOKING BP	
• Systolic (median)	110.5
• Min/Max	80/171
• Diastolic (median)	70
• Min/ Max	36/121
MEDICAL HISTORY	
• Chronic HT	29 (19.6)
• DM	2 (1.4)
• Syphilis	N=144
I. Positive	10 (6.9)
II. Negative	134 (93.1)
• TB	3 (2.0)

• Hypothyroidism	3 (2.0)
SOCIAL HISTORY • Smoking • Alcohol • Employed • Unemployed	 9 (7.0) 9 (7.0) 28 (20.7) 107 (79.3)

Cardiac disease was commonly diagnosed among black women (89.7%) and least among Indians (0.7%). 68.9% of the study population were multiparous with a highest parity of seven, while 31.1% were primigravidas. Approximately 80% of the cohort was unemployed. The majority of the patients tested negative for HIV (71.6%). Only 27% tested positive and more than 90% of them were on ARVs. 8.3% were not yet on treatment. Anaemia was diagnosed in 13.8% (n=15) of patients at booking with the lowest HB of 6.4g/dl. Only 21 patients had their heart rate recorded at booking. A common co-morbidity among the study population was chronic hypertension (19.6%). Other co-morbidities are summarised in table 1. Only 7% of patients indicated during their first antenatal visit that they either smoked or used alcohol.

The median age of the cohort was 27.0 years. The youngest patient was 16 years old and the oldest was 43. More than half of the women were between 20 and 29 years old (53.4%) - see figure 3.2 below.

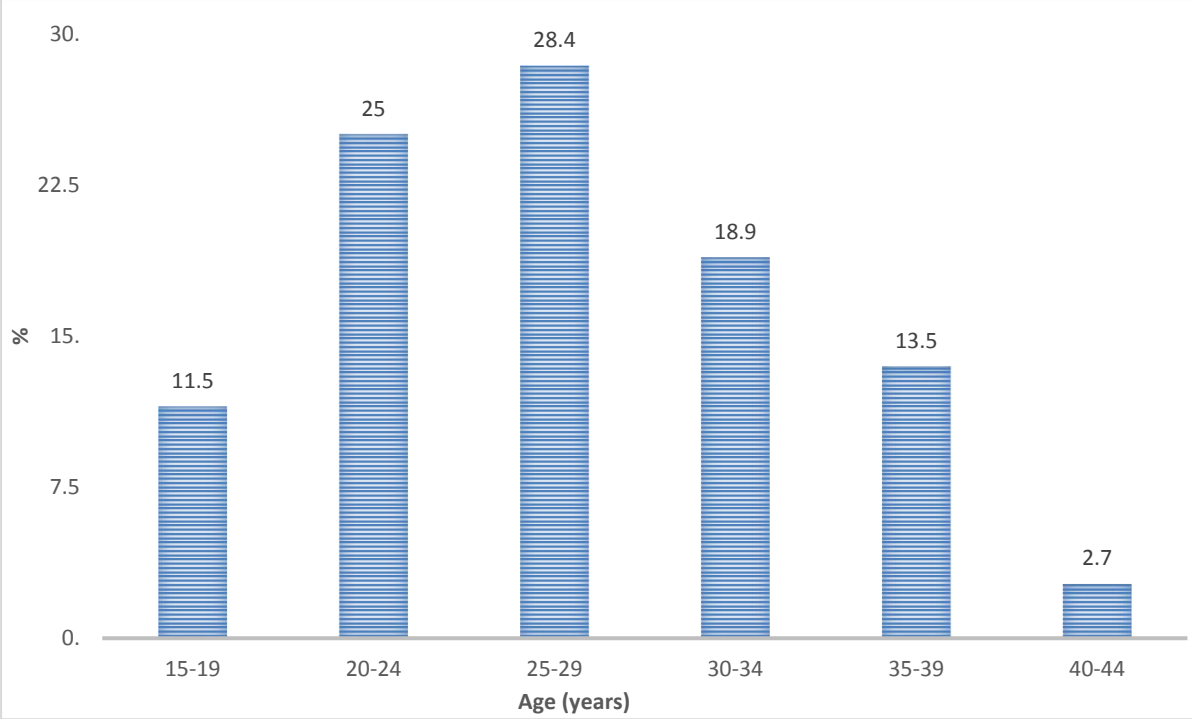

FIGURE 3.2 Age distribution graph

Addendum to Figure 3.2 Age distribution graph

N	148
Mean	27.4
Median	27
IQR	23-32
Min/Max	16/43

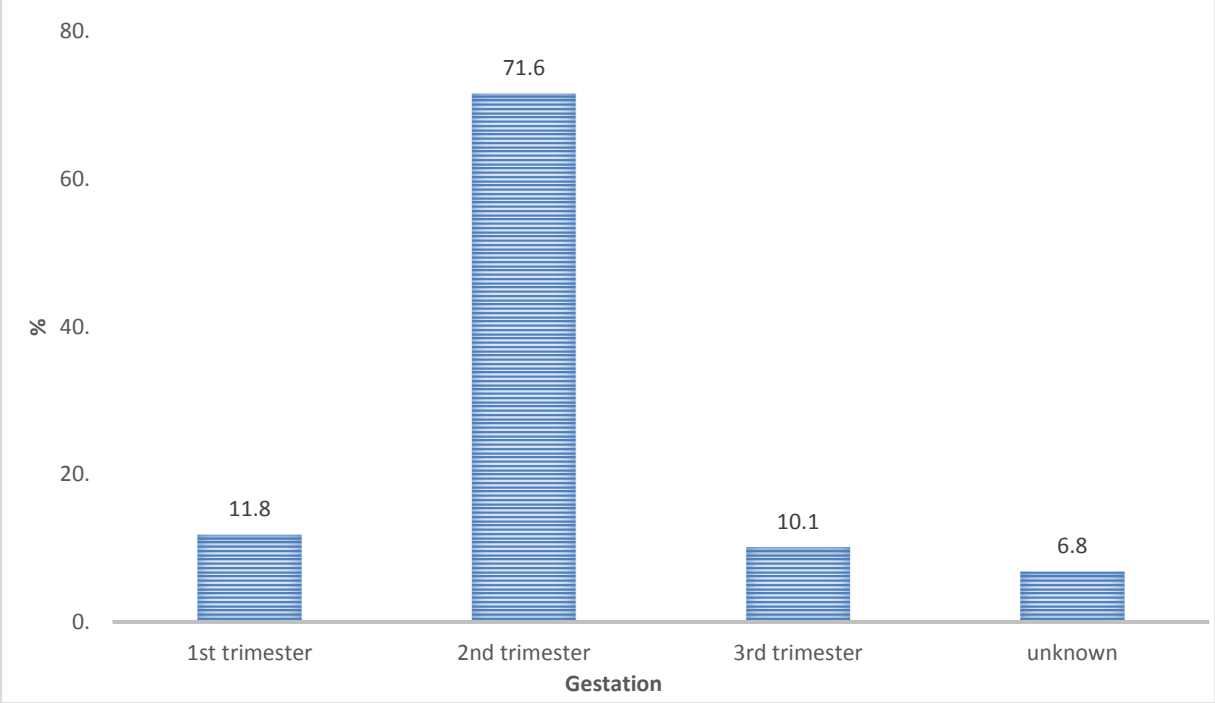

FIGURE 3.3 Booking gestation

The mean gestational age of the study cohort at booking was 19.8 weeks. The median was 19.5 weeks and the interquartile range between 15 and 24 weeks. Minimum and maximum gestation at booking was 6 and 38 weeks respectively. The majority of patients, 71.6% (n=106), had their first contact with a health care worker in the second trimester. A percentage of 11.8 %(n=17) had their first antenatal visit before 12 weeks, and 10.1% (n=15) only had it in the third trimester. See figure 3.3 above.

OBSTETRIC OUTCOME

TABLE 3.2 Obstetric Outcome

OUTCOME VARIABLES	N (%)
MODE OF DELIVERY	
NVD	47 (32.41)
AVD	15 (31.9)
OPERATIVE DELIVERY	98 (67.6)
Elective C/S	51 (52.0)
Emergency C/S	47 (48)
Undelivered	2 (1.4)
ANASTHESIA	
Epidural	12 (12.4)
Spinal	35 (36.1)
GA	50 (51.6)
LABOUR ANALGESIA	
Epidural	18 (34.6)
Other	34 (65.4)
IOL	34 (23)
MEDICAL TOP	1 (0.7)
GESTATIONAL AGE AT DELIVERY	
Mean	36.7
Median	38
IQR	36 - 39
Min/max	21/41

Of the 145 deliveries, 97.9% was singletons and 2.1% was twins. The mean gestational age at delivery was 36.7 weeks. One patient underwent medical termination at 21 weeks. Two patients did not deliver due to maternal deaths. Most of the patients (98 - 67.7%) were delivered by caesarean section, and the majority of these were electives (52.0%). Almost 25% of the caesarean sections were done for maternal reasons. Obstetric indications were fetal distress (22.5%), CPD (9.2%) and breech presentation (4.1%). See graph below. General anaesthesia was given in 51% of the cases, 36% utilised spinal and 12.4% epidural anaesthesia respectively. Induction of labour was carried out in 23% of patients. Of the cohort, 47% delivered vaginally and 31.9% of these were assisted with either vacuum or forceps. Epidural analgesia was provided for only 34.6% of these cases.

