# Maternal and neonatal outcomes in pregnant women with congenital heart disease in a South African tertiary referral healthcare centre


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## Part B: Publication-ready Manuscript

# List of Abbreviations

## Part A: Study Protocol

| | |
|---|---|
| ASD | Atrial septal defect |
| CHD | Congenital heart disease |
| CRF | Case report form |
| CVD | Cardiovascular disease |
| ECG | Electrocardiogram |
| GSH | Groote Schuur Hospital |
| ID | Identity number |
| IQR | Interquartile range |
| LVEF | Left ventricular ejection fraction |
| NICU | Neonatal Intensive Care Unit |
| NVD | Normal vaginal delivery |
| NYHA | New York Heart Association functional classification of heart failure |
| PDA | Patent ductus arteriosis |
| SD | Standard deviation |
| VSD | Ventricular septal defect |
| WHO | World Health Organisation |

Part B: Publication-ready Manuscript

| | |
|---|---|
| BPM | Beats per minute |
| CARPREG | CARdiac disease in PREGnancy |
| CHD | Congenital Heart Disease |
| CVD | Cardiovascular disease |
| CDM | Cardiac Disease in Maternity Registry |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| GSH | Groote Schuur Hospital |
| HREC | Human Research Ethics Committee |
| ICU | Intensive Care Unit |
| IQR | Interquartile range |
| LMIC | Low- and middle-income country |
| LVEF | Left ventricular ejection fraction |
| mWHO | Modified World Health Organisation risk stratification |
| NICU | Neonatal Intensive Care Unit |
| NYHA | New York Heart Association functional classification of heart failure |
| REDCap | Research Electronic Data Capture |
| ROPAC | Registry Of Pregnancy And Cardiac disease |
| SBP | Systolic blood pressure |
| VSD | Ventricular septal defect |
| ZAHARA | Zwangerschap bij Aangeboren HARtAfwijking |

# PART A: Study Protocol

# Maternal and neonatal outcomes in pregnant women with congenital heart disease in a South African tertiary referral healthcare centre

Protocol

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## Background

Pregnancy causes reversible physiological changes to the cardiovascular system, which include increased blood volume, heart rate and cardiac output.(1,2) These changes are usually well tolerated, but could be detrimental to women with structural heart disease.(3) Cardiac disease remains one of the leading causes for maternal death during pregnancy worldwide.(4,5) Moreover, maternal mortality is 14 times higher in low and middle income countries than in the developed world.(6)

Congenital heart disease (CHD) is a group of conditions that are caused by an embryonic malformation of the heart walls, valves or blood vessels. Although there is little data available for South Africa, there is a rapid documented increase in the prevalence of congenital heart disease worldwide. This increase in prevalence could be explained by the advances made in earlier detection of CHD, as well as better treatment and management thereof, which in turn contributes to longer survival.(7–9) In 2015, it was estimated that the prevalence of the adult population with CHD is 6 in 1 000, while the prevalence in those older than 65 years of age is 4 in 1 000.(7,8)

CHD is a collective term for a heterogenous group of cardiac defects that are present from birth. Because of the increased survival of patients with CHD, more women with CHD reach the reproductive age and choose to become pregnant.(12) Even though CHD is rarely the cause of maternal death, CHD is often associated with maternal complications (such as pre-eclampsia) and/or adverse neonatal outcomes (such as prematurity and admission to neonatal intensive care units), which require careful monitoring and specialised care.(15,16) Furthermore, most people with CHD in low and middle income countries do not have the access to surgery. This means that if and when women with CHD reach reproductive age and fall pregnant, they are at higher risk for maternal and neonatal morbidity and mortality.(17)

Though pregnancy is usually well tolerated in women with CHD, poor outcomes are more prevalent in patients with complex disease,(9) and/or poor systolic function. The level of care required during pregnancy therefore depends on complexity and severity

of CHD. In order to improve the management of pregnant women with CHD, the World Health Organisation (WHO) has developed a stratification tool that informs on the risk and care that these patients require, based on their diagnosis. The Modified WHO classification tool stratifies women in one of five categories, based on their risk for mortality and morbidity.(12) A copy of this tool can be found in Appendix A.

Swan(16) noted that the true outcomes of pregnancy in women with CHD cannot be established yet as there is limited data available for this population group, specifically. She also noted that most research studies have focused on maternal outcomes and few on neonatal outcomes.(16) This holds true especially for the South African context.

## Rationale for doing the study

Data that describe the outcomes of pregnancy in women with CHD are rare(9,16,32) and little is known about this population in South Africa. In order to improve on specialised management for this population, the outcomes during and after pregnancy, for the mother and baby, need to be assessed.

## Research question

What are the maternal and neonatal outcomes during and after pregnancy amongst women with congenital heart disease in Cape Town, South Africa?

## Purpose of the study

### Aim of the study

The primary aim of the study is to describe the maternal and neonatal outcomes during and after pregnancy amongst women with CHD in Cape Town, South Africa.

### Objectives of the study

The objectives will be to stratify the participants in subgroups to further assess the outcomes in each subgroup. The objectives of the study thus are to:

- Describe the overall group's maternal and neonatal outcomes.
- Compare the maternal and neonatal outcomes based on cyanotic CHD versus acyanotic CHD.
- Compare the maternal and neonatal outcomes based on previous surgical repaired versus unrepaired.
- Compare the maternal and neonatal outcomes based on Modified WHO classification.

## Methodology

### Source population

The Cardiac Diseases in Maternity (CDM) registry is compiled from prospectively enrolled patients with previously diagnosed or suspected cardiovascular disease (CVD), that have been referred to a joint cardiac-obstetric clinic at Groote Schuur Hospital (GSH). Patients are referred to this clinic at GSH from all referring hospitals and clinics (primary and secondary maternity facilities) that fall within the GSH catchment area. This registry does not include patients seeking care in private facilities. This parent study is a prospective cohort study and commenced on 1 July 2010 and is ongoing. Ethical approval was granted for this single-centre study and registry by the Ethics Committee of the University of Cape Town (HREC ref: 173/2010).(25)

### Study design

The study design for this study, that will descriptively assess the maternal and neonatal outcomes during and after pregnancy in women with CHD, will be a retrospective cohort study. It is retrospective because only patients that have been enrolled in the registry at the time of study commencement, will be used in the analysis.

## Effect size

The study will be descriptive and will include all patients from the CDM registry that meet the eligibility criteria (described below). Sample size calculations will therefore not be appropriate. However, this cohort will roughly have 50 participants, of which 10 is estimated to have uncorrected CHD. When calculating per bed day costs, a two-tailed Mann-Whitney test with 80% power and 5% level of significance, delivers a large effect size of 1. This adequately detects whether maternal and neonatal length of stay is significantly different in the uncorrected CHD population, as compared to those with corrected CHD. A similar result is seen in cyanotic vs. acyanotic population groups.

## Recruitment, enrolment and follow-up

Due to the complexities in managing women with CVD during pregnancy and due to the considerable risk they pose, GSH hosts the joint cardiac-obstetric clinic. A senior cardiology and obstetric consultant run this clinic. Referral to the joint cardiac-obstetric clinic is done via a referral pathway based on severity of diagnosis and risk stratification. Patients who have been classified as Modified WHO Classification II, II-III or III get referred to the joint clinic. Patients who have been classified as Modified WHO Classification I and have abnormal blood pressure, electrocardiogram or echocardiogram (as diagnosed at a tertiary maternity facility), will also be referred to the joint clinic. The patients are followed up for the duration of their pregnancy, frequency depending on the severity of the disease.(25)

Once a new patient is referred to the clinic, they are also recruited for the CDM registry. After education is given and informed consent is received, they are enrolled into the study and registry. The patients are followed up for the duration of their pregnancy and followed-up at 42 days, six months and one year after delivery. The complete CDM registry will be used to screen for eligibility (described below) in this study.

## Characteristics of the study population

*Number of participants*

The CDM registry has enrolled more or less 200 participants with different CVD at the time of writing this protocol. All of the participants in the registry will be screened for eligibility.

*Inclusion and exclusion criteria*

To be included in the study, participants should be diagnosed with any CHD as the primary diagnosis for enrollment in the CDM registry.

Patients will be excluded from the study if they have been diagnosed with any CVD other than CHD as primary diagnosis for enrollment in the CDM registry.

## Research procedures and data collection methods

The data on the CDM registry includes demographic and socio-economic information, data on comorbidities and obstetric history, routine clinical assessments and special investigations (routine blood tests, electrocardiogram [ECG], echocardiography). Participants are not subjected to any interventional groups.

The parent study's data are captured on an Excel spreadsheet, to which only the CDM investigators have access.

All data for this study will be retrospectively collected from information already captured by the CDM registry. The outcome variables assessed in this study will be date of birth, type of CHD, whether the CHD is cyanotic or acyanotic and previously surgically repaired or not. In order to have a clear understanding of the predictor variables of CHD in pregnancy, they need to be assessed antenatally, perinatally and postnatally. Figure 1 below describes the variables assessed during each phase.

## Table 1: Maternal and neonatal outcomes assessed

| Maternal | | Neonatal |
|---|---|---|
| Antenatal | Perinatal | |
| Need for hospitalisation | Caesarean section | Gestational age at delivery |
| Number of hospital admissions | ICU admission | Preterm delivery |
| Number of days admitted to hospital | Number of days admitted to ICU | Birth weight |
| Hospitalisation > 3 days | Number of days admitted to ward | Admission to NICU |
| Maternal death | Hospitalisation > 4 days | Number of days admitted to NICU |
| | Maternal death | Admission to NICU > 2 days |
| | | Admission to geneward |
| | | Number of days admitted to ward |
| | | Admission to ward > 2 days |
| | | Neonatal death |
| | | Miscarriage |

ICU = Intensive Care Unit ; NICU = Neonatal Intensive Care Unit

The variables that will be assessed in this study were selected, based on knowledge gained from reviewing literature. The justification of the variable selection can be found in a Table in Appendix B.

Data will be collected by reviewing the information available on the registry and where necessary, reviewing hospital folders for missing data. A paper based data collection sheet (case report form, CRF, Appendix C) will be used to record the data for each patient. The primary investigator will perform the data capturing.

Internal validity is ensured by using standardised and objective outcome measures, such as New York Heart Association and Modified WHO Classification tools, and not subjective findings. Furthermore, senior consultants, who are experts in the field, run

the joint cardiac-obstetric clinic. The information that they recorded in the folders is presumably of high validity.

Reliability is improved by using a case report form (Appendix C) that has been developed a priori and will be filled in consistently by using a codebook as reference guide. This codebook, that describes all variables and how they will be measured, can be found in Appendix D.

### Data safety and monitoring

The CDM registry uses participant identity numbers (ID's) to ensure anonymity. During data collection of the nested study, these participant ID's will be used instead of participant names. The data collection sheets will subsequently be recorded on Research Electronic Data Capture (REDCap Version 7.5.2), a secure electronic database hosted by the University of Cape Town. This will further ensure confidentiality and prevent loss of information.

### Data analysis

Anonymised data from REDCap will be exported to R (Version 1.1.463, RStudio, Inc.) for statistical analysis.

Descriptive statistics will be used to summarise data. Continuous variables will be summarised as means with standard deviations (SD) for parametric data or median with interquartile range (IQR) for non-parametric data. Categorical variables will be expressed as frequencies and percentages. Continuous variables will be compared using either the Student's t-test (parametric data) or Wilcoxon rank-sum test (non-parametric data). Categorical variables will be compared with chi-squared or Fisher's exact test. Logistic regression will be done to assess associations between cyanotic or acyanotic CHD and predictor variables, between surgically repaired or unrepaired CHD and predictor variables as well as between Modified WHO classification and predictor variables. All tests will be two-tailed and a p-value of $<0.05$ will be interpreted as statistically significant.

To describe the overall group's maternal and neonatal outcomes, descriptive statistics will be done and reported in a table format.

To assess the association between maternal and neonatal outcomes based on cyanotic CHD versus acyanotic CHD, as well as between maternal and neonatal outcomes based on previous surgically repaired CHD versus unrepaired CHD, multivariate logistic regression will be used. Furthermore, the association between the maternal and neonatal outcomes and Modified WHO classification will be assessed.

## Description of risks and benefits

Because this study is a retrospective study that uses data that have been collected before, there are no further risks or discomfort involved for the participants.

