

Prevalence and associated risk factors of adverse maternal
and newborn outcomes in inner-city Johannesburg: a cross-
sectional analysis of birth registers



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Declaration

I hereby declare that this research report is project work carried out by me under the guidance of Prof Lee Fairlie and Shobna Sawry. I have taken care in all respects to honour the intellectual property rights of others and have acknowledged the contribution of others. I further declare that the work reported in this project has not been submitted and will not be submitted, either in part or in full, for the award of any other degree or diploma in this institute or any other institute or university.

Hillbrow, Johannesburg, July 2024


Jean Gilbert le Roux

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Prof Lee Fairlie, Director: Maternal and Child Health, Wits RHI

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Dedication

This report is dedicated to the women of inner-city Johannesburg, who overcome vast adversities and difficult circumstances, all in the name of giving their children the best possible care.

Abstract

Background

Improved maternal and newborn health are important WHO sustainable development goal targets. In the inner-city of Johannesburg, a population with specific vulnerabilities, information on the extent of adverse maternal and neonatal outcomes is scarce. To address this gap, we aimed to estimate the prevalence and risk factors for adverse maternal and newborn outcomes among women and their infants in two inner-city health facilities in Johannesburg, South Africa.

Methods

Birth register data from the Hillbrow Community Healthcare Centre (HCHC) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) were extracted for deliveries from 1 July 2017-30 June 2018. Demographic and clinical data included age, comorbid conditions, obstetric history, intrapartum factors, maternal and newborn outcomes, and neonatal anthropometry. Prevalences of eight outcomes of interest were estimated: any hypertensive disorder, prolonged labour, haemorrhage, maternal death, preterm birth, low birth weight (LBW), stillbirth, and congenital anomalies. A separate logistic regression model was used for each outcome to determine risk factors associated with each outcome.

Results

Of the 11520 deliveries, 3018 (26.2%) were from HCHC and 8502 (73.8%) were from CMJAH. Most women (79.1%) were 20-34 years old, 6.6% of pregnancies were among adolescents and 13.8% among women aged >35 years. Of 8359 patients with nationality

recorded, 53.8% were South African, 31.9% were Zimbabwean, and 14.3% were from other (predominantly African) countries. Almost 5% of women had no record of antenatal care during pregnancy. Women living with HIV (WLHIV) comprised 26.8%; HIV status was unknown in 1.8%. The Caesarean Section rate was 50.5% at CMJAH and 37.3% overall.

Among pregnant women, 935 (8.1%) had a hypertensive disorder, 618 (5.4%) had prolonged labour in, and 447 (3.9%) had maternal haemorrhage. Risk factors for hypertensive disorders included maternal age >34 years (aOR 1.60 95% CI 1.34-1.91), nulliparity (aOR 1.18, 95% CI 1.00-1.39), and pre-existing diabetes (aOR 1.67, 95% CI 1.00-2.79), while HIV had a protective effect (aOR 0.69, 95% CI 0.58-0.82). Nulliparity was the only risk factor for prolonged labour (aOR 2.94 (95% CI 2.50-3.46). Risk factors for maternal haemorrhage were delivering by Caesarean section (aOR 1.71, 95% CI 1.30-2.26), pre-viable deliveries (aOR 3.46, 95% CI 1.83-6.53), preterm deliveries (aOR 2.51, 95% CI 1.97-3.18) post-term deliveries (>42 weeks) (aOR 2.85, 95% CI 1.12-7.24), retained placenta (aOR 7.01, 95% CI 3.65-13.49), and genital lacerations (aOR 1.66, 95% CI 1.25-2.21); hypertension had a protective effect (aOR 0.55, 95% CI 0.38-0.79). Five maternal deaths occurred (45 per 100 000 live births); all were preterm deliveries, and 3 (60.0%) had hypertensive disorders.