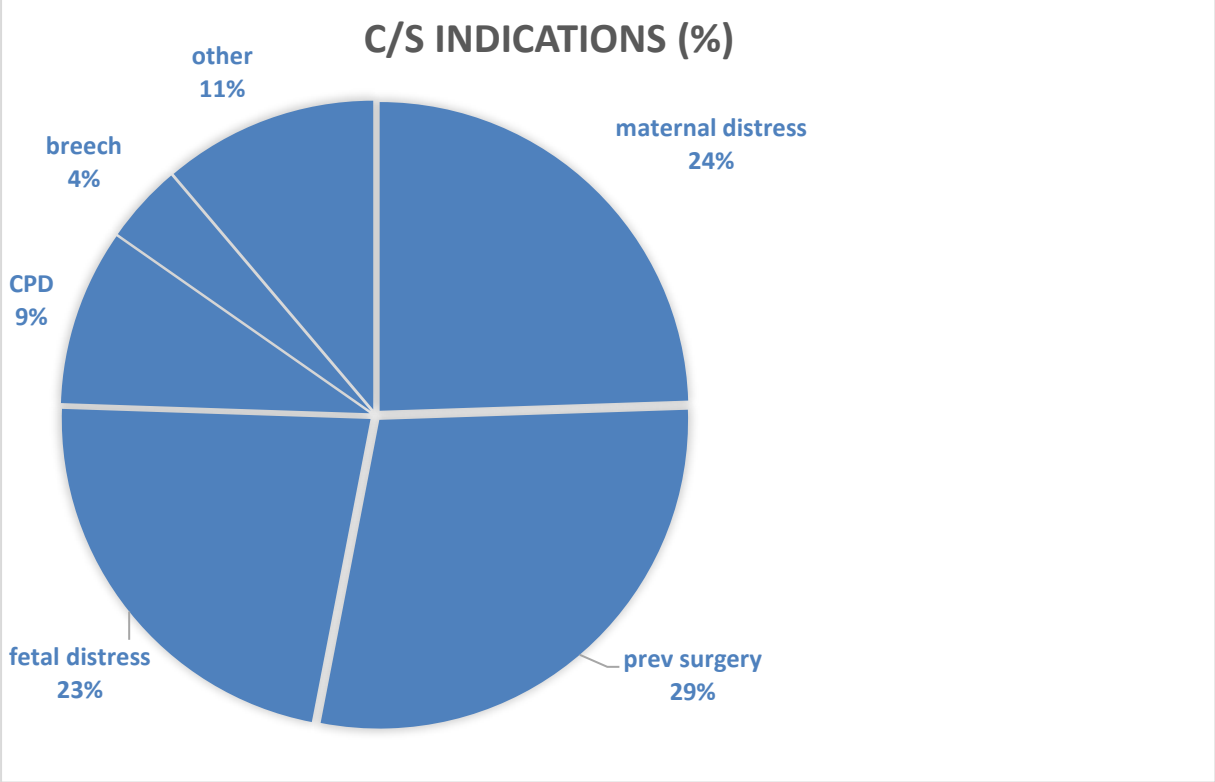

FIGURE 3.4 Cesarean section indications

PATHOLOGY

Cardiac disease distribution is shown in figure 3.5 below. Rheumatic heart disease was diagnosed in 48.7% of patients. Congenital heart disease was reported in 24.3% of cases and cardiomyopathy in 18.9%. More than half of the congenital heart lesions were VSD (54.3%). TOF was diagnosed in five patients (14.3%), and other diagnoses included AVSD, pulmonary stenosis and ASD (in 8.7% of patients in both cases). See summary in figure 3.6 below. The majority (94.4%) of these congenital heart lesions were repaired. Valvular disease with prosthetic heart valves were seen in 72 patients, all due to rheumatic heart disease. Figure 3.7 shows the distribution of valvular

lesions. Mitral regurgitation was the major valvular lesion, diagnosed in 35.7% of the study population. Mixed valvular lesions were found in 22.9% of patients, followed by mitral valve prolapse and mitral stenosis (both in 15.7% of the cases). Tricuspid regurgitation, aortic regurgitation and aortic stenosis were diagnosed in 5.7%, 2.9% and 1.4% of cases respectively. Of the patients, 30.6% were only diagnosed with cardiac disease in pregnancy, and among those with prior diagnosis only 37.3% attended the cardiac clinic.