The potential benefits are however that gaining knowledge in the maternal and neonatal outcomes will ultimately improve the management of women with CHD that wish to fall pregnant. There will also be a better understanding of how different subgroups fair in pregnancy.

## Informed consent process

Once a patient is referred to the joint cardiac-obstetric clinic, they are informed about the parent study and registry. A research nurse discusses the process, risks and benefits with the patients and allows them time to consider participation.

Patients are followed up at the joint clinic, regardless of whether they participate in the study or not and can consequently give consent for participation on a subsequent follow-up appointment date. This will allow patients to make an informed, unpressured decision after having discussed it with family, friends and / or advisors. Furthermore,

to avoid undue pressure, participants are allowed to withdraw from the study and registry at any time.

The informed consent form also allows patients to participate in certain aspects of the study but not other if they so wish, e.g. it allows participants to have their blood samples destroyed after initial assessment. The informed consent form for the parent study (approved by the Ethics Committee of the University of Cape Town) can be found in Appendix F.

## Privacy and confidentiality

The data from the CDM registry is stored at the Hatter Institute of Cardiovascular Research for Africa. The data can only be accessed by authorised personnel. If there is missing information that needs to be collected, the primary investigator will access folders that are safely stored in the Cardiac Clinic Research unit.

The Hatter Institute of Cardiovascular Research for Africa will also securely store the paper-based sheets, which will assist in maintaining data confidentiality. The information will be stored for a duration of five years after the completion of the study. Thereafter, it will be destroyed by shredding.

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Appendices

## Appendix A: The Modified WHO Classification tool

Table 2: Risk of mortality and morbidity according to the Modified WHO Classification tool(12)

| | Modified WHO Classification I | Modified WHO Classification II | Modified WHO Classification II - III | Modified WHO Classification III | Modified WHO Classification IV |
|---|---|---|---|---|---|
| *Diagnosis* | • Uncomplicated small or mild pulmonary stenosis, patent ductus arteriosus and mitral valve prolapse<br>• Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) | If otherwise well and uncomplicated:<br>• Unoperated atrial or ventricular septal defect<br>• Repaired tetralogy of Fallot<br>• Most arrhythmias | Depending on individual:<br>• Mild left ventricular impairment<br>• Hypertrophic cardiomyopathy<br>• Native or tissue valve disease not considered WHO 1 or 4<br>• Marfan without aortic dilatation<br>• Repaired coarctation | • Mechanical valve<br>• Systemic right ventricle<br>• Fontan<br>• Unrepaired cyanotic heart disease<br>• Other complex heart disease<br>• Mild aortic dilatation (Marfan syndrome: 40–45mm; bicuspid aortic valve: 45–50mm) | • Pulmonary arterial hypertension of any cause<br>• Severe systemic ventricular dysfunction (EF 45mm; BAV >50mm)<br>• Previous peripartum cardiomyopathy with any residual impairment of left ventricular function<br>• Severe mitral stenosis, severe symptomatic aortic stenosis<br>• Marfan syndrome with aorta dilated >45 mm<br>• Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve<br>• Native severe coarctation |
| *Risk of mortality during pregnancy* | No detectable increased risk of maternal mortality | Small increased risk of maternal mortality | Intermediate increased risk of maternal mortality | Significantly increased risk of maternal mortality | Extremely high risk of maternal mortality |

| | | | | | |
|---|---|---|---|---|---|
| *Risk of morbidity during pregnancy* | No or mild increased risk in morbidity | Moderate increase in morbidity | Moderate to severe increase in morbidity | Severe morbidity | Severe morbidity |

**Abbreviations:** WHO, World Health Organisation

## Appendix B: Justification of variable selection

## Table 3: Justification for variable selection

| Maternal baseline information | |
|---|---|
| Variable | Justification for inclusion in study |
| Date of birth | Date of birth is used to calculate maternal age at times of incidences. Maternal age is often assessed in similar studies.(33–35) It will be a used as a descriptor of the population. |
| Type of CHD | There are different types of CHD, based on the lesions they present with. This variable will be included as it is used to define if the Modified WHO classification. This variable is widely tested in similar studies.(33,36) |
| Left ventricular ejection fraction (LVEF) at time of enrolment | LVEF is a known cardiac function that is used in literature.(37) |
| Cyanotic vs. Acyanotic CHD | CHD is classified as cyanotic or acyanotic, based on the type of lesion. This variable will also be used as a stratified independent variable to see whether it influences the maternal or neonatal outcomes. |
| Surgically repaired CHD | CHD is usually diagnosed at a young age. Certain conditions can be surgically repaired and afterwards patients can have normal to near-normal functioning. This variable will also be used as a stratified independent variable to see whether it influences the maternal or neonatal outcomes. This variable was also included similar studies.(38) |
| New York Heart Association functional classification | The New York Heart Association functional classification system is an easy tool that assesses the severity of heart failure. It is widely used in clinical practice and research.(33,35,36,39,40) This variable is the only variable that will be assessed at different intervals and can therefore be used to describe performance during pregnancy, at birth and at follow-up after delivery. |
| Modified WHO risk stratification classification | This risk stratification tool (as seen in Appendix A) will be used to describe the population group and as a stratified independent variable to see whether it influences the maternal or neonatal outcomes. |
| Systolic blood pressure | Blood pressure and pulse are known clinical measures of haemodynamic stability. |
| Diastolic blood pressure | |
| Pulse | |

| | |
|---|---|
| Gravidity | These variables are used to describe previous pregnancies and whether there were complications. This variable was included in similar studies, assessing maternal outcomes.(33–36,38,40) |
| Parity | |
| **Antenatal maternal outcomes** | |
| Variable | Justification for inclusion in study |
| Gestational age at first presentation | This variable was included in similar studies, assessing maternal outcomes.(38,40) |
| Need for hospitalisation during pregnancy | Hospitalisation is a major cost for the healthcare system and it also is associated with the more severely affected patients. This variable will subsequently be included in the study to describe the need for hospitalisation in each of the independent variables. |
| Number of hospital admissions | The number of hospital admissions is usually associated with the severity of a condition. This variable will be included to describe the number of admissions in each of the independent variables. |
| Number of days hospitalised | The length of stay in an intensive care unit (ICU) and in a general ward will be described in order to calculate costs to the healthcare system. Once again, longer admissions and admissions to ICU are also usually indicative of poorer functioning patients. The number of days in hospital in the independent variables will be described. |
| **Perinatal maternal outcomes** | |
| Variable | Justification for inclusion in study |
| Date of delivery | The date of delivery can be used to calculate the age of the mother. |
| Mode of delivery | The mode of delivery describes the circumstances under which the baby was delivered. It is often reported in descriptive and other studies.(33,34,36) |
| Maternal death | Maternal mortality is the most severe outcome in pregnancy and obviously should be avoided at all cost. It is widely assessed in similar studies.(33,34) This variable is included in this study to evaluate whether the reason for maternal death was cardiac in nature or for other reasons. It will also describe the reasons for maternal death. |

| Neonatal outcomes at birth | |
|---|---|
| Variable | Justification for inclusion in study |
| Gestational age at delivery | The gestational age at delivery will determine whether a baby was born preterm. If born preterm, a baby is expected to have more complications, longer hospitalisation and possible lifelong consequences. Prematurity is the most common neonatal complication of CHD.(36) These variables will be assessed to describe the gestational ages. |
| Preterm delivery | |
| Birth weight | Low birth weight is usually an indication for admission to neonatal intensive care unit (NICU) and the need for specialised care. It is also associated with adverse outcomes. Birth weight will be used to calculate whether the infants were small for gestational age and both variables will be used to describe the independent variables. These variables are often reported in descriptive and other studies.(34,36) |
| Admission to NICU | Admission to NICU is seen as a major cost to health and at times also associated with adverse health outcomes. This variable will be included in the study to describe how many infants were admitted to NICU. This variable is often assessed in similar studies reporting neonatal outcomes.(33,34) |
| Length of stay in NICU | Length of stay in the NICU will be a determinant of severity of adverse outcomes as well as a major cost to health. This variable will be included in the study to describe the number of days infants were admitted to NICU in each of the independent variables. |
| Admission to general ward | Admission to a general ward and length of stay have cost implications to the healthcare. These variables will therefore be described. |
| Length of stay in general ward | |
| Neonatal death | Neonatal death is a serious outcome and should be avoided. It is however often measured in neonatal outcomes of studies.(34,36) This variable is included in the study as it will describe the number of deaths in this cohort as well as in each of the stratified independent variables. |
| Miscarriage | In order to understand miscarriages and in which subgroups they presented, this variable will be assessed. |

CHD = Congenital heart disease; NICU = Neonatal Intensive Care Unit

Appendix C:  Case report form for the nested study

## Case report form

| | |
|---|---|
| Patient ID | |

BASELINE MATERNAL CHARACTERISTICS

| | | | | | |
|---|---|---|---|---|---|
| Date of birth | DD / MM / YYYY | | | | |
| Type of CHD (tick all that apply) | Atrial septal defect (ASD) | Ventricular septal defect (VSD) | Patent ductus arteriosus (PDA) | | |
| | Aortic coarctation | Tetralogy of Fallot | Pulmonary stenosis | | |
| | Other, specify: _____ | | | | |
| Left ventricular ejection fraction (LVEF) at time of enrollment | _____ | | | | |
| Cyanotic vs. Acyanotic CHD | Cyanotic CHD | Acyanotic CHD | | | |
| Surgically corrected CHD | Previously surgically repaired CHD | Unrepaired CHD | | | |
| Modified WHO risk stratification classification | I | II | II – III | III | IV |
| NYHA functional classification | I | II | III | IV | |
| Systolic blood pressure | _____ mmHg | | | | |
| Diastolic blood pressure | _____ mmHg | | | | |
| Pulse | _____ beats per minute | | | | |
| Gravidity | _____ | | | | |
| Parity | _____ | | | | |
| Neonatal death | Yes | No | | | |
| Miscarriage | Yes | No | | | |

ANTE-NATAL MATERNAL OUTCOMES

| | | | |
|---|---|---|---|
| Gestational age at first presentation | _____ Weeks + _____ Days = _____ Total days | | |
| Need for hospitalisation during pregnancy | Yes | No | Unknown |
| Number of hospital admissions | _____ Times | | Unknown |

| | | | |
|---|---|---|---|
| First admission: Number of days hospitalised | _____ Days in ICU<br>_____ Days in general ward | Not hospitalised | Unknown |
| Second admission: Number of days hospitalised | _____ Days in ICU<br>_____ Days in general ward | Not hospitalised | Unknown |
| Third admission: Number of days hospitalised | _____ Days in ICU<br>_____ Days in general ward | Not hospitalised | Unknown |
| Antenatal hospitalisation > 3 days | Yes | No | |

PERINATAL MATERNAL OUTCOMES

| | | |
|---|---|---|
| Date of delivery | DD / MM / YYYY | |
| Mode of delivery | NVD | Caesarean section |
| Reason for mode of delivery (except for uncomplicated NVD) | _____ | |
| Maternal death | Yes | No |
| Number of days hospitalised | _____ Days in ICU<br>_____ Days in general ward | Unknown |
| Perinatal admission > 4 days | Yes | No |

NEONATAL OUTCOMES AT BIRTH

| | | | |
|---|---|---|---|
| Gestational age at delivery | _____ Weeks + _____ Days = _____ Total days | | |
| Preterm delivery | < 33 weeks 6 days | 34 weeks to 37 weeks | > 37 weeks 1 day |
| | Unknown | Neonatal death | |
| Birth weight | _____ Grams | | |
| Admission to NICU | Yes | No | Unknown |
| Number of days hospitalised in NICU | _____ Days | | Not admitted to NICU |

| | | | | |
|---|---|---|---|---|
| NICU admission > 2 days | Yes | | No | |
| Admission to general ward | Yes | No | Unknown | |
| Number of days hospitalised in general ward | ____ Days | | Not admitted to general ward | |
| General ward admission > 2 days | Yes | | No | |
| Cause of neonatal death | N/A Neonate alive | Neonatal death | Miscarriage | Termination of pregnancy |