Multiple gestation occurred in 2.3% of deliveries; 11791 neonates were born, of which 48.6% were female. Among neonates, 24.3% were preterm (<37 weeks), 17.5% had LBW, 3% were stillborn, and 1.8% had congenital anomalies (most commonly polydactyly, unspecified dysmorphic features, club foot and umbilical hernia). Maternal factors associated with preterm birth included age <20 years (aOR 1.38, 95% CI 1.15-1.66), living with HIV (aOR 1.34, 95% CI 1.21-1.48), unknown HIV status (aOR 2.51, 95% CI 1.87-3.37), maternal hypertensive disorders (aOR 2.39, 95% CI 2.07-2.75), nulliparity (aOR 1.12, 95% CI 1.02-1.23), multiple gestation (aOR 6.37, 95% CI 5.28-7.68), placental abruption (aOR 3.46, 95% CI 1.76-6.77) and obstetric haemorrhage (aOR 2.43, 95% CI 1.98-3.00). Risk factors for LBW included

maternal age >34 (aOR 1.24 (95% CI 1.05-1.47), WLHIV and HIV unknown (aOR 1.61 (95% CI 1.41-1.83) and 1.73 (95% CI 1.19-2.53), respectively), nulliparity (aOR 1.32 (95% CI 1.14-1.52), gestational age <26W (aOR 87.17, 95% CI 54.53-139.34) and 26-36W (aOR 15.30, 95% CI 13.51-17.33), and multiple gestation (aOR 4.69, 95% CI 3.74-5.88). Stillbirth was significantly associated with unknown HIV status (aOR 2.55, 95% CI 1.58-4.12), maternal hypertensive disorders (aOR 1.84, 95% CI 1.33-2.57) and haemorrhage (aOR 3.57, 95% CI 2.41-5.29), birth before arrival (aOR 3.83, 95% CI 2.10-6.97), delivery at 26-36 weeks (aOR 2.61, 95% CI 1.84-3.70), LBW (aOR 10.56, 95% CI 7.44-15.00), and infant congenital anomalies (aOR 3.24, 95% CI 1.81-5.80). No significant associations were found with congenital anomalies in the multivariable model.

Conclusion

We report high prevalences of haemorrhage and preterm birth from birth registers in 2 inner-city health facilities in Johannesburg, South Africa. Women younger than 20 years or older than 35 years, and women living with HIV are at increased risk of certain adverse maternal outcomes and are more likely to deliver infants with adverse outcomes. Maternal and newborn health, important SDG targets, are difficult to achieve in vulnerable populations such as the inner-city of Johannesburg. The birth register maintained at delivery facilities is a useful source of routine information on maternal and early neonatal outcomes. Improving completeness of birth register data, and electronic data capture will allow for additional analyses that can help further examine inner-city maternal and neonatal health outcomes.

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179 Abbreviations

180

AMA	Advanced Maternal Age
aOR	Adjusted Odds Ratio
BBA	Born Before Arrival
CBD	Central Business District
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence Interval
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
GA	Gestational Age
ART	Antiretroviral Therapy
HCHC	Hillbrow Community Healthcare Centre
HELLP	Haemolysis, Elevated Liver Enzymes, Low Platelets
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight
LNMP	Last Normal Menstrual Period
MDG	Millennium Development Goals
MOU	Midwife Obstetric Unit
NVD	Normal Vaginal Delivery
OR	Odds Ratio
PET	Pre-Eclampsia
PPH	Post-Partum Haemorrhage
REDCap	Research Electronic Data Capture
RMMCH	Rahima Moosa Mother and Child Hospital
SDG	Sustainable Development Goals
SGA	Small For Gestational Age
SRH	South Rand Hospital
SSL	Secure Sockets Layer
STI	Sexually Transmitted Infection
WLHIV	Women Living With HIV

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Chapter 1 Introduction

Background

Maternal and neonatal health are two of the most important health problems of the current century (1). In the year 2000, improvement of both were selected as targets of the Millennium Development Goals (MDG) (2). More specifically, the goals were to reduce child mortality by two thirds, and the maternal mortality ratio by three quarters. The MDG identified major systemic and societal causes for poor outcomes in these categories, and mentioned Sub-Saharan Africa as one of the regions where these issues were prominent. Despite the weight attributed to these challenges, and intensive efforts to achieve these goals in South Africa, progress was hampered by a number of obstacles (3). Poverty was identified as the root cause of persistently high child mortality rates, while efforts to address maternal mortality were inadequately implemented (3). This means that the challenges described by the MDG still remain prominent in South Africa, and more work is required to make satisfactory progress. The MDG were replaced by the UN Sustainable Development Goals (SDG) in 2015 (4). This renewed the world's commitment to tackling the issues identified in the MDG, and maternal and child health featured very prominently once again. Importantly, accurate data are required to monitor progress towards the SDG as well as to inform health systems planning. These data need to be relevant to, and ideally sourced from, the context in which they are used. While data are widely available at the national level, data for smaller levels such as sub-districts or wards, are difficult to come by (5). One of the specific areas where such data are difficult to find is the inner-city of Johannesburg. This area, defined as Region F by the City of Johannesburg Metropolitan Municipality, comprises the central business district (CBD) and some peri-urban suburbs to the south. The high density and mobility of this population, large number of economic migrants, and presence of vulnerable populations like refugees and sex workers make it a