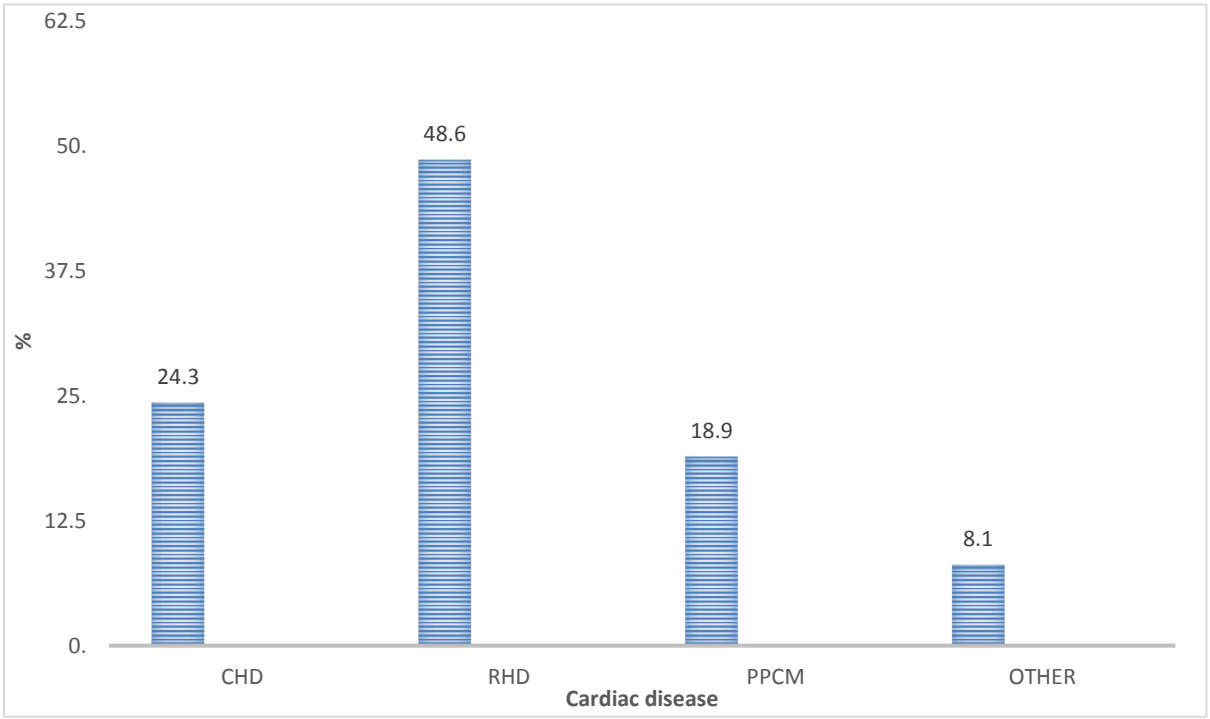

FIGURE 3.5 Cardiac disease distribution

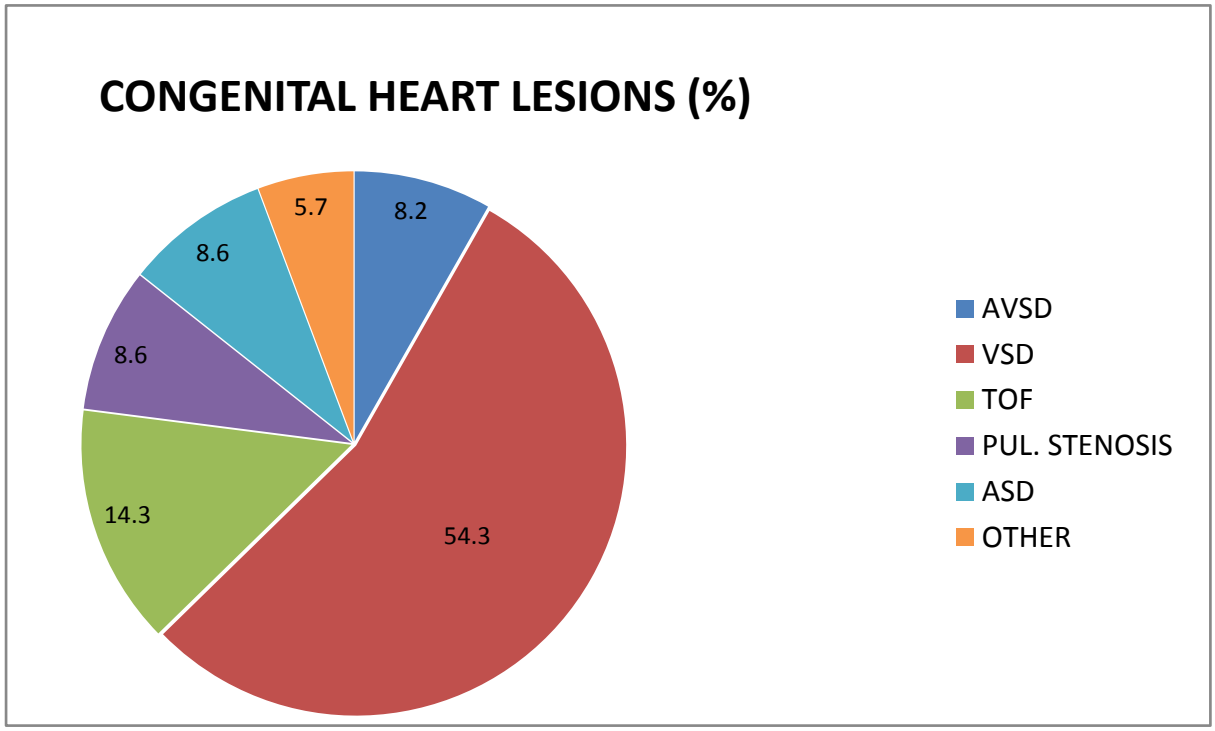

FIGURE 3.6 Congenital heart disease distribution

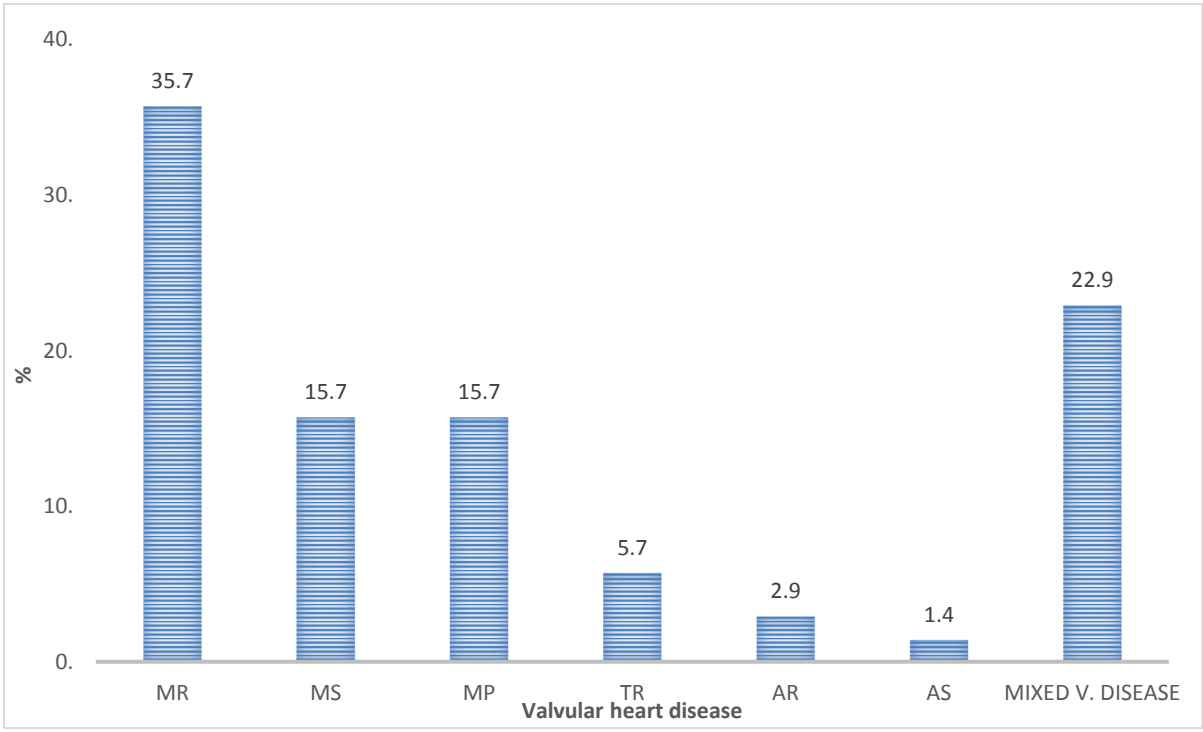

FIGURE 3.7 Valvular heart lesion distribution

The majority of patients were NYHA functional class I (n=85; 63.9%). Patients with class II NYHA were 28 (21.1%). NYHA class III and IV were reported in a total of only 20 patients, 8 (6%) and 12 (9.2%) respectively. Figure 3.8 shows NYHA class distribution.

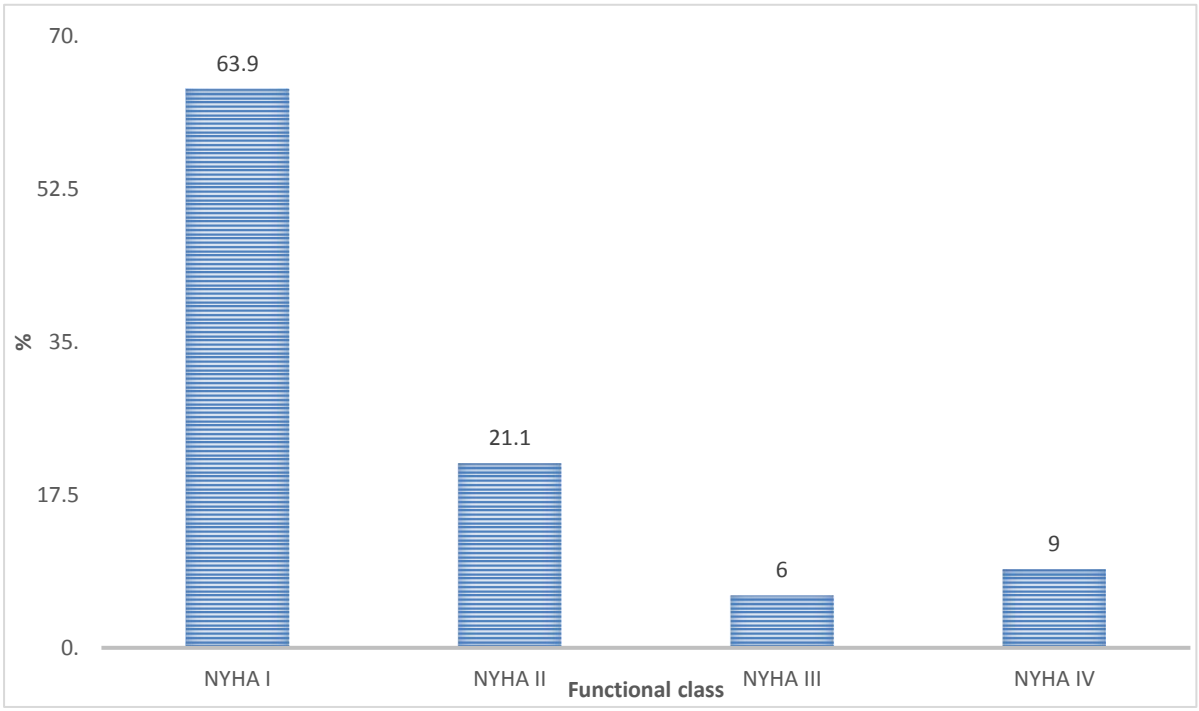

FIGURE 3.8 NYHA class distribution

PERINATAL OUTCOME

TABLE 3.3 Perinatal outcome

OUTCOME VARIABLES	N=145 (%)
Live births	137 (93.8)
Stillbirths	7 (4)
Multiple delivery	3 (2.1)
Medical TOP	1 (0.7)
NICU	21 (15.3)
Preterm (<37weeks)	39 (27.3)
Low birth weight (<2500g)	46 (32)
Congenital abnormalities	6 (4.1)

Of the 145 deliveries, 137 (93.8%) were live births, 4% were stillbirths and there was one termination of pregnancy for maternal cardiac reasons. The stillbirth rate was 51/1 000 and 48/1 000 PNMR. Of the live births, 15.3% of the babies were admitted to the neonatal Intensive care unit. There were 27.3% babies born preterm. The mean fetal weight was 2598.2g and 33.9% had low birth weight. See figure 3.9 below. Congenital anomalies were reported in six (4.1%) cases, with one third of these (two) being cardiac.