## Appendix D: Codebook for the nested study

## Table 4: Codebook for the nested study

| MATERNAL BASELINE INFORMATION | | |
|---|---|---|
| Variable | Numerical / Categorical | Measures |
| Date of birth | Numerical<br>- Discrete | Day / Month / Year |
| Type of CHD | Categorical<br>- Nominal | 0 = Atrial septal defect (ASD)<br>1 = Ventricular septal defect (VSD)<br>2 = Patent ductus arteriosus (PDA)<br>3 = Aortic coarctation<br>4 = Tetralogy of Fallot<br>5 = Pulmonary stenosis<br>6 = Other |
| Left ventricular ejection fraction (LVEF) at time of enrollment | Numerical<br>- Discrete | % |
| Acyanotic vs. Cyanotic CHD | Categorical<br>- Binary | 0 = Acyanotic CHD<br>1 = Cyanotic CHD |
| Surgically corrected CHD | Categorical<br>- Binary | 0 = Unrepaired CHD<br>1 = Previous surgical repair |
| Modified WHO risk stratification classification | Categorical<br>- Ordinal | 0 = I<br>1 = II<br>2 = II – III<br>3 = III<br>4 = IV |
| Systolic blood pressure | Numerical<br>- Discrete | mmHg |
| Diastolic blood pressure | Numerical<br>- Discrete | mmHg |
| Pulse | Numerical<br>- Discrete | beats per minute (bpm) |

| | | |
|---|---|---|
| Gravidity | Numerical<br>- Discrete | Times |
| Parity | Numerical<br>- Discrete | Times |

| ANTENATAL MATERNAL OUTCOMES | | |
|---|---|---|
| Variable | Numerical / Categorical | Measures |
| Gestational age at first presentation | Numerical<br>- Discrete | Days |
| Need for hospitalisation during pregnancy | Categorical<br>- Binary | 0 = No<br>1 = Yes<br>2 = Unknown |
| Number of hospital admissions | Numerical<br>- Discrete | Times |
| First admission:<br>Number of days hospitalised – ICU | Numerical<br>- Discrete | Days |
| First admission:<br>Number of days hospitalised – general ward | Numerical<br>- Discrete | Days |
| Second admission:<br>Number of days hospitalised – ICU | Numerical<br>- Discrete | Days |
| Second admission:<br>Number of days hospitalised – general ward | Numerical<br>- Discrete | Days |
| Third admission:<br>Number of days hospitalised - ICU | Numerical<br>- Discrete | Days |
| Third admission: | Numerical | Days |

| | | |
|---|---|---|
| Number of days hospitalised – general ward | - Discrete | |
| Antenatal hospitalization > 3 days | Categorical<br>- Binary | 0 = No<br>1 = Yes |

**PERINATAL MATERNAL OUTCOMES**

| Variable | Numerical / Categorical | Measures |
|---|---|---|
| Date of delivery | Numerical<br>- Discrete | Day / Month / Year |
| Mode of delivery | Categorical<br>- Nominal | 0 = Normal vaginal delivery (including using support of external devices to assist delivery, e.g. forceps, vacuum, etc.)<br>1 = Caesarean section (planned and unplanned |
| Maternal death | Categorical<br>- Binary | 0 = No (mother alive)<br>1 = Yes |

**NEONATAL OUTCOMES ASSESSED AT BIRTH**

| Variable | Numerical / Categorical | Measures |
|---|---|---|
| Gestational age at delivery | Numerical<br>- Discrete | Days |
| Preterm delivery | Categorical<br>- Ordinal / Nominal | 0 = < 33 weeks 6 days<br>1 = 34 weeks to 37 weeks<br>2 = Term (> 37 weeks 1 day)<br>3 = Unknown<br>4 = Neonatal death |
| Birth weight | Numerical<br>- Discrete | Grams |
| Low birth weight | Categorical<br>- Binary | 0 = No<br>1 = Yes |
| Admission to NICU | Categorical<br>- Ordinal | 0 = No<br>1 = Yes |

| | | |
|---|---|---|
| | | 2 = Unknown |
| Length of stay in NICU | Numerical<br>- Discrete | Days |
| Admission to NICU > 2 days | Categorical<br>- Binary | 0 = No<br>1 = Yes |
| Admission to general ward | Categorical<br>- Ordinal | 0 = No<br>1 = Yes<br>2 = Unknown |
| Length of stay in general ward | Numerical<br>- Discrete | Days |
| Admission to general ward > 2 days | Categorical<br>- Binary | 0 = No<br>1 = Yes |
| Cause of neonatal death | Categorical<br>- Ordinal | 0 = N/A Neonate alive<br>1 = Neonatal death<br>2 = Miscarriage<br>3 = Termination of pregnancy |

**Abbreviations:** CHD, Congenital heart disease; N/A, Not applicable; NICU, Neonatal Intensive Care Unit

Appendix E:  Informed consent form of the parent study

# Cardiac Disease in Maternity Registry (CDM-II)

## PATIENT INFORMATION AND CONSENT FORM


| | |
|---|---|
| Name of Principal Investigator: | Prof. Karen Sliwa |
| | Department of Cardiology & |
| | Hatter Cardiovascular Research Institute |
| Phone: | +27 21 4066457 |
| Fax: | +27 21 4478789 |
| Email: | Karen.Sliwa-Hahnle@uct.ac.za |

| | |
|---|---|
| Research nurse: | Mrs Olivia Briton |
| Telephone No: | 021 650 1735 |

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

### Informed Consent Form

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

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

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

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

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

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

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

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

☐ I agree to take part in this study.
☐ I am willing to be re-contacted by the researcher about possible future use of my tissue samples in future research.
If any of the blood I have provided for this research is unused or left over,
☐ I give permission for my blood sample to be stored indefinitely, if the research has been approved by the HREC.
☐ I want my blood sample destroyed immediately.
☐ I want my blood sample destroyed after ___ years

| _____ | _____ | _____ |
|---|---|---|
| Participant's name | Participant's signature | Date |
| _____ | _____ | _____ |
| Witness's name | Witness's signature | Date |
| _____ | _____ | _____ |
| Investigator's name | Investigator's signature | Date |

PART B: Publication-ready Manuscript

## Abstract

### Introduction

Although pregnancy is generally well tolerated in women with congenital heart disease (CHD), little is known about maternal and neonatal outcomes of these pregnancies in sub-Saharan Africa. This study aimed to describe the maternal and neonatal outcomes as stratified by cyanotic vs. acyanotic CHD, previous surgically repaired vs. unrepaired CHD, and between the different Modified World Health Organisation risk stratification (mWHO) classes.

### Methods

A nested retrospective cohort study was conducted that included 83 women with CHD out of the 243 women with CVD enrolled to a Cape Town-based registry from patients seen at a tertiary referral healthcare centre by November 2015. This study analysed poor maternal and neonatal outcomes in women with CHD. Poor maternal outcome was defined as maternal death, antenatal hospitalisation, and/or perinatal ICU admission. Poor neonatal outcome was defined as preterm birth, low birth weight, NICU admission, general ward admission over 2 days, neonatal death, and/or miscarriage. Data were collected using REDCap, and statistical analyses included descriptive statistics, non-parametric tests, and logistic regressions to assess associations. Risk factors were adjusted for, and a two-tailed p-value <0.05 was considered significant.

### Results

This cohort had a median age of 27 years (IQR 23 – 32) and gravidity of 2 (IQR 1 – 2). Women were enrolled with a median gestational age of 24 weeks (IQR 19 – 30). There were no statistically significant differences in clinical presentation at enrolment between those who had cyanotic CHD or not, and those who had surgically repaired CHD or not. More than half (54.2%) of women required either antenatal hospitalisation and/or perinatal intensive care unit (ICU) admission. Women classified as mWHO class II, II-III, III or IV were at increased risk of poor maternal outcome (OR 4.239, 95% CI 1.4 – 12.5), even when corrected for confounders. Neonates born from mothers from mWHO classes II-III, III and IV had an odds ratio of 3.1 (95% CI 1.8 – 8.2) for poor neonatal outcome but did not show significance when corrected for

confounders. Univariable and multivariable regression analysis showed that the risk for poor neonatal outcome increased with maternal age.

## Conclusion

As more women with CHD are reaching child-bearing age, risk stratification is imperative to ensure optimal care and favourable maternal and neonatal outcomes. We found the mWHO classification a useful tool to predict poor outcomes and recommend its use to tailor appropriate level of care for women with CHD in pregnancy.

## Introduction

Pregnancy causes reversible physiological changes to the cardiovascular system, which include increased blood volume, heart rate and cardiac output.(1,2) These changes are usually well tolerated, but could be detrimental to women with structural heart disease.(3) Cardiac disease remains one of the leading causes for maternal death during pregnancy worldwide.(4,5) Moreover, maternal mortality is 14 times higher in low- and middle-income countries (LMICs) than in the developed world.(6)

Congenital heart disease (CHD) is a collective term for a heterogenous group of cardiac defects that are present from birth. Indeed, CHD results from embryonic malformation of the heart walls, valves and/or blood vessels. Although there is little data available for CHD in South Africa, there is a rapid increase in the prevalence of CHD reported worldwide. The increase in prevalence could be explained by advances in health care, allowing for earlier detection of CHD, as well as better treatment and management thereof, which in turn contributes to longer survival.(7–9) Moreover, the risk for CHD recurrence is significantly higher in children born from mothers with CHD, compared with the general public.(10,11) In 2015, it was estimated that the prevalence of the adult population with CHD is six in 1 000, while the prevalence in those older than 65 years of age is four in 1 000.(7,8) As medical advancements lead to increased survival rates among patients with CHD, more women with CHD are now reaching reproductive age and choosing pregnancy. Although CHD itself rarely causes maternal death, it is often linked to maternal complications leading to frequent extended hospitalisation, as well as adverse neonatal outcomes like prematurity and neonatal intensive care units (NICU) admissions, all of which require specialised care. Moreover, in low- and middle-income countries, many individuals with CHD lack access to surgery, placing women with CHD at higher risk for maternal and neonatal morbidity and mortality during pregnancy.

Due to the increased survival of patients with CHD, more women with CHD reach the reproductive age and choose to become pregnant.(12) Even though there were no maternal deaths in a previous study conducted on women with CHD in South Africa(13), there was an almost 5% maternal mortality amongst women with cyanotic CHD reported in a larger international study.(14) CHD is, however, often associated with maternal complications (such

as heart failure and pre-eclampsia) and/or adverse neonatal outcomes (such as prematurity and admission to neonatal intensive care units [NICU]), which require careful monitoring and specialised care.(15,16) Furthermore, most people with CHD in LMICs do not have the access to surgery. This means that if and when women with CHD reach reproductive age and fall pregnant, they are at higher risk for maternal and neonatal morbidity and mortality.(17)

The clinical presentation of women with CHD varies from mild to severe disease, depending on the type and complexity of lesions, prior corrective surgery, and the development of complications. The Modified World Health Organisation risk stratification (mWHO) classification system assists in risk stratification of women with cardiovascular disease (CVD) during pregnancy and can be used for CHD. The mWHO classification has five classes, mWHO class I, II, II-III, III and IV. This classification system stratifies women based on diagnosis, severity of lesions, previous surgically repair, development of left ventricular (LV) systolic dysfunction, pulmonary hypertension, etc. The mWHO classification recommends the level of care required during pregnancy to reduce poor outcomes.(18)

Although there are various registries for women with heart disease in pregnancy, there is limited literature about CHD in particular. In this regard, the Registry Of Pregnancy And Cardiac disease (ROPAC) is the largest of its kind. It has 60 participating countries worldwide, of which South Africa is the only sub-Saharan country.(19) CARdiac disease in PREGnancy (CARPREG)(20) and Zwangerschap bij Aangeboren HARtAfwijking (ZAHARA)(21) are other large registries in Canada and Belgium and the Netherlands respectively. Other smaller but similar registries are done in countries such as Germany, Brazil, India and the United States. (22–24) To address this dearth of knowledge, the Cardiac Diseases in Maternity (CDM) registry was established in 2010 to study CVD in pregnant women from sub-Saharan Africa. Apart from CHD, the CDM registry also enrols pregnant women with valvular heart disease, cardiomyopathy, and other forms of structural heart disease.(25)

The aim of this study was to describe the maternal and neonatal outcomes of pregnant women with CHD in the sub-Saharan context. The study objectives were to assess the differences in outcomes between women with cyanotic CHD or not, and between those with previous

surgically repaired CHD or not. An important study objective was to describe these outcomes according to severity of disease, as categorised by the mWHO classification.