unique area that deserves directed attention (6). There are also major infrastructural challenges. Despite this, the area has been the site of various innovations in the healthcare space and is served by a relatively high number of healthcare facilities. These include: Hillbrow Community Healthcare Centre (HCHC) (a primary clinic with a midwife obstetric unit), South Rand Hospital (SRH) (a secondary hospital), and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) (a quaternary referral hospital). This is in addition to several primary care clinics that provide antenatal services but no delivery facilities. It is therefore valuable to estimate the prevalence and determine risk factors of adverse maternal and newborn outcomes that are specific to this area.

Literature Review

Extent of adverse maternal and newborn outcomes

A literature review was performed in PubMed searching for “maternal + neonatal outcomes inner-city Johannesburg.” Because of the low number of results, a date range was not applied to this search. The search was then widened to studies from elsewhere in South Africa. Lastly, to find known risk factors for the maternal outcomes under study, another search was performed in PubMed for each outcome as the MeSH major term, along with “epidemiology” or “risk factors.” The search was restricted first to systematic reviews, then any review if no systematic reviews were found, with priority given to articles released in the past five years, and articles focusing on Africa. Several studies have been conducted to quantify the extent of adverse maternal and neonatal outcomes in Africa. The 2021 MTN-042B study reviewed hospital files from 10138 mothers delivering in primary and tertiary facilities in Zimbabwe, Uganda, South Africa, and Malawi (7). The overall rate of HIV positivity was 13.8%, the Caesarean section rate was 26.0%, 12.7% of deliveries were premature, and 4.0% of pregnancies ended in stillbirth. Frequencies of a specific set of pregnancy complications were

233 reported: low birth weight (15.5%), any hypertension (10.6%), post-partum haemorrhage
 234 (PPH) (3.2%), endometritis (0.4%), chorioamnionitis (0.2%), and fever of unclear aetiology
 235 (0.1%). In the Tsepamo study in Botswana, data were abstracted from 142258 maternity
 236 records and assessed for outcomes (8). Common adverse events found for both adolescents and
 237 adults included sexually transmitted infections (STI) (31.6% and 31.4%, respectively), anaemia
 238 (18.5% and 15.5%, respectively), hypertensive disorders (17.2% and 19.2%, respectively),
 239 preterm birth (19.5% and 15.4%, respectively), and small for gestational age (SGA) (17.5%
 240 and 15.3%, respectively). Stillbirths occurred in 1.6% of deliveries among adolescents and
 241 1.5% among adults. In South Africa, a cohort study conducted in Kwa-Zulu Natal on 2850
 242 women enrolling for antenatal care in nine urban, semi-urban and rural clinics found that
 243 important maternal adverse outcomes were stillbirth (3.7%), spontaneous abortion (0.6%), and
 244 antenatal maternal death (0.2%) (9). In Johannesburg, a retrospective record review conducted
 245 from 2004-2012 in Soweto (located to the South-West of Johannesburg), focussed on maternal
 246 deaths at the Chris Hani Baragwanath Academic Hospital (CHBAH) maternity ward (10).
 247 Findings included declining mortality rates over time, with maternal mortality rates (MMR)
 248 dropping from 139 per 100 000 live births in 2004, to 86 per 100 000 live births in 2012. The
 249 most prominent causes of maternal mortality were nonpregnancy-related infection (39.9%),
 250 hypertensive disorders (16.5%), and obstetric haemorrhage (12.5%). Merwe et al. conducted a
 251 retrospective, observational cohort study on birth outcomes from 2004-2007 using data
 252 collected at routine clinical visits (11). Study sites were CMJAH and Rahima Moosa Mother
 253 and Child Hospital (RMMCH), a tertiary hospital located outside of the catchment area for the
 254 inner-city in the Western suburbs of Johannesburg. The analysis was restricted to women living
 255 with HIV (WLHIV) with low CD4 counts (< 250 cells/mm³) and their infants, and investigated
 256 the impact of duration and regimen of antiretroviral therapy (ART) on infant low birth weight
 257 (LBW). Common infant outcomes among WLHIV with low CD4 counts included low birth