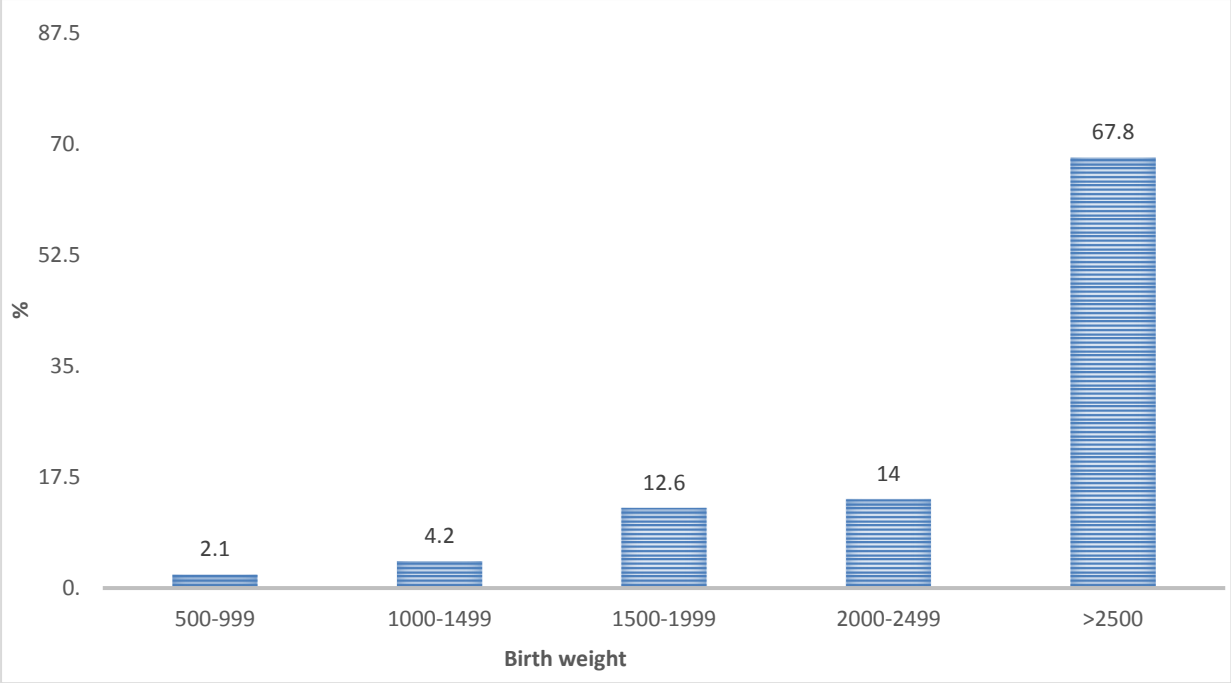

FIGURE 3.9 Neonatal weight distribution

Addendum to Figure 3.9 Neonatal weight distribution

Mean	2598.2g
Median	2770g
IQR	2240-3020g
Min/Max	800/3947

MATERNAL OUTCOME

Only one patient was admitted postpartum and demised 11 days later. There were no postpartum follow-up data of the study population. Sixty-one (61) patients had adverse events, including two maternal deaths. The morbidity rate was 37.1%, with cardiac failure and pulmonary oedema contributing in the majority of cases (27.9% each). See summary of adverse events and ICU admissions in figures 3.10 and 3.11 below. Cardiac failure was also the reason in 43.8% of the ICU admissions. Cardiac arrhythmias complicated 9.8% of patients, and were the reason for 12.5% of the ICU admissions. PPH and pulmonary hypertension each complicated 4.9% of the cases. Pulmonary embolism was diagnosed in 3.3% of the study cohort. ICU admission was indicated in 16 (11%) cases.