## Methods

### Study design

The CDM registry consists of prospectively enrolled women with previously diagnosed or suspected cardiovascular disease (CVD), that have been referred to a joint cardiac-obstetric clinic at Groote Schuur Hospital (GSH) in Cape Town, South Africa. Pregnant women with cardiac disease who have been classified according to the modified WHO classification (classes II, II-III, III, IV) are referred for assessment by the cardiac-obstetric clinic at GSH. In addition, those who have been classified as Modified WHO class I and have abnormal blood pressure, electrocardiogram or echocardiogram (as diagnosed at a tertiary maternity facility), will also be referred to the joint clinic. The patients are followed up for the duration of their pregnancy, after which they return to the adult Cardiology services. The frequency of their visits depends on the severity of the disease, as recommended by contemporary guidelines.(18,25) Patients are referred to this clinic at GSH from all referring hospitals and clinics (primary and secondary maternity facilities) that fall within the GSH catchment area. This registry does not include patients seeking care in private facilities.

The CDM registry was formally approved by Human Research Ethics Committee (HREC) of the University of Cape Town, South Africa (HREC ref: 173/2010)(25) and complies with Declaration of Helsinki. All participants provided written informed consent prior to enrolment. The CDM registry started enrolment on 1 July 2010 and is ongoing. This study (HREC ref: 733/2020) was a nested retrospective cohort study. Of the 243 women with CVD enrolled to the CDM registry by November 2015, we included all 83 women with CHD.

### Eligibility criteria

To be included in this study, participants had to be diagnosed with any form of CHD as the primary diagnosis. For women with multiple pregnancies during this period, each pregnancy was considered an independent event.

### Baseline visit

Eligible women were enrolled at the baseline visit at which time their age, gestational age, obstetric and medical history were obtained. All known congenital defects were recorded and women were categorised according to the mWHO classification, to describe the risk and care that these women require based on their diagnosis, and the New York Heart Association (NYHA) functional classification of heart failure, to describe their clinical presentation at the time. Clinical parameters at the baseline visit included blood pressure measurement and pulse and echocardiography.

### Outcomes

Poor maternal outcome was determined as a composite endpoint for maternal death, and any antenatal hospitalisation and/or perinatal intensive care unit (ICU) admission. Poor neonatal outcome was determined as a composite endpoint for preterm birth (prior to 37 weeks), low birth weight (less than 2500 grams), admission to NICU, admission to a general ward for longer than 2 days, neonatal death and / or miscarriage. These composite endpoints aimed to capture a more comprehensive view of the adverse events and health outcomes for both mothers with CHD and babies born from mothers with CHD, enabling a more meaningful and detailed analysis of the study's results.

### Statistical analysis

Data was collected on Research Electronic Data Capture (REDCap Version 7.5.2), a secure electronic database hosted by the University of Cape Town, before the anonymised data were exported to R (Version RStudio 2022.02.0+443) for statistical analyses, and in this way ensuring patient confidentiality and data protection. Descriptive statistics were used to summarise data. Non-parametric continuous variables were summarised as median with interquartile range (IQR), while categorical variables were expressed as frequencies and percentages. Where appropriate, continuous variables were compared using Wilcoxon rank-sum test or Kruskal-Wallis test for non-parametric data and categorical variables were compared with chi-squared or Fisher’s exact tests. Clinical presentation and outcomes were compared for women with cyanotic CHD vs. acyanotic CHD, previous surgically repaired CHD vs. unrepaired CHD, and

women within the different mWHO classes. Univariable and multivariable binary logistic regressions were done to assess the associations of outcome with cyanotic CHD and unrepaired CHD. Univariable and multivariable multinomal logistic regressions were done to assess the associations of outcome between the mWHO classes. To assess for associations between outcome and complexity of disease, three models were created from mWHO classes. Model 1 included mWHO classes II, II-III, III and IV, model 2 included mWHO classes II-III, III and IV and model 3 mWHO classes III and IV. Risk factors for poor outcome that were previously described in the literature were used to adjust for confounding. All tests were two-tailed and a p-value of $<0.05$ was interpreted as statistically significant.

## Results

This cohort of 83 women with CHD had a median age of 27 years (IQR 23 – 32) and gravidity of 2 (IQR 1 – 2). Women were enrolled with a median gestational age of 24 weeks (IQR 19 – 30). There were no twin pregnancies in this cohort. As shown in Figure 1, the most common diagnosis was ventricular septal defect (VSD) (26, 31.3%). Cyanotic CHD accounted for 16.9% of the cohort, and half of the women had previous surgical repair. A quarter of this cohort (25.3%) were categorised as mWHO class I and 37.3% as mWHO class II (mWHO class II-III 15.7%; mWHO class III 13.3%; mWHO class IV 8.4%). Approximately a third of women were asymptomatic at the time of enrolment (NYHA functional class I 36.6%). The median left ventricular ejection fraction (LVEF) was 64% (IQR 58 - 69). As shown in Table 1A, there were no statistically significant differences in clinical presentation between those who had cyanotic CHD or not, and those who had surgically repaired CHD or not. However, as elaborated in Table 1B, there were significant differences in the NYHA functional classes amongst women categorised according to the mWHO classification (p = 0.011).

### Maternal outcomes

As shown in Table 2, less than half of this cohort (42.7%) were admitted to hospital between the time of enrolment and delivery. The median number of days admitted antenatally was 3 (IQR 1 – 5). The length of antenatal hospital stay was more than three days in 20.7% of this cohort. Although there was no statistically significant difference in the number of antenatal admissions or length of antenatal hospital stay between women with cyanotic CHD or not, or those with previous surgical repair or not (Table 2A), women from mWHO class I had the smallest proportion of antenatal admissions, as compared to all of the other classes combined (25.0% vs 48.4%, p = 0.043).

A quarter of women (25.0%) from this cohort were admitted to ICU perinatally and more than half (55.0%) had a perinatal hospitalisation of more than 4 days. Women from mWHO class I were less frequently admitted to ICU, as compared to all their counterparts combined (5.3% vs 31.1%, p= 0.048).

Overall, more than half (54.2%) of women required either antenatal hospitalisation and/or perinatal ICU admission (poor maternal outcome). There were no statistically significant differences between women with cyanotic CHD or not and those with prior surgical repair or not (Table 3A). As demonstrated in Figure 2A, women from mWHO class I were least likely to have a poor maternal outcome (28.6% vs 63.9% in the other classes combined, p = 0.027). Indeed, those classified as mWHO class II, II-III, III or IV were at increased risk of poor maternal outcome (OR 4.239, 95% CI 1.4 – 12.5). When correcting for risk factors previously described in the literature (age, cyanotic CHD, unrepaired CHD, NYHA functional classes II / III / IV, pulmonary hypertension), women from mWHO classes II, II-III, III or IV were still associated with more frequent admissions (Table 4).

## Neonatal outcomes

Even though the median gestational age at delivery was 38 weeks (IQR 37 – 39), a third of women in this cohort (33.3%) delivered their babies preterm. In this regard, 43% of those with unrepaired CHD had preterm deliveries. Overall, 12.5% of women delivered prior to 34 weeks of gestational age. Women from mWHO class III and IV were more likely to deliver before 34 weeks gestation, than those from classes I, II and II-III combined (53.3% vs 28.1%, p = 0.021).

The median birth weight for neonates born from women in this cohort was 2850 grams (IQR 2491 – 3240). Although 28.2% of these neonates were born with low birth weight, there were no statistically significant differences between any of the subgroups.

Almost a third of neonates (31.9%) born from women in this cohort required admission to NICU (median of 2 days [IQR 1 – 3]). NICU admission was, however, less common amongst neonates born from women in mWHO class I when compared to all the other mWHO classes combined (10.5% vs 39.6%, p = 0.054). As seen in Figure 3, neonates born from women from mWHO classes II, II-III, III and IV combined were associated with an increased risk of NICU admission (OR 5.6, 95% CI 1.4 – 37.5, p = 0.031).

Neonatal death (2.0%) and miscarriage (2.0%) occurred in 4.0% of the total cohort.

As illustrated in Figure 2B, there was a greater proportion of poor outcome amongst neonates whom mothers were from mWHO classes II-III, III and IV. Indeed, these neonates were associated with an odds ratio of 3.1 (95% CI 1.8 – 8.2) for poor outcome. However, when correcting for risk factors previously described in the literature (age, cyanotic CHD, unrepaired CHD, NYHA functional classes II / III / IV, pulmonary hypertension), the mWHO classification was not predictive of poor neonatal outcome. Univariable and multivariable regression analysis showed that the risk for poor neonatal outcome increased with maternal age (Table 4).

## Discussion

In this study on pregnant women with CHD, conducted at a South African tertiary referral healthcare centre, we found that the mWHO classification for cardiovascular risk had a predictive value for maternal hospitalisation. Women from mWHO class I had significantly less hospital admissions (albeit antenatal ward admission or perinatal ICU admission) as compared to those from other mWHO classes. All mothers in this cohort survived the pregnancy. Although neonatal and foetal mortality combined occurred in only 4% of pregnancies, poor neonatal outcome (i.e., composite of preterm delivery, low birth weight, admission to NICU, miscarriage and/or neonatal death) were found in more than half of the neonates born from this cohort. In this regard, poor neonatal outcomes were more frequent when born from mothers categorised as either mWHO class II-III, III or IV. Maternal age was an important risk factor for neonatal outcome.

In keeping with literature from LMICs(24), this cohort of South African pregnant women with CHD was younger (27 years) than similar cohorts in developed countries (31 years)(22). Similar to previous studies on pregnant women with CHD(14,22), we found that the risk of poor neonatal outcome increased with maternal age. This is an important finding, as more women with structural heart disease delay pregnancy to a more advanced maternal age.(26) Therefore, women with CHD should be cautioned of these neonatal risks.

Studies in developed countries found a significant difference in outcomes between women with CHD as compared to those without.(27,28) Furthermore, the ROPAC study reported that adverse neonatal outcomes in women with CHD were common. Premature births in this cohort were however more frequently than in the ROPAC study, especially amongst those born from women form mWHO classes II-III, III or IV. Studies in the global North also reported that the rates of premature births amongst women with CHD is more frequent than in a healthy cohort.(28,29) A study done on a healthy cohort in the Drakenstein area (one hour from Cape Town), reported preterm births in 17% of infants(30), which is almost half of what was seen in this study on women with CHD. Furthermore, birth weight in this cohort was less than what was found in the healthy cohort in Drakenstein. Only 7% of infants from the healthy cohort required hospitalisation after birth.(30) Comparingly, in this study, rates of admission to the

NICU were more than seven times as much. There is a definite need for counselling during pregnancy to discuss neonatal risks and the impact that these would have on the mothers and their families.

The ROPAC investigators previously reported that women with cyanotic CHD and unrepaired CHD were at increased risk for poor maternal outcome.(14) In this study of 83 women, there were no maternal deaths and there were no statistically significant differences in the variables we studied between women with cyanotic CHD and those with acyanotic CHD, or between those with surgically repaired CHD and those with unrepaired CHD. It may be a confounder to consider surgical repair in isolation, as the cohort with unrepaired CHD may consist of women with mild congenital lesions not requiring surgery, as well as those with significant disease not yet operated or even inoperable disease. The mWHO classification, however, corrects for these shortcomings, as it considers cyanosis and surgical repair as part of its risk stratification.

Pregnancy is discouraged in women from mWHO class III and contra-indicated in women with mWHO class IV(18), as these women are at significant risk for maternal mortality and morbidity. This cohort, however, had a greater proportion of women from mWHO classes III and IV and women with cyanotic CHD than what was reported by the ROPAC investigators(19), but less than what was reported by M-PAC in India(24). This is possibly explained by a greater number of unplanned pregnancies in LMICs. As expected, our study found that poor maternal and neonatal outcomes were mostly driven by events that occurred in women from higher mWHO classes.

The information from this study confirms that the referral algorithm that the combined cardiac-obstetric clinic uses for referral of suspected and previously known CHD is imperative to the successful management of these patients. In this algorithm, women from mWHO class III and IV require urgent referral to the joint cardiac-obstetric clinic, while women from mWHO II and those with abnormal blood pressure, electrocardiogram (ECG), echocardiogram and/or murmurs require a non-urgent referral to the clinic. Women from mWHO class I with normal blood pressure, ECG, echocardiogram and/or murmurs, can follow up with their regular maternity service. The mWHO classification accurately predicted poor outcome in this study

and can be used in conjunction with other clinical assessments to assist with risk stratification for optimised patient care.