weight (22.4%) and preterm birth (13.3%). In inner-city Johannesburg, a retrospective review of birth registers between 2008 and 2009 at HCHC and SRH, and between 2011 and 2012 at CMJAH, investigated the impact of antenatal care on birth outcomes (12). The prevalences of preterm birth were 0.3% at HCHC, 1.1% at SRH, and 26.9% at CMJAH respectively, while the rates of stillbirth were 4.3/1000 at HCHC, 3.9/1000 at SRH, and 28.0/1000 at CMJAH. While much information on adverse outcomes is available at country level, there is a lack of more recent data on outcomes in facilities in the inner-city of Johannesburg, and more research is required.

Risk factors for adverse outcomes

In terms of risk factors for adverse maternal outcomes, several papers focussed more broadly on the African region or worldwide, have reported risk factors for adverse maternal and neonatal outcomes. These studies are summarised in Appendix B. More specific to Southern Africa, Balkus et al., in the MTN 042B study, found hypertensive disorders to be significantly less common, and chorioamnionitis to be significantly more common, among mothers living with HIV than those who were HIV-negative in Malawi, South Africa, Uganda and Zimbabwe (7). Of note, the South African sites for this study were also HCHC and CMJAH, which assists in contextualising the findings from our study with recent statistics from the same sites. The increased risk of adverse birth outcomes among mothers living with HIV was also found in the Tsepamo study in Botswana (8). Specifically in adolescent pregnancies, the odds of anaemia (aOR 1.89, 95% CI 1.66-2.25), Caesarean section (aOR 1.49, 95% CI 1.3-1.72), very preterm birth at a gestational age (GA) under 32 weeks (aOR 1.35, 95% CI 1.0-1.8), and small for gestational age (aOR 1.37, 95% CI 1.20-1.58) were higher in adolescents living with HIV compared to those who were HIV-negative. In South Africa, a prospective cohort study in Kwa-Zulu Natal among women from both urban and rural settings, reported that adverse

outcomes (antenatal maternal death, spontaneous abortions, and stillbirths) were significantly associated with HIV infection (aOR 1.63, 95% CI 1.10-2.41) and non-hospital delivery (aOR 13.63, 95% CI 8.79-21.14), while enrolment from an urban environment was protective (aOR 0.39, 95% CI 0.18-0.86) (9). From the above studies, it appears likely that HIV is an important risk factor for adverse outcomes in the inner-city of Johannesburg. This is especially important considering the relatively high prevalence of WLHIV in the area: a 2021 study to assess the background rate of SARS-CoV-2 antibody seropositivity in pregnant women reporting for antenatal care in the inner-city reported an HIV positivity rate of 26.2% (13). Furthermore, hypertensive disorders, diabetes, haemorrhage, both advanced and adolescent maternal age, and prior history of pregnancy-related disorders, appear to be additional potentially important risk factors.

Problem Statement

There is a lack of recent data on maternal and newborn outcomes specific to the inner-city of Johannesburg. The most recent data reported from birth registers are from 2008-2012 (12). This makes it challenging for stakeholders at the health facilities supporting this population to plan and allocate resources effectively, and to meet the targets set by the SDG. Quantifying adverse maternal and newborn outcomes and determining the associated risk factors during pregnancy is vital to better identify women who are at risk, which in turn can potentially decrease the incidence of these outcomes. These data are also crucial for monitoring and tracking progress towards the UN SDG, for health systems planning, informing directions for further research in the field, and to determine the overall health of this specific population. In addition, the data may contribute to safety surveillance for use of medications and vaccinations in pregnant women. These data may also help establish valid and reliable outcome data, which can be used as a control group for clinical trials and surveillance (7). Without these data,

assessment of rates of adverse outcomes in clinical trials or as part of surveillance may be stymied.

Justification

There is a dearth of information on risk factors associated with adverse outcomes in this population. Current research, which is often restricted to geographical areas outside of the inner-city, has limited usefulness in being applied to this area, with its unique combination of high density, large migrant population, and concentration of vulnerable groups (6). This cross-sectional study aims to quantify the prevalence of adverse maternal and newborn outcomes and the risk factors associated with these outcomes, among women delivering in inner-city facilities in Johannesburg, South Africa. With the results from this study, health planning from the facility-level upwards can be tailored to the challenges faced by mothers and their neonates in this area. Furthermore, it can assist the decision-making of clinicians working in the area, tailoring care to specific needs. Information can also be used to educate mothers on their health challenges. This will hopefully contribute to improving health outcomes in this under-researched setting. While the inner-city of Johannesburg has unique characteristics, research from this area may also be generalised to other similar inner-city districts in Southern Africa and other countries. This will also help target important areas for future research. To this end, data were collected from birth registers in facilities in inner-city JHB, to evaluate adverse maternal and newborn outcomes.