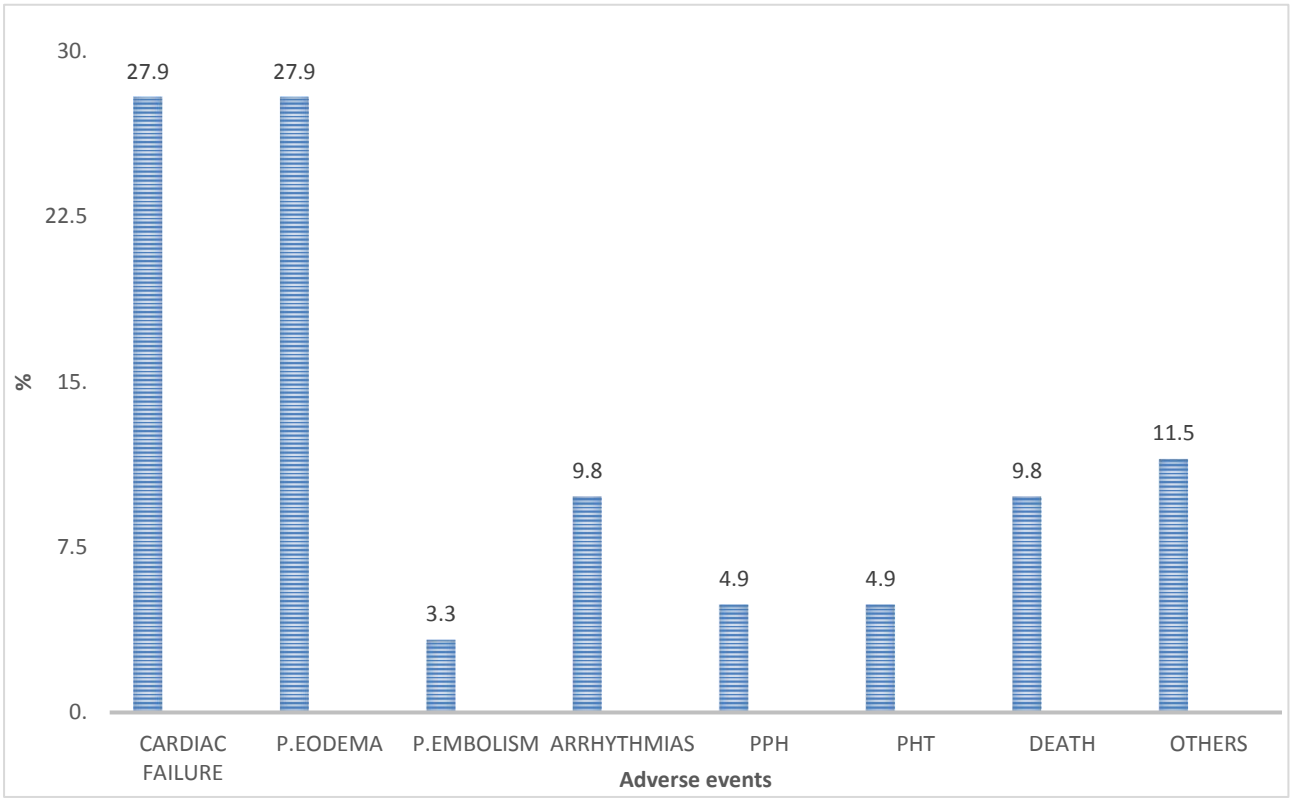

FIGURE 3.10 Maternal adverse events distribution

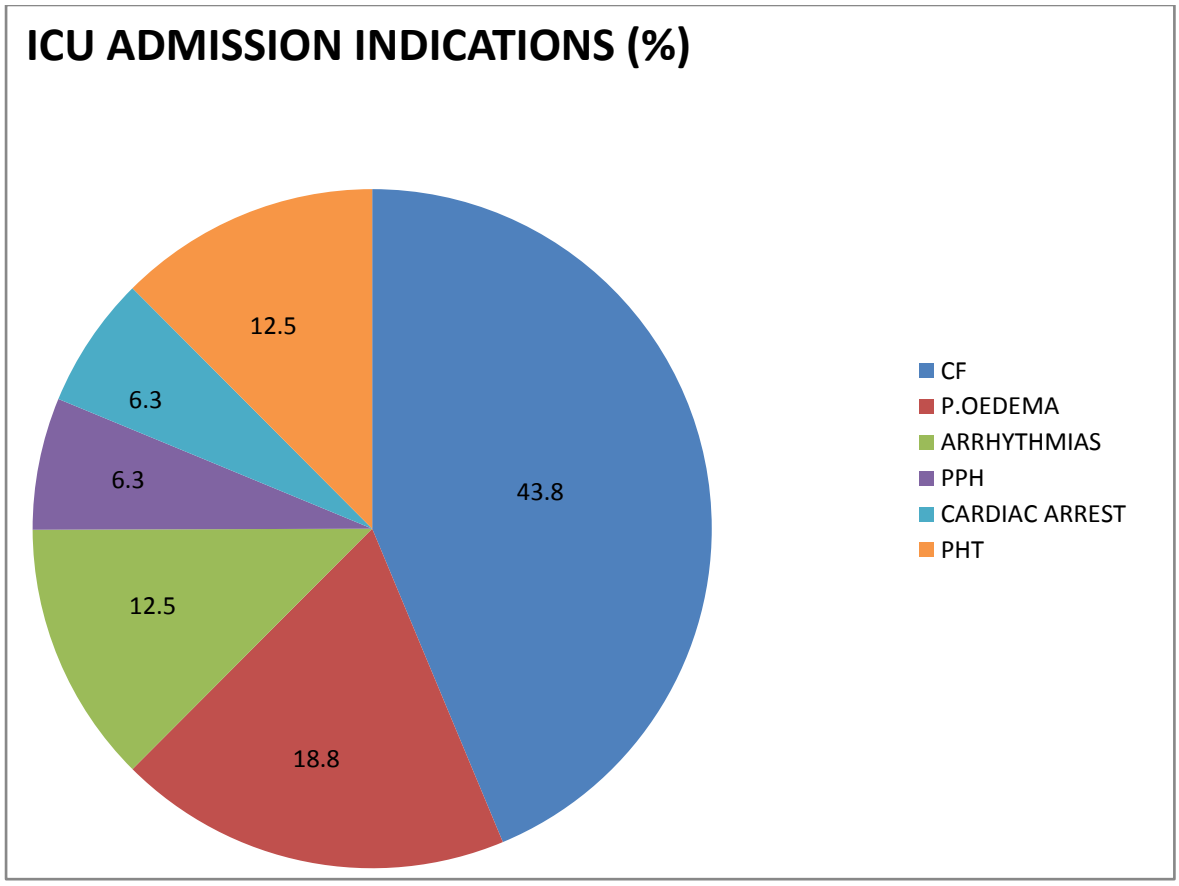

FIGURE 3.11 ICU admission indications

MATERNAL MORTALITY

There were six maternal deaths, which is a case fatality rate of 3.15%. Maternal mortality rate due to cardiac disease was 190/10 0000 for the entire study period, which translates to 36/10 0000 annually. Five maternal deaths were diagnosed with PPCM, and CFR due to PPCM at 17.9%. One of these presented postpartum and the rest in the third trimester. One patient died of mechanical valve thrombosis complications in the first trimester. Cardiac failure was the major complication in maternal deaths occurring in four patients (66.7%). See Table 4 below. All deaths were functional NYHA class IV.

TABLE 3.4: Maternal deaths profile.

PROFILE	N(6)
TIMING OF DEATH Antenatal 2nd trimester 3rd trimester Postnatal	 4 1 1
PATHOLOGY PPCM Prosthetic heart valve	 5 1
NEONATAL OUTCOME Alive SB Undelivered	 2 2 2
CONTRIBUTING CAUSES Pulmonary oedema Valve thrombosis Cardiac failure	 1 1 4
FUNCTIONAL CLASS NYHA I-II NYHA III-IV	 0 6

CHAPTER 4

4.1 DISCUSSION

PREVALENCE

This study provides a recent assessment of maternal and perinatal outcomes of women with cardiac disease, in addition to profiling their characteristics in the Free State. The prevalence of cardiac disease in pregnancy in UAH during the six-year study period is 4.7%. This is slightly higher than the 0.9 - 3.7% reported worldwide[33]. Similar prevalence rates were reported in India[40]. A prevalence of 4.7% represents a significant increase in the province from the numbers previously reported by Schoon et al[42] in 1997 and Schoon[43] in 2000 of 0.6% and 0.12% respectively. This notable difference could be due to the nature of the data, and the utilisation of different study methodologies. This study represents an institutional prevalence that has a referral bias, while Schoon's 2000 study probably represents a truer picture of population-based prevalence. This increase could however also point to a true increase in congenital heart lesions, without a significant fall in rheumatic heart disease and cardiomyopathy over the same period in the province. A systematic review of similar studies done in South Africa reported a prevalence of between 123 and 943/10 0000 (0.12% - 0.94%)[33]. Other recent African studies show an increase of close to 2%[41].

MATERNAL AGE

The average age of the study population was 27 years. This was similar to that of earlier studies by Schoon[41], Soma-Pillay et al[13] in Pretoria, and Sliwa et al[45] in Cape Town. The average age in this study is lower than seen in similar studies in Canada[29], the Netherlands[32], and France[38]. Poor socio-economic status, poor education and a lack of reproductive health services in low resource countries could explain the low maternal age at conception compared to that in high-income countries. This can also be seen in the number of women with advanced maternal age. In this study, 18% of the women were older than 35 years, with the eldest parturient being 43 years old. The youngest parturient was 16 years old. Similar results were reported in Pretoria by Soma-Pillay et al[13] and Gavi et al[46].

In lieu of the results from this study and others in the country, a shift of focus is required to upscale reproductive health services with an emphasis on family planning, as extremes of ages are associated with adverse pregnancy outcomes.

GRAVIDITY AND PARITY

Primiparity remains controversial as a risk factor of PPCM, and data relating to parity and heart disease has been inconsistently reported. This will become important to find out as we continue to report increasing numbers of PPCM-related mortality and

morbidity. The 2014-2016 Saving Mothers report stated The majority of the study cohort were multigravidas (68.9%) ranging from gravida 2 to 7, highlighting possible low contraception uptake. Similar results were reported in South Africa by Schoon et al[42], Soma-Pillay et al[13]and Gavi et al[46]. European and American studies show a contrasting picture with primigravidas accounting for more than 50% of pregnant women with cardiac disease[35,32,38].

RACIAL DISTRIBUTION

In this study, the majority of the population was of Black descent (89.7%). Caucasians and coloureds made up 4.1% and 5.5% of the population respectively. Low socio-economic status, evident from the high unemployment rate (79.3%) and increased risk of cardiomyopathy in blacks, could explain this distribution pattern. This pattern was also reported in studies done in the Free State[42,43]. Sliwa et al[45] further reported the high rate of cardiac disease in black Africans.

ANTENATAL CARE

The majority of women in this study (71.6%) presented for antenatal care for the first time in the second trimester, with an average booking gestation at 19.8 weeks. This seems to be a common pattern found across similar studies in South Africa. Mazibuko et al[47] reported that 61% of patients with a prosthetic valve only presented in the second trimester. In Natal, Nqayana and colleagues[44] reported that 61.6% of women were seen for the first time in the third trimester. Sliwa et al[45] reported fewer patients seen in the second trimester compared to other South African studies, but still reported a figure of 45%. Studies in high income countries show mixed results with 35% seen for the first time after 20 weeks in the CARPREG II study[29].

Late booking is associated with adverse maternal and perinatal outcomes[45]. Cardiac patients are normally on teratogenic medication, among others warfarin, ACE inhibitors and statins, so early presentation provides an opportunity to change to less teratogenic medication. Early presentation also provides a chance to optimise patients in terms of risk stratification and appropriate individualised care with counselling regarding pregnancy outcomes. Referral to other multidisciplinary teams is essential early in pregnancy. It is clear that planning for pregnancy in these patients is a priority. This can be achieved by community and health care worker education, in setting up combined multidisciplinary clinics for pre-conception counselling and family planning. Sliwa et al[45] and Lay Kok et al[39]attribute good maternal and perinatal outcomes to joint services providing multidisciplinary maternity care.

OBSTETRIC AND PERINATAL OUTCOMES

The obstetric outcome for the cohort studied was not good. There were seven stillbirths and no neonatal deaths, which translates to 48/1 000 PNMR. This is

worryingly above the provincial average of 28.54/1 000[48]. Although high perinatal mortality rates were reported, a significant decline was seen compared to earlier studies by Schoon[43]. A systematic review of similar studies in South Africa reported a PNMR of 89-238/1 000[33]. Saima et al[40] as well as Beaton et al[41] reported similar results (167/1 000 and 116/1 000 respectively) to South African studies, but higher figures than that presented in the study cohort. Early neonatal death data needed to calculate the overall PNMR was not available in this study. This might be the reason why we reported significantly lower PNMR than other South African studies. Very low perinatal mortality rates (7/1 000), comparable to high-resourced countries, were however reported in the Western Cape by Sliwa and colleagues[45]. This could be credited to intensive provincial neonatal surveillance.

The average gestational age at delivery was 36.7 weeks, with 27.3% babies delivered before 37 weeks. The average birth weight was 2598.2g, with a low birth weight rate of 32%. This represents trends similar to other studies done in Africa. This study reported a rate of 15.3% for neonatal intensive care unit admissions. Six congenital anomalies were reported, of which one third had congenital cardiac anomalies. One stillbirth due to congenital anomalies was reported. A percentage of 42% fetal congenital anomalies were reported in mothers who were exposed to warfarin in the first trimester. The patient files contained scant descriptions of such abnormalities, so it was difficult to ascertain warfarin embryopathy. Warfarin embryopathy and stillbirth rates have been reported to be dose dependent with adverse events increasing in women who require higher doses than 5mg daily[47]. Mazibuko and colleagues[47] reported a slightly higher rate of congenital anomalies (66%) due to warfarin. Warfarin usage in the first trimester is associated with high rates of congenital malformation and fetal loss[47]. Data from ROPAC also reported fewer live births among women using warfarin in the first trimester[49].