In summary, the findings from the within-group comparison of women with CHD in this setting showed various insights into maternal and neonatal outcomes. The results suggest that maternal mWHO class status might influence certain outcomes such as NICU admission and neonatal length of hospital stay. However, the type of CHD or its surgical status may not significantly impact outcomes. Nevertheless, these findings should be interpreted with caution due to the limitations of the study's sample size and the specific setting.

## Strengths and limitations

Little is known about pregnant women with CHD in LMICs and especially in sub-Saharan Africa. This study therefore adds to the body of evidence that describes maternal and neonatal outcomes in this population. However, the size of this cohort was small and therefore a limitation to the study. Furthermore, we had limited information about reason for hospitalisation, timing of antenatal hospitalisation and long-term follow-up of these women.

## Implications for future research

There is a dearth of knowledge about antenatal and perinatal admissions in pregnant women with CHD from LMICs and Sub-Saharan Africa in particular. Further exploring the reasons for hospitalisations ante- and perinatally and timing of antenatal hospitalisation, will assist in future improved management of pregnant women with CHD. It was seen in previous studies that most of the complications in women with CVD occur between the end of the second trimester and the middle of the third trimester or postpartum(31) and this could further be investigated for women with CHD.

Future studies that compare women with CHD with a matched healthy cohort and also explore the social impact of CHD on families are necessary in a sub-Saharan cohort.

## Conclusion

The number of women with CHD that are reaching child-bearing age are increasing. Risk stratification is important to ensure optimal care and favourable outcomes to both mother and child. We found the mWHO classification a useful tool to predict poor maternal and neonatal outcomes and recommend its use to tailor appropriate level of care for women with CHD in pregnancy.

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Table 1A: Baseline maternal characteristics at time of enrolment as classified by cyanotic vs. acyanotic CHD and whether CHD was previously surgically repaired or not

| | | All<br>n = 83 | Acyanotic CHD<br>n = 69 | Cyanotic CHD<br>n = 14 | p-value | Surgically repaired CHD<br>n = 40 | Unrepaired CHD<br>n = 41 | p-value |
|---|---|---|---|---|---|---|---|---|
| Age (years) | Median (IQR) | 27 (23 – 32) | 27 (24 – 32) | 26 (22 – 30) | 0.500 | 26 (22 – 33) | 27 (24 – 30) | 0.500 |
| Gestational age (weeks) | Median (IQR) | 24 (19 – 30) | 24 (20 – 31) | 20 (16 – 26) | 0.500 | 24 (17 – 30) | 23 (20 – 29) | 0.500 |
| Gravidity | Median (IQR) | 2 (1 – 2) | 2 (1 – 2) | 2 (1 – 2) | 0.346 | 2 (1 – 3) | 2 (1 – 2) | 0.346 |
| Parity | Median (IQR) | 1 (0 – 1) | 1 (0 – 1) | 1 (0 – 1) | 0.346 | 1 (0 – 1) | 1 (0 – 1) | 0.346 |
| NYHA | | | | | | | | |
| I | N (%) | 30/82 (36.6%) | 26/68 (38.2%) | 4 (28.6%) | 0.558 | 20 (50.0%) | 9/40 (22.5%) | 0.019 |
| II | N (%) | 44/82 (53.7%) | 35/68 (51.4%) | 9 (64.3%) | 0.558 | 18 (45.0%) | 25/40 (62.5%) | 0.178 |
| III | N (%) | 7/82 (8.5%) | 6/68 (8.8%) | 1 (7.1%) | 1.000 | 2 (5.0%) | 5/40 (12.5%) | 0.432 |
| IV | N (%) | 1/82 (1.2%) | 1/68 (1.5%) | 0 | 1.000 | 0 | 1/40 (2.5%) | 1.000 |
| SBP (mmHg) | Median (IQR) | 120 (110 – 130) | 120 (110 – 130) | 110 (110 – 119) | 0.500 | 119 (110 – 125) | 120 (110 – 130) | 0.500 |
| DBP (mmHg) | Median (IQR) | 70 (68 – 80) | 72 (68 – 80) | 70 (63 – 70) | 0.500 | 70 (66 – 80) | 70 (68 – 80) | 0.346 |
| Pulse (bpm) | Median (IQR) | 80 (74 – 86) | 80 (74 – 86) | 80 (73 – 87) | 0.346 | 80 (70 – 84) | 84 (78 – 88) | 0.500 |
| LVEF (%) | Median (IQR) | 64 (58 – 69) | 64 (58 – 69) | 62 (59 – 67) | 0.500 | 62 (57 – 68) | 65 (60 – 70) | 0.500 |

bpm = beats per minute; CHD = Congenital Heart Disease; DBP = diastolic blood pressure; IQR = Interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association classification of heart failure; SBP = systolic blood pressure

## Table 1B: Baseline maternal characteristics at time of enrolment as per mWHO classification

| | | All<br>n = 83 | mWHO I<br>n = 21 | mWHO II<br>n = 31 | mWHO II-III<br>n = 13 | mWHO III<br>n = 11 | mWHO IV<br>n = 7 | p-value |
|---|---|---|---|---|---|---|---|---|
| Age (years) | Median (IQR) | 27 (23 – 32) | 26 (22 – 29) | 25 (23 – 29) | 32 (29 – 33) | 29 (25 – 33) | 33 (24 – 34) | 0.590 |
| Gestational age (weeks) | Median (IQR) | 24 (19 – 30) | 24 (17 – 30) | 26 (20 – 32) | 22 (17 – 27) | 24 (20 – 30) | 22 (16 – 27) | 0.970 |
| Gravidity | Median (IQR) | 2 (1 – 2) | 2 (2 – 3) | 2 (2 – 2) | 2 (2 – 2) | 2 (1 – 2) | 1 (1 – 2) | 0.647 |
| Parity | Median (IQR) | 1 (0 – 1) | 1 (0 – 2) | 1 (1 – 1) | 1 (1 – 1) | 1 (0 – 1) | 0 (0 – 1) | 0.784 |
| NYHA | | | | | | | | **0.011** |
| I | N (%) | 30/82 (36.6%) | 12 (57.1%) | 5/30 (16.7%) | 6 (46.2%) | 6 (54.5%) | 1 (14.3%) | |
| II | N (%) | 44/82 (53.7%) | 9 (42.9%) | 20/30 (67.7%) | 7 (53.8%) | 4 (36.4%) | 4 (57.1%) | |
| III | N (%) | 7/82 (8.5%) | 0 | 4/30 (13.3%) | 0 | 1 (9.1%) | 2 (28.6%) | |
| IV | N (%) | 1/82 (1.2%) | 0 | 1/30 (3.3%) | 0 | 0 | 0 | |
| SBP (mmHg) | Median (IQR) | 120 (110 – 130) | 120 (110 – 131) | 122 (110 – 131) | 120 (114 – 130) | 117 (110 – 125) | 111 (110 – 118) | 0.856 |
| DBP (mmHg) | Median (IQR) | 70 (68 – 80) | 77 (61 – 80) | 70 (69 – 82) | 70 (70 – 81) | 70 (68 – 76) | 70 (64 – 70) | 0.865 |
| Pulse (bpm) | Median (IQR) | 80 (74 – 86) | 80 (69 – 85) | 85 (79 – 93) | 80 (76 – 83) | 75 (69 – 85) | 80 (80 – 87) | 0.230 |
| LVEF (%) | Median (IQR) | 64 (58 – 69) | 63 (57 – 68) | 64 (58 – 70) | 65 (63 – 70) | 61 (52 – 67) | 63 (62 – 67) | 0.910 |

bpm = beats per minute; DBP = diastolic blood pressure; IQR = Interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association classification of heart failure; SBP = systolic blood pressure

Table 2A: Maternal and neonatal outcomes as classified by cyanotic vs. acyanotic CHD and whether CHD was previously surgically repaired or not

| | | All n = 83 | Acyanotic CHD n = 69 | Cyanotic CHD n = 14 | p-value | Surgically repaired CHD n = 40 | Unrepaired CHD n = 41 | p-value |
|---|---|---|---|---|---|---|---|---|
| **Antenatal maternal outcomes** | | | | | | | | |
| Antenatal hospitalisation | N (%) | 35/82 (42.7%) | 26/68 (38.2%) | 9 (64.3%) | 0.239 | 15/39 (38.5%) | 19 (46.3%) | 0.502 |
| Number of hospital admissions | Median (IQR) | 1 (1 – 2) | 1 (1 – 2) | 1 (1 – 2) | 0.346 | 1 (1 – 2) | 1 (1 – 2) | 0.346 |
| Number of days admitted to ward* | Median (IQR) | 3 (1 – 5) | 3 (2 – 5) | 1 (1 – 5) | 0.500 | 3 (1 – 8) | 3 (2 – 5) | 0.346 |
| Antenatal hospitalisation > 3 days* | N (%) | 17/82 (20.7%) | 14/68 (20.6%) | 3 (21.4%) | 1.000 | 6/39 (15.4%) | 11 (26.8%) | 0.277 |
| | | | | | | | | |
| **Perinatal maternal outcomes** | | | | | | | | |
| Caesarean section | N (%) | 14/51 (27.5%) | 12/44 (27.3%) | 2/7 (28.6%) | 1.000 | 10/29 (34.5%) | 3/21 (14.3%) | 0.191 |
| Perinatal ICU admission | N (%) | 20/80 (25.0%) | 16/66 (24.2%) | 4 (28.6%) | 0.741 | 9/38 (23.7%) | 11/40 (27.5%) | 0.798 |
| Number of days admitted to ICU | Median (IQR) | 0 (0 – 0) | 0 (0 – 0) | 0 (0 – 1) | - | 0 (0 – 0) | 0 (0 – 0) | - |
| Number of days admitted to ward | Median (IQR) | 4 (2 – 5) | 4 (2 – 6) | 3 (2 – 4) | 0.500 | 4 (2 – 4) | 4 (3 – 6) | 0.346 |
| Perinatal hospitalisation > 4 days | N (%) | 44/80 (55.0%) | 38/66 (57.6%) | 6 (42.9%) | 0.382 | 20/38 (52.6%) | 23/40 (57.5%) | 0.820 |
| | | | | | | | | |
| **Neonatal outcomes** | | | | | | | | |
| Gestational age at delivery (weeks) | Median (IQR) | 38 (37 – 39) | 38 (37 – 39) | 39 (37 – 39) | 0.346 | 38 (38 – 39) | 38 (36 – 39) | 0.346 |
| Preterm delivery (< 37 weeks) | N (%) | 24/72 (33.3%) | 21/60 (35.0%) | 3/12 (25.0%) | 0.739 | 8/35 (22.9%) | 15/35 (42.9%) | 0.126 |
| Gestation < 33 weeks 6 days | N (%) | 9/72 (12.5%) | 7/60 (11.7%) | 2/12 (16.7%) | 0.639 | 4/35 (11.4%) | 5/35 (42.9%) | 1.000 |
| Gestation 34 weeks to 37 weeks | N (%) | 15/72 (20.83%) | 14/60 (23.3%) | 1/12 (8.3%) | 0.438 | 4/35 (11.4%) | 10/35 (28.6%) | 0.133 |
| Gestation > 37 weeks 1 day | N (%) | 48/72 (66.7%) | 39/60 (65.0%) | 9/12 (75.0%) | 0.739 | 27/35 (77.1%) | 20/35 (57.1%) | 0.126 |
| Birth weight (grams) | Median (IQR) | 2850 (2491 – 3240) | 2850 (2460 – 3232) | 2822 (2556 – 3415) | 0.500 | 2825 (2500 – 3100) | 2895 (2425 – 3260) | 0.500 |
| Low birth weight (< 2500 grams) | N (%) | 20/71 (28.2%) | 17/59 (28.8%) | 3/12 (25.0%) | 1.000 | 9/35 (25.7%) | 11/34 (32.4%) | 0.603 |
| Admission to NICU | N (%) | 23/72 (31.9%) | 18/59 (30.5%) | 5/13 (38.5%) | 0.631 | 11/35 (31.4%) | 11/35 (31.4%) | 1.000 |
| Number of days admitted to NICU | Median (IQR) | 2 (1 – 3) | 2 (1 – 3) | 4 (1 – 8) | 0.500 | 1 (1 – 3) | 2 (2 – 4) | 0.500 |
| Admission to NICU > 2 days | N (%) | 9/72 (12.5%) | 6/59 (10.2%) | 3/12 (25.0%) | 0.343 | 4/35 (11.4%) | 5/35 (14.3%) | 1.000 |
| Admission to ward | N (%) | 11/72 (15.3%) | 9/59 (15.3%) | 2/13 (15.4%) | 0.740 | 4/35 (11.4%) | 7/35 (20.0%) | 0.611 |
| Number of days admitted to ward | Median (IQR) | 1 (1 – 2) | 1 (1 – 2) | 1 (1 – 1) | 0.346 | 2 (2 – 3) | 1 (1 – 1) | 0.500 |
| Admission to general ward > 2 days | N (%) | 2 (2.4%) | 2 (2.9%) | 0 | 1.000 | 1 (2.5%) | 1 (2.4%) | 1.000 |
| Neonatal death | N (%) | 2/82 (2.4%) | 2/68 (2.9%) | 0 | 1.000 | 1 (2.5%) | 1/40 (2.5%) | 1.000 |
| Miscarriage | N (%) | 2/82 (2.4%) | 1/68 (1.5%) | 1 (7.1%) | 0.314 | 1 (2.5%) | 1/40 (2.5%) | 1.000 |
| | | | | | | | | |
| **Poor maternal outcome** | N (%) | 45 (54.2%) | 36 (52.2%) | 9 (64.3%) | 0.566 | 20 (50.0%) | 24 (58.5%) | 0.648 |
| **Poor neonatal outcomes** | N (%) | 48 (57.8%) | 41 (59.4%) | 7 (50.0%) | 0.407 | 22 (55.0%) | 24 (58.5%) | 0.609 |
| **Poor maternal or neonatal outcome** | N (%) | 66 (79.5%) | 55 (79.7%) | 11 (78.6%) | **< 0.000** | 31 (77.5%) | 33 (80.5%) | 0.803 |