Research Question

What is the prevalence of adverse maternal and newborn outcomes and the associated risk factors among mothers and their newborns who delivered at two inner-city hospitals in Johannesburg from 2017-2018?

333

334 **Aim**

335 To establish the prevalence of adverse maternal and newborn outcomes, and risk factors for
336 these outcomes, in Inner-City Johannesburg.

337

338 **Objectives**

- 339 1. To estimate the prevalence of adverse maternal and newborn outcomes such as
340 hypertensive disorders of pregnancy, haemorrhage, maternal death, low birth weight,
341 premature delivery, stillbirth and congenital anomalies in the study population.
- 342 2. To ascertain the prevalence of obstetric risk factors such as HIV infection, adolescent
343 pregnancy, nulliparity, and comorbid illness among those delivering at maternity units
344 in Inner-City Johannesburg
- 345 3. To investigate demographic and clinical factors associated with adverse pregnancy and
346 newborn outcomes in the study population.

347

Chapter 2 Methods

Study Design

Primary study: As a companion study to a clinical trial evaluating a group B streptococcus vaccine in pregnant women, a cross-sectional epidemiologic analysis was undertaken at various sites across South Africa to describe maternal and infant outcomes as a baseline comparator. Maternity case records for the study period (1 July 2017-30 June 2018) were randomly selected for detailed file review, with variables extracted from the clinical notes and evaluated for maternal and newborn risk factors and outcomes. As part of that study, the student (as an employee at Wits RHI, a research institution that was to participate in the clinical trial) designed a database to capture data from birth registers at CMJAH and HCHC, as these were the sites at which the clinical trial would be recruiting participants. Other inner-city facilities were not included, as they were not selected as recruiting facilities for the primary study. This birth register database was used as a sampling frame from which to randomly select files for the main analysis; it was not analysed as part of the primary study, and was therefore available for secondary analysis.

Nested secondary study: Results from this cross-sectional, secondary analysis are presented in this report. Data were extracted from the primary study using an existing database of birth register entries of all births taking place between 1 July 2017-30 June 2018 at both Charlotte Maxeke Johannesburg Academic Hospital and Hillbrow Community Healthcare Centre, Johannesburg, South Africa.

Study Sites

Birth Register data were collected from the Department of Obstetrics and Gynaecology at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and the Shandukani midwife obstetric unit (MOU) of the Hillbrow Community Healthcare Centre (HCHC), both in inner-city Johannesburg, Gauteng Province, South Africa. CMJAH is a tertiary centre accepting referrals from all over Gauteng province and even other provinces, while HCHC is a primary midwife obstetric unit. Complicated cases are referred from HCHC to CMJAH. This referral may occur at any point during antenatal care or delivery: women with previous adverse outcomes or known co-morbidities are referred at their first antenatal care visit to continue care at CMJAH; additionally, women who develop a complication during a previously normal pregnancy are also referred. A woman who presents for labour at HCHC but then develops a complication during or directly after labour may be referred and transferred urgently by ambulance to CMJAH; this also applies to neonates who develop complications, although in this scenario, their birth information (but not necessarily the outcome) would be captured in the HCHC birth register, as that is where the birth occurred. In addition to these referrals, a large number of deliveries at CMJAH include uncomplicated cases among patients living nearby who self-refer there, whether for reasons of convenience or because of a perception of improved quality of care. Maternity ambulances may also be diverted from HCHC to CMJAH if there are no free labour ward beds at HCHC. Overall, information from the birth registers indicates that around three quarters of deliveries at CMJAH and over 90% of deliveries at HCHC, are from women who report an address within the inner-city. This indicates that pooled data from the two facilities broadly represents patients within the inner-city; however, the referred, complicated patients from further afield mean that the CMJAH birth register may not be a fully representative reflection of the inner-city population.

Inclusion/exclusion criteria

Data for all women delivering at the above sites during the above time period were collected, with no inclusion or exclusion criteria applied. Birth register information for a two-week period in October 2017 were not available at CMJAH, as the registers for these dates could not be located; data for the High Care Unit and Obstetric Theatre were available during this time. All records (N = 11520) captured from the birth register into the database were included in the analysis. This included cases of multiple gestation, and women presenting with chronic conditions at their first ANC visit.