The caesarean section rate was 67.6%, which is significantly higher than the national and provincial rates of 25.7% and 25.3% respectively[2]. The majority of caesarean sections were because of obstetric indications. Maternal indications were around 25%, similar to obstetric indications. Nqayana et al[44], Mazibuko et al[47] and Schoon et al[42] reported higher than 40% caesarean section rates. Poor antenatal care, late booking and the lack of a combined obstetric and cardiology clinic for maternal optimisation could explain the high caesarean section rate in this study. This idea is supported by the lower than 40% caesarean section rates in Pretoria and other areas where multidisciplinary clinics have been incorporated into the total care of pregnant women with cardiac disease[32,38].

More recent studies have reported excellent outcomes with vaginal delivery, assisted, induced or not induced, in many cases with cardiac lesions, thereby challenging the predominant dogmatic point of view surrounding caesarean sections[38]. Caesarean

section has been shown to increase morbidity and mortality compared to vaginal delivery[2], so vaginal deliveries with epidural, especially in low-resource settings, should be encouraged. In this study, 34% of the cohort had epidural analgesia. The low uptake could be due to a shortage of skilled human resources. The rate of assisted vaginal delivery (31.9%), which is similar or higher compared to centres conducting more vaginal deliveries locally and abroad[30,32,38], is however encouraging.

PATHOLOGY

The majority of the study cohort had acquired valvular lesions (48.6%), which could be attributed to rheumatic heart disease in this specific setting. This represented a significant decline from 77.4%, reported by Schoon[42] in 1997. This decline could be due to a proportional increase in other cardiac pathologies, especially congenital heart disease, from 1.225% to 24.3%. RHD is a physical manifestation of poverty and social inequality, so that explains similar trends of high prevalence in low and medium income countries. A South African systematic review reported a prevalence of up to 84%[33]. Similar studies from LMIC in India and Uganda show similar patterns of 56.6% and 87.9% respectively[40,41].

The increasing trend of congenital heart disease is visible globally, with a reported 5% growth rate annually in the USA since 2005[30]. Improved survival rates up to reproductive age is due to improved neonatal surgical interventions and medical treatments.

Cardiomyopathy remained the same at 18%, similar to the reported prevalence by Schoon et al[42] in 1997. In 2000 Schoon[43] reported 55% of cases with PPCM. The difference could be due to a difference in methodology that was utilised in this study. The study cohort proportion of cardiomyopathy in this study (18%) is higher than the reported South Africa rate of 1: 1000. Consistent with reported risk factors, all patients with cardiomyopathy were black, 44% were older than 30, one third had chronic hypertension and 36.8% had anaemia. The reported prevalence in this study could still be an underestimation as patient post-partum data was lacking in many cases. Sliwa et al[45] reported case identification beyond six weeks and up to one-year post delivery. They reported that eight out of nine deaths due to PPCM in their study were beyond 42 days postpartum. The UK and Ireland Confidential Enquiry into Maternal Deaths and Morbidity reported that 12% of patients died between six months and one year after the end of pregnancy[37]. There is a case to be made from the evidence about following up patients beyond six weeks to find the true extend of the disease.

In the case of this study, 17.6% of the study cohort had metallic prosthetic valves and were on warfarin (dose range 5mg - 7.5mg daily). The predominant valvular lesion was mitral regurgitation (35.7%). Schoon[43] reported similar trends but with mitral stenosis being the predominant lesion. Different valvular diseases appear across similar studies

in South Africa with no particular pattern. This trend is also observed in American, European, Asian and Indian cohorts[32,35,38,39,40].

MATERNAL OUTCOME

Cardiac disease in pregnancy is associated with maternal and perinatal morbidity. This is seen globally with heart failure and pulmonary oedema as the leading adverse cardiac events, and valve thrombosis in women with prosthetic valves. This study recorded a morbidity rate of 37.1%, which is lower than in studies by Gavi et al[46] and Beaton et al[41], which are 62% and 51.8% respectively. It is also significantly lower than that reported by Schoon[43] in earlier studies (75.6%). Lower complication rates have been reported in Canadian and European cohorts, of 16% and 11% respectively[29,38]. Soma Pillay[13] reported similar lower results of 11.6%. Cardiac failure complicated 27% of cases in this study, and 37% of these patients had anaemia which could be one of the contributing factors. Other factors could be late booking and the poor to non-attendance of cardiac clinics by patients with known cardiac disease prior to becoming pregnant. Sixty-three percent (63%) of women did not attend cardiac clinic prior to falling pregnant. Thrombosis complicating prosthetic valves were seen in 3.8% of the cases, and caused one death. Nqayana et al[44] and the ROPAC study[49] reported similar trends of 3.2% and 4.7% respectively. Reasons for these differences in the reported morbidity compared to developed countries could be due to extensive surveillance and the establishment of multidisciplinary clinics focusing on optimum care for these high-risk cardiac patients.

This study population with NYHA class III and IV (15%) were associated with severe morbidity. All six maternal deaths were functional class III/IV. In this study 47% of NYHA III/IV presented with cardiac failure, while the others had pulmonary oedema and pulmonary hypertension. Poor perinatal and maternal outcomes were also reported in studies by Hink et al[32]and Sliwa et al[45].

MORTALITY

This study reported six maternal deaths. A case fatality rate of 4.1% was reported. This was a sharp decrease from 9.1% and 9.8% as reported by Schoon[42,43] in 1997 and 2000 respectively. Other than a different study methodology, an increase in awareness of cardiac disease by health care workers with all patients seen at UAH for their entire pregnancy could have contributed to this decline. The maternal mortality rate in this study is comparable to South African institutions with established multi-disciplinary clinics. Soma-Pillay[13] and Sliwa et al[45] reported 3.27% and 5.92% case fatality rates respectively. Studies in other LMIC showed similar results, such as 4.4% in India. CFR in developed countries are lower as reported by Hink et al[32] and Lima et al[35] at 1.6% and 0.7% respectively.

Five (5) out of the six maternal deaths had PPCM (88.3%), CFR of 17.9%. Cardiac failure, pulmonary oedema and valve thrombosis were contributing factors with 66%,

and 16% each respectively. Sliwa reported similar results, with PPCM being a major cause of maternal mortality (77.8%), followed by thrombosis of prosthetic valves (22.2%). Salam[40] in India reported cardiac failure and pulmonary oedema as the major contributors to maternal death. There was one death reported in the second trimester and four in the third trimester. Only one postpartum death was reported in this study at 11 days postpartum compared to eight days in the Western Cape[45] (88.9%). A large number of deaths due to cardiomyopathy occur in the postpartum period[23,45,50]. This study did not have access to postpartum data, could have led to an underestimation of maternal deaths due to PPCM.

4.2 LIMITATIONS

1. Due to the retrospective nature of this study, it had a missing file bias

2. UAH is a tertiary Hospital with referrals from five district hospitals, the Northern Cape Province and Lesotho, so there was a risk of referral bias.

3. Postnatal follow-up data was missing, so morbidities and/or deaths that occurred beyond hospital discharge would have been missed.

4. No other neonatal data beyond delivery notes was available for analysis, so neonatal deaths occurring in NICU or the neonatal /baby room was missing.

CHAPTER 5

5.1 CONCLUSION

Disease patterns at UAH continue to be different from those in developed countries, but displays a significant increase in congenital heart diseases. Maternal and perinatal mortality remain unacceptably high despite raised national and global concerns. Mortality due to cardiomyopathy is increasing at an alarming rate. Health care workers caring for these patients in regional hospitals must be conscious to facilitate appropriate referral of these patients. HIV prevalence among the study population is high, although the impact on cardiac disease is not as clear as initially believed. Despite this, almost all of the study cohort were on treatment. Access to sexual and reproductive health services should be a national priority, as this could go a long way in reducing the numbers of unplanned pregnancies as reflected by late antenatal booking in this study. Multidisciplinary cardiac–obstetric clinics seem to be the answer to improving outcomes for pregnant women with cardiac disease. Tertiary health care centres should be active in setting up these clinics.

5.2 RECOMMENDATIONS

1. Upscaling sexual and reproductive health services, especially among patients with cardiac disease
2. Establishment of joint obstetric-cardiology clinics.
3. Upskilling physicians in contraception proficiency regarding patients with cardiac disease.
4. In line with the WHO 2025 action plan of reducing non-communicable diseases, RHD prevention and active disease surveillance should be prioritised in lieu of its public health impact.