* Per admission

CHD = Congenital Heart Disease; ICU = Intensive Care Unit; IQR = Interquartile range; mWHO = Modified World Health Organisation classification risk stratification tool; NICU = Neonatal Intensive Care Unit

# Table 2B: Maternal and neonatal outcomes as per mWHO classification

| | | All<br>n = 83 | mWHO I<br>n = 21 | mWHO II<br>n = 31 | mWHO II-III<br>n = 13 | mWHO III<br>n = 11 | mWHO IV<br>n = 7 | p-value |
|---|---|---|---|---|---|---|---|---|
| **Antenatal maternal outcomes** | | | | | | | | |
| Antenatal hospitalisation | N (%) | 35/82 (42.7%) | 5/20 (25.0%) | 16 (51.6%) | 6 (46.2%) | 4 (36.4%) | 4 (57.1%) | 0.502 |
| Number of hospital admissions | Median (IQR) | 1 (1 – 2) | 2 (2 – 2) | 1 (1 – 2) | 2 (1 – 3) | 1 (1 – 2) | 1 (1 – 1) | 0.174 |
| Number of days admitted to ward* | Median (IQR) | 3 (1 – 5) | 4 (3 – 11) | 3 (1 – 4) | 5 (3 – 5) | 2 (2 – 3) | 1 (1 – 3) | 0.119 |
| Antenatal hospitalisation > 3 days* | N (%) | 17/82 (20.7%) | 2/20 (10.0%) | 8 (25.8%) | 3 (23.1%) | 1 (9.1%) | 3 (42.9%) | 0.295 |
| | | | | | | | | |
| **Perinatal maternal outcomes** | | | | | | | | |
| Caesarean section | N (%) | 14/51 (27.5%) | 4/15 (26.7%) | 2/14 (14.3%) | 3/9 (33.3%) | 4/7 (57.1%) | 1/5 (20.0%) | 0.305 |
| Perinatal ICU admission | N (%) | 20/80 (25.0%) | 1/19 (5.3%) | 8/30 (26.7%) | 4 (30.8%) | 4 (36.4%) | 3 (42.9%) | 0.187 |
| Number of days admitted to ICU | Median (IQR) | 0 (0 – 0) | 0 (0 – 0) | 0 (0 – 0) | 0 (0 – 1) | 0 (0 – 1) | 0 (0 – 2) | 0.948 |
| Number of days admitted to ward | Median (IQR) | 4 (2 – 5) | 3 (2 – 4) | 4 (2 – 6) | 5 (3 – 6) | 4 (3 – 5) | 4 (4 – 9) | 0.545 |
| Perinatal hospitalisation > 4 days | N (%) | 44/80 (55.0%) | 9/19 (47.4%) | 15/30 (50.0%) | 8 (61.5%) | 6 (54.5%) | 6 (85.7%) | 0.456 |
| | | | | | | | | |
| **Neonatal outcomes** | | | | | | | | |
| Gestational age at delivery (weeks) | Median (IQR) | 38 (37 – 39) | 39 (38 – 39) | 38 (37 – 39) | 38 (36 – 38) | 38 (34 – 39) | 37 (34 – 39) | 0.879 |
| Preterm delivery (< 37 weeks) | N (%) | 24/72 (33.3%) | 4/18 (22.2%) | 8/29 (27.6%) | 4/10 (40.0%) | 4/8 (50.0%) | 4 (57.1%) | 0.353 |
| Gestation < 33 weeks 6 days | N (%) | 9/72 (12.5%) | 1/18 (5.6%) | 3/29 (10.3%) | 0/10 (0%) | 2/8 (25.0%) | 3 (42.9%) | 0.052 |
| Gestation 34 weeks to 37 weeks | N (%) | 15/72 (20.8%) | 3/18 (16.7%) | 5/29 (17.2%) | 4/10 (40.0%) | 2/8 (25.0%) | 1 (14.3%) | 0.573 |
| Gestation > 37 weeks 1 day | N (%) | 48/72 (66.7%) | 14/18 (77.8%) | 21/29 (72.4%) | 6/10 (60.0%) | 4/8 (50.0%) | 3 (42.9%) | 0.353 |
| Birth weight (grams) | Median (IQR) | 2850 (2491 – 3240) | 2730 (2360 – 3052) | 2950 (2534 – 3251) | 2895 (2520 – 3431) | 2825 (2400 – 3100) | 2725 (2432 – 3272) | 0.963 |
| Low birth weight (< 2500 grams) | N (%) | 20/71 (28.2%) | 6/17 (35.3%) | 5/28 (17.9%) | 3/10 (30.0%) | 3/9 (33.3%) | 3 (42.9%) | 0.595 |
| Admission to NICU | N (%) | 23/72 (31.9%) | 2/19 (10.5%) | 9/29 (31.0%) | 4/12 (33.3%) | 6/8 (75.0%) | 2/4 (50.0%) | **0.020** |
| Number of days admitted to NICU | Median (IQR) | 2 (1 – 3) | 2 (1 – 2) | 2 (1 – 3) | 2 (1 – 4) | 3 (1 – 4) | 2 (2 – 3) | 0.795 |
| Admission to NICU > 2 days | N (%) | 9/72 (12.5%) | 1/19 (5.3%) | 2/29 (6.9%) | 0 | 1/8 (12.5%) | 2/4 (50.0%) | 0.159 |
| Admission to ward | N (%) | 11/72 (15.3%) | 1 (4.8%) | 2 (6.4%) | 0 | 1 (9.1%) | 2 (28.6%) | 0.058 |
| Number of days admitted to ward | Median (IQR) | 1 (1 – 2) | 2 (2 – 2) | 1 (1 – 1) | 2 (1 – 3) | 1 (1 – 1) | 2 (1 – 2) | **0.026** |
| Admission to ward > 2 days | N (%) | 2 (2.4%) | 0 | 0 | 1 | 0 | 1 (14.3%) | 0.753 |
| Neonatal death | N (%) | 2/82 (2.4%) | 0 | 0 | 1/12 (8.3%) | 0 | 1 (14.3%) | 0.114 |
| Miscarriage | N (%) | 2/82 (2.4%) | 1 (4.8%) | 0 | 0/12 (0%) | 1 (9.1%) | 0 | 0.438 |
| | | | | | | | | |
| **Poor maternal outcome** | N (%) | 45 (54.2%) | 6 (28.6%) | 19 (61.3%) | 8 (61.5%) | 7 (63.6%) | 5 (71.4%) | 0.188 |
| **Poor neonatal outcomes** | N (%) | 48 (57.8%) | 10 (47.6%) | 15 (48.4%) | 8 (61.5%) | 9 (81.8%) | 6 (85.7%) | 0.389 |
| **Poor maternal or neonatal outcome** | N (%) | 66 (79.5%) | 13 (61.9%) | 24 (77.4%) | 11 (84.6%) | 11 (100%) | 7 (100%) | 0.014 |

* Per admission

ICU = Intensive Care Unit; mWHO = Modified World Health Organisation classification risk stratification tool; NICU = Neonatal Intensive Care Unit

Table 3A: Maternal and neonatal outcomes associated with cyanotic CHD and unrepaired CHD, as determined by univariable logistic regression analyses

| | Cyanotic CHD | | | Unrepaired CHD | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p-value | OR | 95% CI | p-value |
| **Maternal outcomes** | | | | | | |
| Poor maternal outcome | 1.500 | 0.466 – 5.329 | 0.506 | 1.350 | 0.551 – 3.342 | 0.512 |
| Antenatal hospitalisation | 2.908 | 0.903 – 10.364 | 0.081 | 1.382 | 0.568 – 3.401 | 0.477 |
| Perinatal ICU admission | 1.250 | 0.310 – 4.328 | 0.734 | 1.222 | 0.440 – 3.458 | 0.700 |
| | | | | | | |
| **Neonatal outcomes** | | | | | | |
| Poor neonatal outcomes | 0.341 | 0.029 - 7.920 | 0.405 | 2.182 | 0.196 – 48.899 | 0.536 |
| Preterm delivery (< 37 weeks) | 0.619 | 0.127 – 2.336 | 0.505 | 2.531 | 0.918 – 7.399 | 0.078 |
| Low birth weight (< 2500 grams) | 0.824 | 0.168 – 3.159 | 0.789 | 1.381 | 0.487 – 4.005 | 0.544 |
| Admission to NICU | 1.424 | 0.385 – 4.889 | 0.578 | 1.000 | 0.362 – 2.765 | 1.000 |
| Admission to general ward > 2 days | - | | | 0.667 | 0.022 - 20.326 | 0.794 |

ICU = Intensive Care Unit; NICU = Neonatal Intensive Care Unit

Table 4: Univariable and multivariable regression analysis for poor maternal and neonatal outcomes, as corrected for confounders previously described in the literature

| | Univariable regression analysis | | | Multivariable regression analysis | | |
|---|---|---|---|---|---|---|
| **Risk factor** | **OR** | **95% CI** | **p-value** | **OR** | **95% CI** | **p-value** |
| **Poor maternal outcome** | | | | | | |
| Age | 1.001 | 0.928 – 1.080 | 0.977 | 0.964 | 0.873 – 1.064 | 0.462 |
| Cyanotic CHD | 1.650 | 0.502 – 5.429 | 0.410 | 1.528 | 0.359 – 6.510 | 0.566 |
| Surgically repaired CHD | 1.412 | 0.587 – 3.395 | 0.441 | 0.618 | 0.170 – 2.248 | 0.465 |
| NYHA functional classes II, III or IV | 1.504 | 0.592 – 3.822 | 0.391 | 1.003 | 0.333 – 3.018 | 0.996 |
| Pulmonary hypertension | 2.769 | 0.525 – 14.611 | 0.230 | 1.133 | 0.132 – 9.745 | 0.909 |
| mWHO classes II, II-III, III or IV | 4.239 | 1.443 – 12.457 | **0.009** | 5.742 | 1.377 – 23.932 | **0.016** |
| | | | | | | |
| **Poor neonatal outcome** | | | | | | |
| Age | 1.112 | 1.020 – 1.212 | **0.016** | 1.128 | 1.016 – 1.252 | **0.024** |
| Cyanotic CHD | 0.683 | 0.216 – 2.162 | 0.517 | 0.731 | 0.183 – 2.918 | 0.657 |
| Surgically repaired CHD | 1.155 | 0.479 – 2.784 | 0.748 | 1.453 | 0.473 – 4.461 | 0.514 |
| NYHA functional classes II, III or IV | 0.634 | 0.245 – 1.639 | 0.347 | 0.654 | 0.216 – 1.975 | 0.451 |
| Pulmonary hypertension | 5.805 | 0.680 – 94.538 | 0.108 | 2.596 | 0.216 – 31.180 | 0.452 |
| mWHO classes II-III, III or IV | 3.105 | 1.176 – 8.200 | **0.022** | 1.403 | 0.444 – 4.431 | 0.564 |