Study Population, sampling, and power

The database exceeds the necessary sample size to detect a proportion of 1% of any outcome with a 95% confidence interval of 0.008-0.012.

Data Collection

Data for 1 July 2017 to 30 June 2018 at both CMJAH and HCHC were collected from paper-based birth registers by a team of data capturers from December 2018 to April 2019, coordinated by the student, who was employed as a researcher at Wits RHI at the time. The birth register is a record of all births, that is kept at delivery facilities in South Africa. It is a ledger-type document where basic information on each delivery is recorded. This includes maternal age, HIV status, clinic where antenatal care was initiated (or a record to indicate that the patient did not attend antenatal care), gestational age at delivery, complications of labour, Apgar scores, birth weight, and neonatal complications, among others. The birth register is usually completed with information up to a patient's (and her child's) departure from the labour room; complications that develop subsequently are usually not recorded. A complete list of data available from the birth registers is included in Appendix C. Outcomes were written into

one or more free-text columns with headings such as “Complications, if any, after labour” (see Appendix D for details). During data capture, these were grouped and categorised into explicit outcomes as far as possible in the database. For example, free-text mention of “pre-eclampsia” or “PET” were captured using a single field titled “Pre-eclampsia (PET).” Conditions or outcomes of interest were also recorded in other spaces in the register, such as antepartum complications, post-partum complications, and indication for Caesarean section. These outcomes were not further reviewed in patient files, as these were not available during collection of birth register data. Outcomes or conditions recorded in the birth register were captured as an accurate clinical record of the diagnosis of that outcome or condition in that patient. The gestational age for each pregnancy was determined by the best available means during routine clinical care. In most cases this would have been done using the last normal menstrual period (LNMP) using pregnancy wheels, however if an ultrasound was available, foetal anthropometry would have been used instead. Where neither LNMP nor ultrasound were available, gestational age was calculated using the symphyseal-fundal height. It was, however, not possible to validate these gestational ages using any standardised criteria, as the method used for calculation was not captured in the birth register, and the patient files were not reviewed in order to validate gestational age dating. Two databases were designed by the student, specifically for the purpose of the study – one for CMJAH and one for HCHC. This was to accommodate the differences in the formats of birth registers used at the two sites, to ease data capture (see Limitations). Data were captured directly into these two databases. For cases recorded in two registers (Caesarean section or high-care patients), it was possible to cross-reference information in the two registers to check if data were recorded accurately. To prevent duplicate entries, for any given time period, the labour ward birth register was captured first; then, when capturing from the Caesarean section theatre and high-care registers, patient hospital numbers were cross-checked against existing entries. Where possible, variable names

were kept the same in the two databases. Where this was impossible, data were re-coded to ensure that both databases could be merged and analysed effectively. The student coordinated data extraction efforts and directly assisted the team of data capturers with queries related to the registers and the database, oversaw quality control activities, and captured some entries directly as required. A total of 8 502 and 3 018 records were captured at CMJAH and HCHC, respectively.

Data Management

The data were captured and stored in REDCap (Research Electronic Data Capture) databases hosted by the University of the Witwatersrand (16). REDCap is software for data capture and database storage, tailored for research use. It is secured by SSL (Secure Sockets Layer) encryption, as well as a firewall. The application server and database server are separate, and connections between the databases are tightly controlled. No data can be accessed without username and password authentication as well as manual approval to access data in a project by the owner of that project. A de-identified database was used for this analysis. The data were exported from REDCap with no identifying fields. Stata 15 (Statacorp LLC, College Station, USA) was used for all analyses. The two databases were merged into a single dataset for data cleaning, quality checks and analysis. Validation checks were performed on the database to check for missing data, implausible data, and out-of-range values. Values that were considered medically impossible and unable to be verified were changed to missing. Continuous variables were split into categories that are related to clinical care. Birth weight was categorised as normal ($\geq 2500\text{g}$) or low birth weight ($< 2500\text{g}$) as defined by the WHO (17); two neonates with no birthweight recorded had free-text mention of LBW or intrauterine growth restriction (IUGR) and were included among cases of LBW. Maternal age at time of delivery was categorized into adolescent (<20 years), usual age (20-34 years), and advanced maternal age