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APPENDIX A

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

21-Jun-2018

Dear **Dr Calvin Makgato**

Ethics Clearance: **Profile of cardiac patients who delivered at Universitas Academic Hospital (UAH) in Bloemfontein: 2012-2017**

Principal Investigator: **Dr Calvin Makgato**

Department: **Obstetrics and Gynaecology (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/0042/3107**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

APPENDIX B

health
Department of Health
FREE STATE PROVINCE

25 May 2018

Dr C Makgato
Dept. of Obstetrics and Gynaecology
UFS

Dear Dr C Makgato

Subject: Profile of cardiac patients who delivered at Universitas Academic Hospital (UAH) in Bloemfontein: 2012-2017.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** lithekom@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 6/6/18

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

APPENDIX C

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

12 January 2018

For attention: Health Sciences Research Ethics Committee, UFS

Title of project:

PROFILE OF CARDIAC PATIENTS WHO DELIVERED AT UNIVERSITAS ACADEMIC HOSPITAL (UAH) IN BLOEMFONTEIN SOUTH AFRICA: 2012-2017

Researcher:

Dr CM Makgato, Dept of Obstetrics and Gynecology

I hereby confirm that I provided inputs on the protocol and approve the study design, sampling, measurement and measuring instruments, as well as statistical analysis.

Yours faithfully

G Joubert

Departement Biostatistiek
Department of Biostatistics
T: +27(0)51 401 3114/5/6/7, F: +27(0)51 401 3641
205 Nelson Mandela Drive/Rylaan, Park West/Parkwes, Bloemfontein 9301, South Africa/Suid-Afrika
P.O. Box/Posbus 339 (G31), Bloemfontein 9300, South Africa/Suid-Afrika, www.ufs.ac.za

APPENDIX D

Dr C. M Makgato

Registrar

Dept. of Obstetrics and Gynaecology

UFS

To: HOD Dept of Obstetrics and Gynaecology

Universitas Academic Hospital

Bloemfontein

Re: **Request for permission to conduct research study at the Universitas Academic Hospital.**

Dear Sir/Madam

I hereby request permission to conduct a research project at Universitas Academic Hospital for the purposes of my MMed Degree in Obstetrics and Gynaecology.

The research project is titled: Profile of cardiac patients who delivered at Universitas Hospital (UAH) in Bloemfontein South Africa: 2012-2017.

The aims of the study are to determine profile of cardiac patients who delivered at the institution together with maternal and neonatal outcomes between 2012 and 2017. It is a retrospective descriptive study looking at Maternity case Records and Meditech summaries for patients seen at cardiology department.

The study protocol will be sent to Faculty of Health Science' Ethics Committee for approval prior to commencement of data collection.

Thank you in advance

Dr C.M Makgato

Registrar: OBS & GYNAE

Date 16/04/18

HOD Obstetrics and Gynaecology, UFS

Permission granted/not granted

Date 16/04/2018

DATA EXTRACTION SHEET. **FILE NO:** ☐

1. **DEMOGRAPHICS**

Age _____

Weight _____ BMI _____ MUAC_____

Race: Black ☐ Indian ☐ Caucasian ☐ coloured ☐

Employment status YES ☐ NO ☐

Marital status YES ☐ NO ☐

If no

- divorced ☐
- widowed ☐
- single ☐
- stable partner ☐

Social habits:

- Smoking YES ☐ NO ☐ if NO previously YES ☐ NEVER ☐
- Alcohol YES ☐ NO ☐ if NO previously YES ☐ NEVER ☐
- Substance abuse YES ☐ NO ☐ if no previously YES ☐ NEVER ☐

2. OBSTETRIC HISTORY

- Gravidity ☐
- Parity ☐
- Misc ☐
- Ectopic ☐
- TOPs ☐ IF ANY medical indications YES ☐ NO ☐ if yes list _____

  _____

  _____

  _____

3. BOOKING STATUS

- Gestation at booking _____
- HIV status: reactive ☐ non reactive ☐ unknown ☐

If reactive ARVs YES ☐ NO ☐ CD4: ☐

If YES DURATION YEARS ☐ MONTHS ☐

- Blood pressure at booking _____
- Heart rate at booking _____
- Haemoglobin _____
- RPR +VE ☐ -VE ☐
- RH +VE ☐ -VE ☐ If –VE Rhogam given YES ☐ NO ☐

4. ANTENATAL

- Antenatal care giver: Specialist ☐ Registrar ☐ M.O ☐ Midwife ☐
- Admissions YES ☐ NO ☐ If yes cardiac ☐ non cardiac ☐
  longest admission duration DAYS ☐

5. DELIVERY

- Gestation @ delivery _____
- NO. Of deliveries: single ☐ multiple ☐
- Mode of delivery: NVD ☐ c/section ☐ if NVD spontaneous ☐
  Induction ☐ Assisted delivery ☐

If C/section: emergency ☐ elective ☐

Indication(s) _____

ANASTHESIA: Epidural ☐ Spinal ☐ GA ☐

6. MATERNAL OUTCOME

- ICU admission YES ☐ NO ☐ if yes indication(s) _____
- Days in hospital _____
- Complication YES ☐ NO ☐ if yes list _____
  ☐ ☐

- Intervention YES NO if yes list _____

7. NEONATAL OUTCOME

- Preterm YES ☐ NO ☐
- ICU ADMISSION YES NO if yes indication(s)
- Weight _____
- Alive YES ☐ NO ☐

If no STILLBIRTH ☐ END ☐ If stillbirth FSB ☐ MSB ☐

- Congenital abnormalities YES ☐ NO ☐ If yes list _____

8. GYNAECOLOGICAL HISTORY

- Contraception counselling YES ☐ NO ☐ If yes pre- conception ☐ antenatal ☐ postpartum ☐
- Ever on contraception YES ☐ NO ☐

If yes method COC ☐ POP ☐ IMPLANON ☐ INJECTABLES ☐ IUCD ☐

9. MEDICAL HISTORY

HT ☐ DM ☐ EPILEPSY ☐ ASTHMA ☐ TB ☐

10. CARDIAC CONDITION PRE PREGNANCY

- Congenital heart disease YES ☐ NO ☐ If yes repaired ☐ not repaired ☐
- Prosthetic heart valves ☐
- Pulmonary Hypertension ☐
- Rheumatic heart disease ☐
- Infective Endocarditis ☐
- Myocardial Infarct ☐
- Peripartum cardiomyopathy ☐
- Other _____

11. Diagnosed in current pregnancy YES ☐ NO ☐ if yes diagnosis

12. NYHA FUNCTIONAL CLASSIFICATION

- Class I ☐
- Class II ☐
- Class III ☐
- Class IV ☐

13. Attending cardiac clinic YES ☐ NO ☐ if yes for how long _____

- ECHO done YES ☐ NO ☐ if yes normal ☐ abnormal ☐
  ejection fraction _____

  If abnormal elaborate _____
- ECG done YES ☐ NO ☐ if yes normal ☐ abnormal ☐

  If abnormal elaborate _____

14. MEDICATION(S) LIST _____

_____

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APPENDIX F

MMed Research Protocol

Title: PROFILE OF CARDIAC PATIENTS WHO DELIVERED AT UNIVERSITAS ACADEMIC HOSPITAL (UAH) IN BLOEMFONTEIN SOUTH AFRICA: 2012-2017

Supervisor(s): Dr S.M BALOYI, DR T. NONDABULA

Dr C.M Makgato

Registrar Dept. of Obstetrics and Gynaecology

University of the Free State

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1. INTRODUCTION

1.1 GENERAL LITERATURE

PREGNANCY AND CARDIAC DISEASE

The numbers of women with heart diseases who die as a result of pregnancy continue to rise globally, despite coordination of specialists' services and international guidelines[1]. Both congenital and acquired cardiac disease may present for the first time in pregnancy and postpartum for example peri-partum cardiomyopathy (PPCM).

CARDIOVASCULAR PHYSIOLOGY

Knowledge of normal cardiovascular adaptations in pregnancy is important in understanding how they affect natural course of cardiac disease and their management during this state[2]. Findings which might reflect a diseased state in a non pregnant patient may represent a normal adaptation in pregnancy and conversely failure of these adaptations may represent pathology[3].

Among the earliest changes is increase in maternal heart rate which occurs from 4 weeks gestation rising to 20% above pre pregnancy values by late pregnancy. Blood volume increases from 6 weeks gestation and reaches 45-50% above pre pregnancy value by early third trimester, a period of high risk for cardiac decompensation. Disproportionate increase between plasma and red cell mass leads to physiological anaemia[2].

Overall cardiac output increases by 30-50% due to increase in stroke volume and heart rate. The peri-partum period represents another high risk period in patients with cardiac disease. Dynamic changes occur in labour with each contraction contributing to auto-transfusion of about 300-500 of blood back to systemic circulation. Blood pressure and heart rate increase due to sympathetic response to pain and this increase cardiac output by up to 34% during contraction and by 12% between contractions[3].

Re-distribution of blood volume and relief of venocaval compression following delivery result in up to 60-80% increase in cardiac output, followed by rapid decline to pre-labour value by one hour after delivery. These women are thus at high risk of pulmonary oedema during second stage of labour and immediate postpartum period. Cardiac output returns to pre-pregnancy values in two weeks postpartum[3].