CHD = Congenital Heart Disease; mWHO = Modified World Health Organisation classification risk stratification tool; NYHA = New York Heart Association classification of heart failure;

Figure 1: CHD Diagnoses

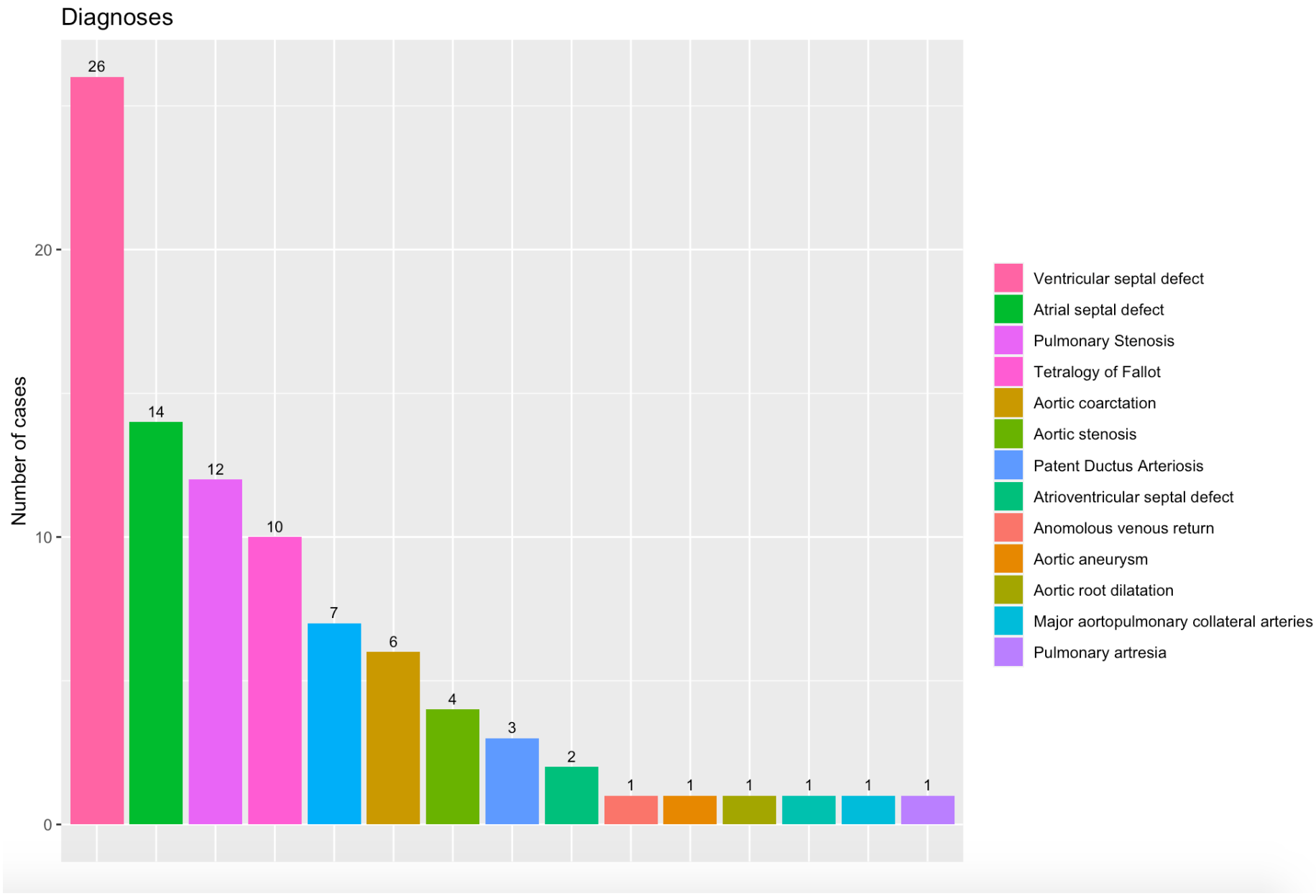

Figure 2A: Poor maternal outcome as categorised per Modified WHO classes

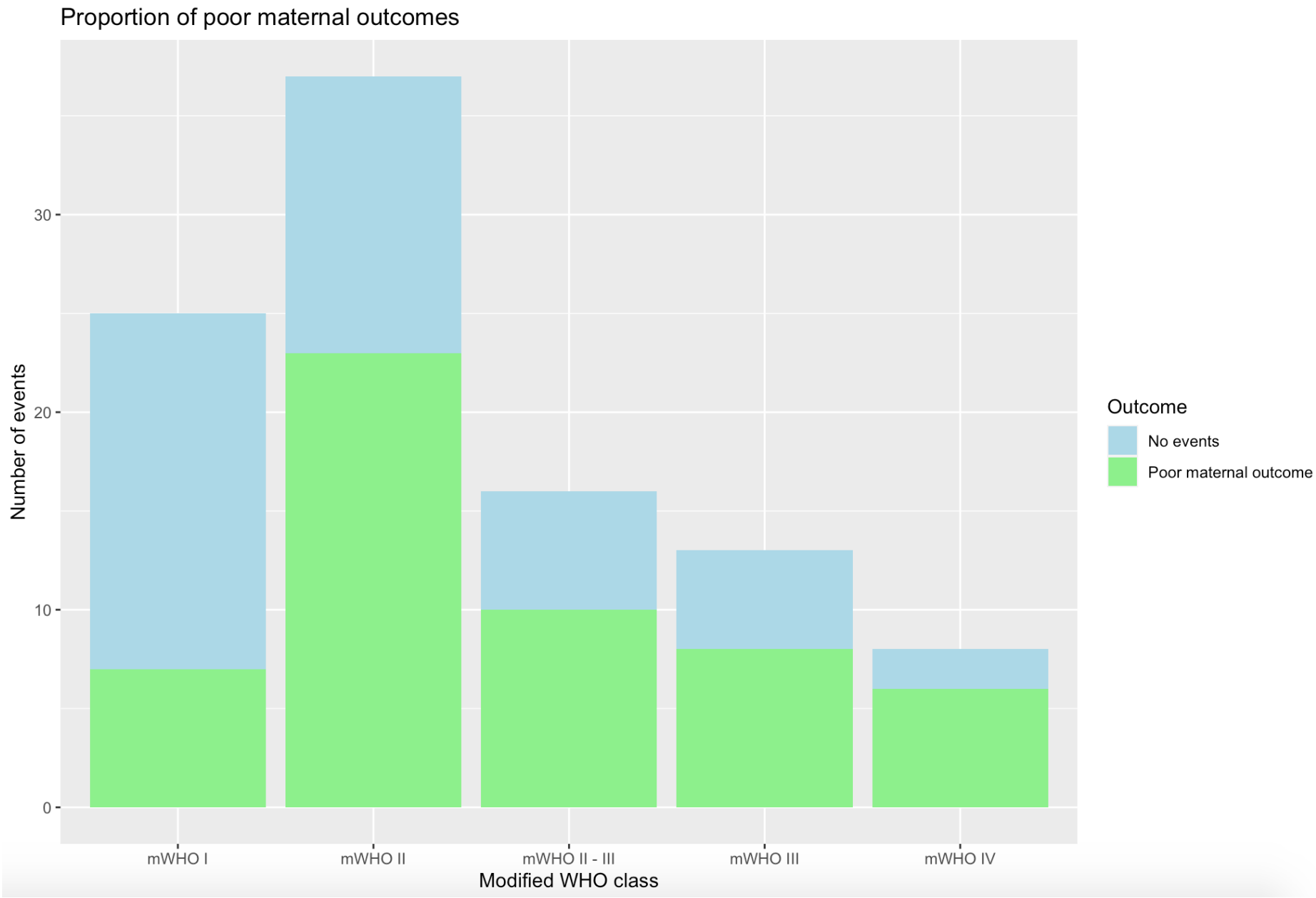

Figure 2B: Poor neonatal outcome as categorised per Modified WHO classes

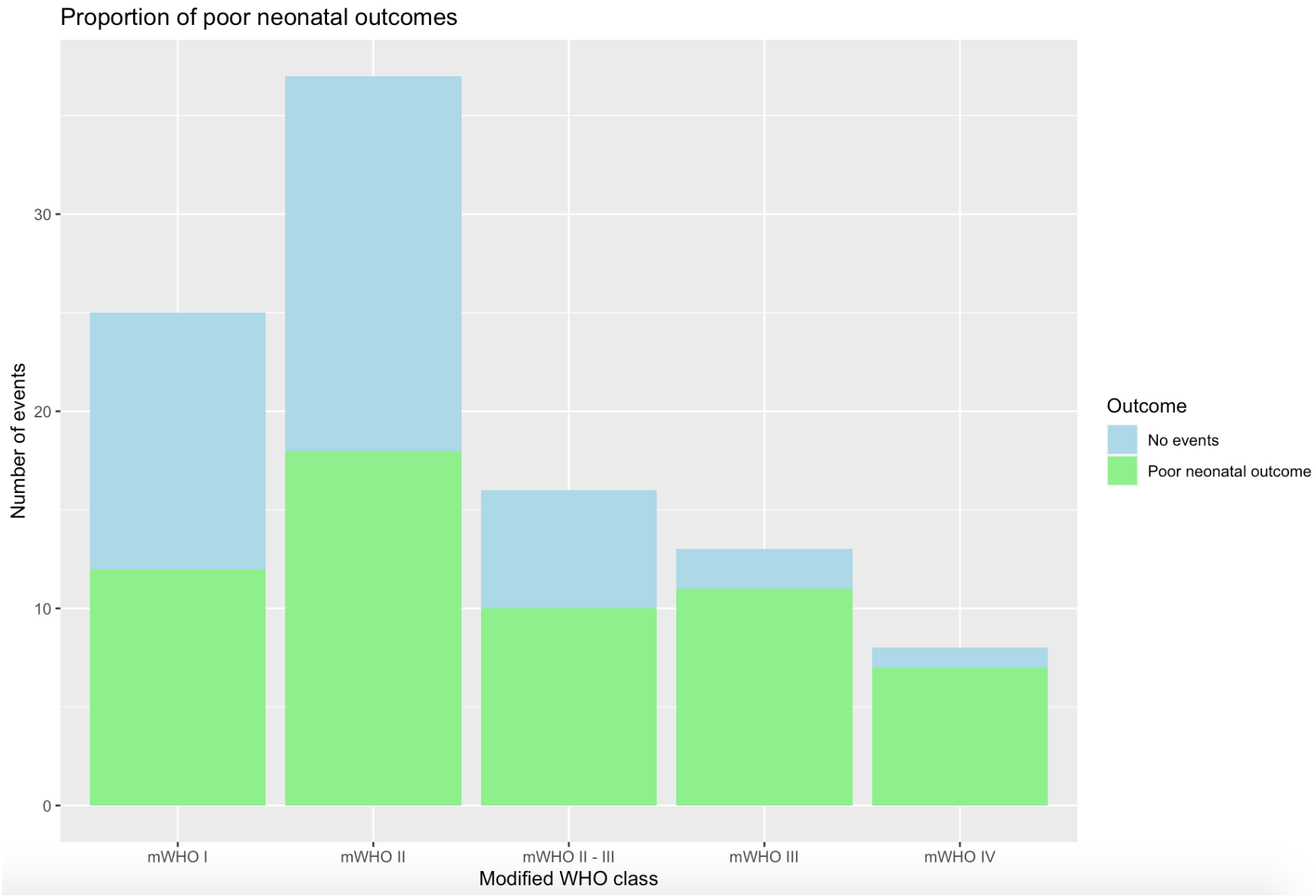

Figure 3: Maternal and neonatal outcomes associated with cardiovascular risk, as categorised by the Modified WHO classification, and as determined by univariable logistic regression analyses