(≥ 35 years) (18,19). Parity was divided into nulliparous (0 previous deliveries), grande multipara (>4), and neither (1-4) (20). Gestational age at delivery was defined as pre-viable (<26 weeks), preterm (26-36 weeks) (21), term (37-42 weeks), and post-term (>42 weeks) (22). Congenital anomalies were classified based on free-text written notes, extracted from the “Congenital Anomalies”, “Emergency Ceasar Indication” and “Maternal Complications” fields. The categories used were: poly/syndactyly; club foot; umbilical hernia; minor skin discolorations or tags; down syndrome or other trisomy; hydrocephalus; neural tube defects; omphalocele/gastroschisis; albinism; cleft lip and/or palate. Additionally, a category “unspecified dysmorphic features” was created for cases where a clear diagnosis was not available, such as “abnormal head shape” or “gross abnormalities;” and the category “cannot be classified/other” was created for cases where a diagnosis did not fit into the main categories or was otherwise unspecified.

Data Analysis

Descriptive statistics included proportions and 95% confidence intervals of demographic and clinical characteristics (potential exposure variables) for categorical variables, and medians and interquartile ranges (IQR) for continuous variables. These exposure variables are summarised in Table 2.1.

Table 2.1. Exposure variables (demographic and clinical characteristics) considered in the study

Variable category	Variables
Demographics	Race; nationality; age
Past medical history	HIV status, hypertension, diabetes, cardiac disease
Obstetric history	Parity, gravidity, previous miscarriage, antenatal booking status
Intrapartum	Location of delivery, born before arrival, mode of delivery, multiple gestation, gestational age

Newborn	Birth weight, congenital anomaly
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Study outcomes are listed in Table 2.2. Maternal outcomes were hypertensive disorders, haemorrhage, maternal death and prolonged labour, and neonatal outcomes were preterm birth, low birth weight, stillbirth, and congenital anomaly. Outcomes were assigned according to the outcome recorded in the birth register for that patient. Since the way in which these outcomes were diagnosed was not described clearly in the birth register (such as the difference between chronic hypertension and pregnancy-induced hypertension), outcomes were grouped into broad categories (“hypertensive disorders”). Table 2.2 also outlines the free-text source fields and the keywords that were used and combined to define each variable.

Prevalences for each demographic and clinical characteristic were calculated and stratified by each of the outcomes under study. Maternal deaths were excluded from this and subsequent analyses, as the low number of cases made analysis unfeasible; instead, a case-series is depicted detailing relevant individual-level demographic and clinical features.

To determine risk factors for each adverse pregnancy outcome, logistic regression models were used, with separate models constructed for each outcome variable. Univariate logistic regression models were used to determine the unadjusted odds ratios for each potential risk factor. This included all variables that could reasonably be associated with the outcome under study.

Multivariable models were then constructed for each outcome. Variables for each multivariable model were selected using a stepwise reverse-selection process, with a significance cut-off of

25%. Delivery site (CMJAH vs. HCHC) was included in all multivariable models to account for site-specific differences in the rates of risk factors and outcomes.

518

Table 2.2 Outcome variables considered in the study

Outcomes		Source Fields on Birth Register	Free-text keywords used to create composite outcome variable
Maternal outcomes	Hypertensive disorders of pregnancy	“Antepartum Complications” “Emergency Caesar reason” “Maternal status/complications post-natal”	Eclampsia, Severe pre-eclampsia (PET), Imminent eclampsia, HELLP (haemolysis, elevated liver enzymes, low platelets) Syndrome, High Blood Pressure (BP), Hypertension, PIH; Pre-eclampsia (PET), or similar free text
	Maternal haemorrhage	“Antepartum Complications” “Emergency Caesar reason” “Maternal status/complications post-natal”	Antepartum Haemorrhage (APH) / Per-vaginal bleeding (PV), Post-partum haemorrhage (PPH), Blood transfusion
	Maternal death	“Maternal status/complications post-natal”	Maternal death
	Prolonged labour	“Antepartum Complications” “Emergency Caesar reason”	Poor progress/Failure to progress/Prolonged labour/Prolonged stage
Newborn outcomes	Preterm birth	Gestational age “Antepartum Complications” “Infant outcome/complications” includes	Gestational age < 37 weeks Pre-term labour (PTL), Pre-term birth
	Birth weight/intra-uterine growth restriction (IUGR)	“Infant outcome/complications” “Antepartum Complications” Birth weight	Birth weight < 2500g Low birth weight Small for gestational age, Small for dates
	Congenital anomalies	“Emergency Caesar reason” “Infant outcome/complications” “Were any abnormalities noted?”	Congenital anomaly, major congenital anomaly
	Stillbirth	“Antepartum Complications” “Emergency Caesar reason” “Infant status” “Infant outcome/complications”	Intrauterine death (IUD/IUFD), Stillbirth, FSB, MSB APGAR scores = 0 at 1, 5, and 10 minutes