RISK ASSESSMENT AND MANAGEMENT OF CARDIAC DISEASE IN PREGNANCY.

Pregnancy increases the risk of mortality and morbidity in women with heart disease, but data on the magnitude of the risks are limited[4].The risk of both the mother and the fetus increases exponentially with the extent and complexity of the underlying disease[5]. It is vital to conduct a systematic, accurate and realistic risk assessment for potential maternal and

fetal adverse events both during pregnancy and postpartum as this will impact on the success and safety of the index pregnancy[5]. Risk stratification helps with counselling in pre conception clinics.

Current risk stratification models described in literature are Cardiac Disease in Pregnancy score (CAPREG score), ZAHARA risk score exclusively for mothers with congenital heart disease (CHD) and the modified WHO classification based on expect consensus[4].

Once diagnosis has been made and cardiac function assessed the effect of pregnancy on the disease and vice versa must be evaluated and documented[5]. Further arrangement in terms of referral antenatal care delivery and postpartum care should be made and discussed with the woman. The best time to discuss and implement management strategy would be before conception as this will allow for a baseline evaluation of cardiac function and provide an opportunity for individualised counselling to take place[5].

Elliott et_al[6] have developed a referral algorithm in Groote Schuur hospital based on the risk scores. It provides guideline to help in the right referral of pregnant patient to a multidisciplinary combined cardiology and obstetric clinic. Tertiary hospitals such as Steve Biko academic and Groote Schuur hospital currently provide biweekly cardiac obstetrics clinics[6,13].

PREGNANCY OUTCOMES IN WOMEN WITH CARDIAC DISEASE

Globally complications of heart disease during pregnancy account for a significant portion of maternal morbidity and mortality[7,8]. Heart disease is the leading cause of death among pregnant women in the United States of America[9].

There has been a 24.7% steady increase in women with heart disease presenting for delivery in USA over the years 2003 to 2012. There was almost 50% increase in pregnancies among congenital heart disease women. Other than the latter being due to improved survival of women with congenital heart disease, lack of pregnancy risk stratification, lack of knowledge by patients and health care providers and poor transition of care between paediatric to adult health care providers seem to contribute to growing trend of pregnant women with cardiac disease[10]. During the same period proportion of pregnant women with cardiac disease was 0.2%, of this congenital heart disease(CHD) formed a larger proportion (41.8%), followed by valvular heart disease (30.9%). 20.8% was due to cardiomyopathy and pulmonary hypertension contributed only 6.5%. Major cardiac adverse effects were among women with cardiomyopathy and lowest among CHD. Pulmonary hypertension had the most in-hospital deaths followed by cardiomyopathy[10].

Women with cardiomyopathy were most affected by cardiovascular adverse events and poor perinatal outcomes[10]. Hink et_al[7] in a recent European study found that even though the prevalence of heart disease in pregnancy is low, it was the most important cause of

indirect maternal mortality in the Netherlands. In 2003-2005 the indirect maternal mortality due to cardiac disease was 9.2 %(1.6/100000 pregnancies) and this was a significant rise compared to earlier studies[7]. This was also consistent with United Kingdom's confidential enquiries into maternal and child health (CEMACH). The Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries MBRRACE-UK report of 2015 recorded 33.79% of indirect death as due to cardiac disease in 2011-2013[1]. NORMANDY study by Vincent et_al concluded that the various cardiopathies were associated with increased maternal, obstetric and foetal complication compared to healthy pregnancy population in France consistent with global trends[11].

1.2 SOUTH AFRICAN LITERATURE

Medical disorders in pregnancy are one of the top 5 causes of maternal mortality in South Africa. Cardiac disease is the main contributor in this group[5].

Acquired heart disease such as Rheumatic Heart Disease and cardiomyopathies contribute more to maternal morbidity in South Africa and other developing countries, where as surgically corrected congenital heart disease contributes greater portion of maternal death due to cardiac disease. According to Saving Mothers Report 2015, for a period of 5years 2010-2015 maternal deaths due to medical and surgical condition declined significantly overall, 17.66% -13.44% with the biggest drop between 2014 and 2015, but cardiac disease category remained the same[12]. An audit of maternal death by Soma-Pillay et_al[13] found that 33.7% of mothers delivered vaginally, 26% by caesarean section while 39.8% were undelivered. There was perinatal morbidity reported in the same study with 71.8% of babies born preterm with average gestation of 32 weeks at delivery. Average birth weight of babies born alive was 2558g. 64% of babies were low birth weight (<2.5kg)[13].

In 2015, 44% of maternal deaths due to medical and surgical condition were due to cardiac disease which is an increase from 34% in 2011-2013. These figures are higher than in developed countries but similar trends in increments[12].

In 2012 Watkins et_al[8] accounted 41% of indirect causes of maternal death in South Africa and among them 77% attended antenatal care. Cardiac disease of poverty rheumatic heart disease made a huge proportion of cardiac disease in pregnancy, consistent with studies showing a high burden of RHD in poorer countries[8]. Demographic data in a study by SOMA-Pillay showed high proportion of cardiac disease burden among African women, 88% of the study population[13]. There is consistency in this observation from other local studies[14].

Schoon et _al[14] did a study at Pelonomi hospital from 1990-1995 and found prevalence of pregnancies complicated by cardiac disease to be 0.6%. Maternal mortality rate due to

cardiac conditions from Bloemfontein district was 3.7% compared to 11% from referring district combined. Rheumatic heart disease accounted for most cases[14]. In a 2012 South African systematic review, Free State province was found to have highest case fatality rate compared to all provinces. Late booking and a lack of insight of the implications of pregnancy complicated by cardiac disease was noted as a major contributor to morbidity and mortality. Caesarean section rate among pregnant cardiac patients was higher that the institution average of 17.2%. Mothers had an average hospital stay of 12 days in obstetrics high care. Women with poor cardiac outcomes also had the highest perinatal mortality rate of 19.3%[15].

1.3 STUDY AIM

- To determine the profile of cardiac patients who delivered at UAH, 2012-2017
- To determine the maternal and neonatal outcomes of cardiac patients who delivered at UAH, 2012-2017.

1.4 STUDY MOTIVATION

- To fill the gap in local literature
- Help to look for interventions to reduce mortality and morbidity by analysing patients' profiles to identify modifiable factors.

2. RESEARCH METHODOLOGY

2.1 Study Design

Descriptive retrospective study

2.2 Study population

Women with cardiac disease who delivered at UAH between 2012 and 2017 will all be included in the study. There are approximately 300 deliveries at UAH yearly. Cardiac patients make less than 10% of this population.

2.3 Data collection and tools

Data collection will be achieved by a standardised abstraction form specifically developed for the study in line with study objectives (appendix 1). Patients will be identified from the delivery records in labour ward by the researcher and information used to look for maternity case record books at the file storage. Data will be collected manually from maternity case record books of all patients with cardiac disease who delivered at UAH

during the study period. Supplementary data will be collected from centralised electronic health records system, Meditech which will include notes from cardiology department for patients who are known to the department.

Different cardiac conditions will be classified according to aetiology and NYHA functional classification[5]. Any complication encountered during pregnancy will be classified into three categories, maternal cardiac, obstetrics or neonatal events.

2.5 Measurement Errors

Errors can occur during transfer of information from clinical patient's record to the data collection sheet by the researcher. This can be mitigated by careful data extraction using a standardised data collection form by the primary researcher.

2.4 Pilot Study

A pilot study of 5-10 cases will be conducted to test adequacy and reliability of data collection tool. It will also identify any problems in finding patients records. The piloted cases will also form part of the study.

3. Data analysis

Data from data collection forms will be transferred to MS excel spread sheet. Descriptive data will be summarised using descriptive statistics, frequency with percentages and 95% confidence interval. Numerical variables will be summarised by means, standard deviations or medians where appropriate. Department of Biostatistics will do the data analysis.

4. Ethical considerations

Permission to conduct the study will be requested from Head of Free State department of health. The research proposal will be submitted to the Health Sciences Research committee of University of the Free State for approval and then Free State Department of Health Ethics committee.

Patients' maternity clinical record books and data collection forms will be kept safe, private and confidential.

Name of patients will not appear in the data collection sheets and clinical record books will be returned to Records in their original form after data collection.

5. Time schedule

The study protocol will be submitted on the 19th January 2018 to the Health Sciences research committee (HSREC) with meeting date on the 30th January 2018. Final approval by the Free State Department of Health ethics committee will be sought by February 2018.

Data collection is expected to start in April through to August 2018. Data analysis will be done between September and October 2018 by department of Biostatistics. Final write up of the study will commence in October to December 2018.

6. Budget

Funds will be required for paper and printing of data collection forms. Cost of paper and printing is estimated to be around R640. (1 packet of A4 paper at R280, printing 360 pages of data collection sheet at R1 per page) The departmental printing facilities will be used and the department will carry the latter expenses. Data collection will be done by the primary researcher. No additional cost for extra personnel will be needed.

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