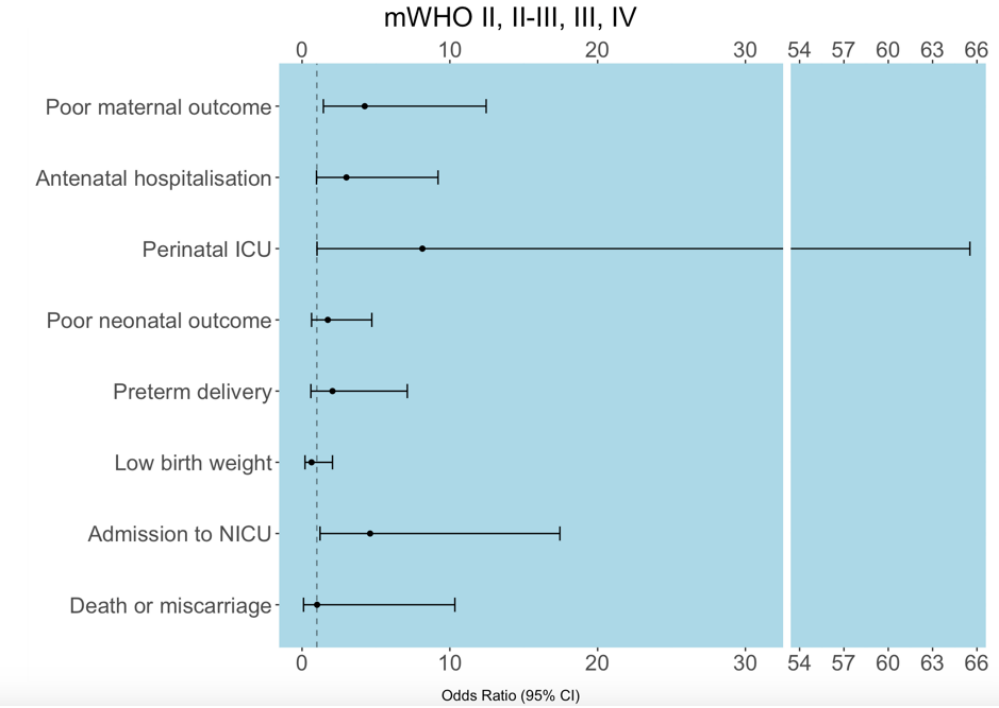


Figure 3A

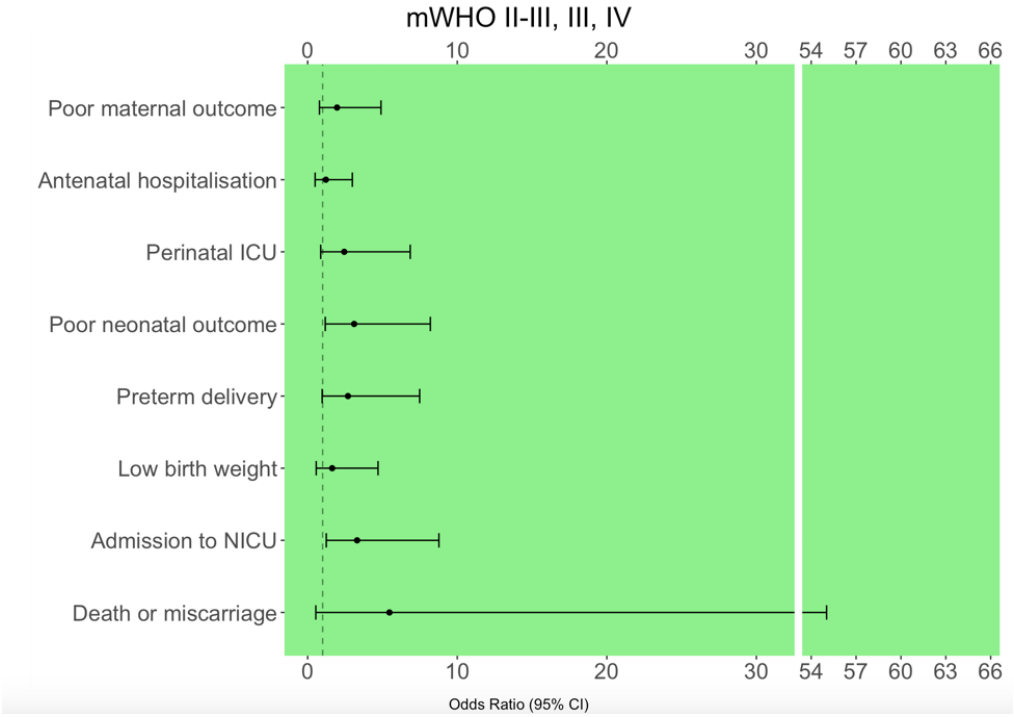


Figure 3B

Figure 3 (continued): Maternal and neonatal outcomes associated with cardiovascular risk, as categorised by the Modified WHO classification, and as determined by univariable logistic regression analyses

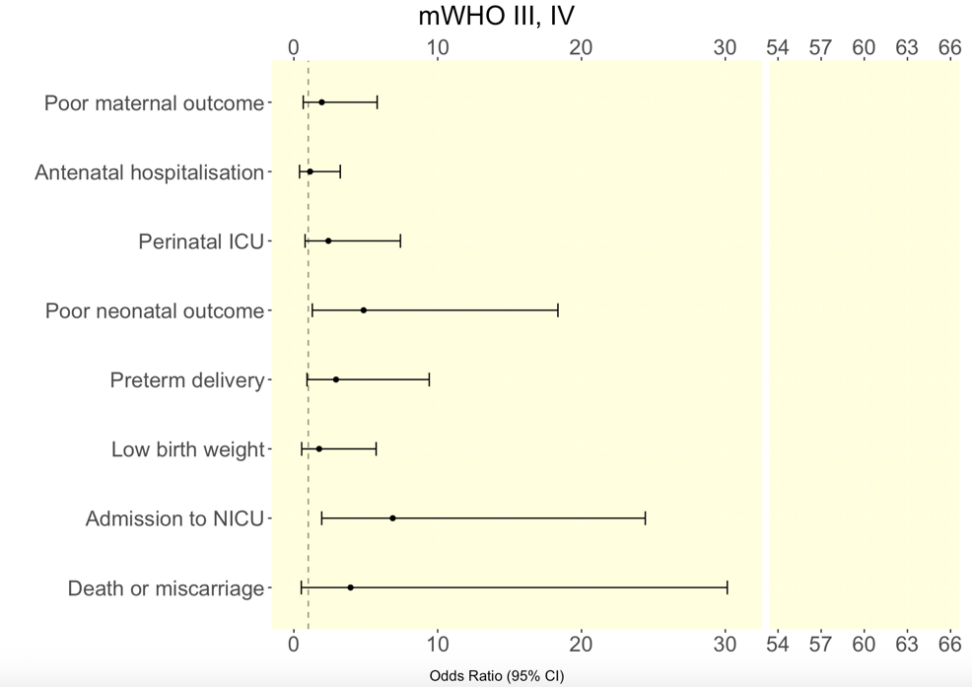


Figure 3C

Supplemental material

Table 3B: Maternal and neonatal outcomes associated with cardiovascular risk, as categorised by the Modified WHO classification, and as determined by univariable logistic regression analyses

| | Model 1 (mWHO II, II-III, III, IV) | | | Model 2 (mWHO II-III, III, IV) | | | Model 3 (mWHO III, IV) | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | p-value | OR | 95% CI | p-value | OR | 95% CI | p-value |
| **Maternal outcomes** | | | | | | | | | |
| Poor maternal outcome | 4.239 | 1.443 – 12.457 | **0.009** | 1.964 | 0.786 – 4.903 | 0.148 | 1.939 | 0.649 – 5.791 | 0.235 |
| Antenatal hospitalisation | 3.000 | 0.978 – 9.203 | 0.055 | 1.216 | 0.495 – 2.985 | 0.670 | 1.126 | 0.393 – 3.225 | 0.825 |
| Perinatal ICU admission | 8.142 | 1.012 – 65.526 | **0.049** | 2.444 | 0.871 – 6.858 | 0.089 | 2.399 | 0.777 – 7.409 | 0.128 |
| | | | | | | | | | |
| **Neonatal outcomes** | | | | | | | | | |
| Poor neonatal outcomes | 1.742 | 0.642 – 4.721 | 0.276 | 3.105 | 1.176 – 8.200 | **0.022** | 4.848 | 1.280 – 18.361 | **0.020** |
| Preterm delivery (< 37 weeks) | 2.059 | 0.595 – 7.121 | 0.254 | 2.692 | 0.968 – 7.485 | 0.058 | 2.929 | 0.911 – 9.411 | 0.071 |
| Low birth weight (< 2500 grams) | 0.642 | 0.200 – 2.059 | 0.456 | 1.636 | 0.569 – 4.704 | 0.361 | 1.757 | 0.540 – 5.719 | 0.349 |
| Admission to NICU | 4.604 | 1.215 – 17.444 | **0.025** | 3.304 | 1.244 – 8.775 | **0.017** | 6.875 | 1.934 – 24.437 | **0.003** |
| Admission to general ward > 2 days | - | | | - | | | 4.000 | 0.167 – 95.756 | 0.392 |
| Death or miscarriage | 1.017 | 0.100 – 10.341 | 0.989 | 5.464 | 0.543 – 55.030 | 0.150 | 3.938 | 0.514 – 30.140 | 0.187 |

ICU = Intensive Care Unit; NICU = Neonatal Intensive Care Unit

# PART C: Appendices

Appendix A:  Human Research Ethics Committee Approval letter

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

**Room G50- Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021] 406 6492
**Email:** hrec-enquiries@uct.ac.za
**Website:** www.health.uct.ac.za/fhs/research/humanethics/forms

12 November 2020

**HREC REF: 733/2020**

**Prof L Myer**
School of Public Health & Family Medicine
Entrance 5, Level 5, Room 5.51
Falmouth Building
Email: landon.myer@uct.ac.za
Student: elavilloen@yahoo.com

Dear Prof Myer

**PROJECT TITLE: MATERNAL AND FETAL OUTCOMES DURING AND AFTE NG WOMEN WITH CONGENITAL HEART DISEASE IN CAPE TOWN, SOUTH AFRICA: MASTERS CANDIDATE-MS ELANI MULLER-SUB-STUDY LINKED TO 173/2010**

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

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

**This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.**

**Approval is granted for one year until the 30 November 2021.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

***The HREC acknowledge that the student: Ms Elani Muller will also be involved in this study.***

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur

Yours sincerely

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

HREC/REF 733/2020sa

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF 733/2020sa

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

# FHS016: Annual Progress Report / Renewal

| HREC office use only (FWA00001637; IRB00001938)<br>This serves as notification of annual approval, including any documentation described below. | | | |
|---|---|---|---|
| ☑ Approved | Annual progress report | Approved until/next renewal date | 30/01/24 |
| ☐ Not approved | See attached comments | | |
| Signature Chairperson of the HREC/ Designee | | Date Signed | 3/2/2023 |

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

| Comments to PI from the HREC |
|---|
| Thank you for your Study Deviation<br>HREC Chair Signature<br>Date: 3/2/2023 |

## Principal Investigator to complete the following:

### 1. Protocol information

| | | | |
|---|---|---|---|
| Date (when submitting this form) | 26.01.2023 | | |
| HREC REF Number | 733/2020 | Current Ethics Approval was granted until | 30.11.2022 |
| Protocol title | Maternal and fetal outcomes during and after pregnancy among women with Congenital Heart Disease in Cape Town, South Africa | | |
| Protocol number (if applicable) | | | |
| Are there any sub-studies linked to this study? | ☐ Yes | ✓ No | |
| If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study. | | | |
| Principal Investigator | Prof Landon Myer | | |

HUMAN RESEARCH ETHICS COMMITTEE
31 JAN 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix B:  Human Research Ethics Committee Approval letter for parent study

# FHS016: Annual Progress Report / Renewal

| HREC office use only (FWA00001637; IRB00001938)<br>This serves as notification of annual approval, including any documentation described below. | | | |
|---|---|---|---|
| ☑ Approved | Annual progress report | Approved until/next renewal date | 31/01/2024 |
| ☐ Not approved | See attached comments | | |
| Signature Chairperson of the HREC/ Designee | | Date Signed | 17/1/2023 |

**Note:** Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

| Comments to PI from the HREC |
|---|
| |

## Principal Investigator to complete the following:

### 1. Protocol information

| | | | |
|---|---|---|---|
| Date (when submitting this form) | 16 January 2023 | | |
| HREC REF Number | 173/2010<br>262/2015-<br>See explanation below | Current Ethics Approval was granted until | 31 Jan 2023 |
| Protocol title | Cardiac Disease in Maternity Phase 2 (CDM II) | | |
| Protocol number (if applicable) | | | |
| Are there any sub-studies linked to this study? | ✓ Yes | ☐ No | |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)