		APGAR scores	
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Additionally, based on the literature, specific exposure variables that were known to be associated with each respective outcome variable, were included *a priori* (“locked”) in the model prior to the stepwise selection. Appendix E lists known risk factors for each outcome. In cases where no direct variable was available, a proxy was used; where no proxy was available, the risk factor was not included in the model. The proxies used, and cases where no proxy was available, are described in detail in Appendix E. This multivariable model was then used to determine the final set of risk factors for each adverse outcome.

Some potential exposure variables could not be included in any models. Since race was only captured in the CMJAH birth register, it was not included in any analyses. Similarly, the proportion of missing nationality differed greatly between the sites: 3.9% (328/8502) of mothers delivering at CMJAH had missing nationality, while 93.9% (2833/3018) of mothers delivering at HCHC had no nationality recorded. Antenatal booking status, an indicator of whether a pregnant woman attended antenatal care or not, was disproportionately more frequently missing at CMJAH (25.4%) compared to HCHC (2.0%) and was therefore also not included in the regression models.

Ethical Considerations

Approval for the primary study was received from the Wits Human Research Ethics Committee (Medical) – ethics reference number 1870707 (Appendices F and G). For that application, the requirement for informed consent was waived as it would have been impossible to retroactively contact all the mothers to ask for consent. For the current study, the waiver of informed consent

continued to be applied. The submission was approved by the Wits Human Research Ethics Committee (Medical) (ethics application study reference number M220310 MED22-01-090) (Appendix H). Permission for research to be conducted was granted by Professor Lee Fairlie, gatekeeper of the birth register database, as well as by Ms. Gladys Bogoshi, CEO of CMJAH, and Professor Shabir Moosa, Chairman of the Johannesburg District Research Committee, on behalf of HCHC. The following measures were applied to ensure patient confidentiality during data extraction and analysis: only de-identified data, with all personally identifying information removed and dates perturbed as required, were analysed; and data were subject to high standards of protection (encrypted in the primary database and accessible only to authorized users, protected by password). Any identifiable data needed, e.g. for data verification were kept in a secured linking file, separate from any clinical data. Data for analysis were saved on Wits RHI's encrypted, secure cloud-based storage, with encryption connected to Authorised Directory user authentication (i.e. only users with the correct username and password login details were able to access the data; sharing of such information to other individuals is prohibited by Wits RHI IT policy). Wits RHI devices are also all equipped with antivirus software to protect against virus and malware threats.

Chapter 3 Results

Population characteristics are described for the entire population, followed by the results from the regression models for each maternal and neonatal outcome.

Population Characteristics

Between 1 July 2017 and 30 June 2018, a total of 11520 births were recorded in the birth registers: 3018 (26.20%) at HCHC and 8502 (73.80%) at CMJAH (Table 3.1). Overall, 6.61% of delivering mothers were adolescents under 20 years of age, and 13.82% were of advanced maternal age (AMA), 35 years or older. The percentages differed between the sites: HCHC had more adolescent pregnancies at 8.18% vs. 6.06%, while CMJAH had 16.21% AMA vs. 7.09% at HCHC. Overall, 26.82% (3090/11520) of women were living with HIV, with 29.52% at HCHC and 25.86% at CMJAH. HIV status was missing/unknown in 1.78% of cases. At both centres, most mothers had a parity of 1-4 (74.12% at HCHC and 70.03% at CMJAH respectively). Both nulliparity (28.43% at CMJAH vs. 24.69% at HCHC) and grande multipara (1.13% at CMJAH vs. 0.23% at HCHC) were higher at the referral centre. Race was captured only in the CMJAH birth register. Of the 8502 deliveries at CMJAH, 8306 (97.72%) of deliveries at CMJAH were to Black African mothers. Nationality was captured sporadically. At CMJAH, 3.86% (328/8502) of delivering mothers had no nationality captured, while 93.87% (2833/3018) were missing/unknown at HCHC. Of the remaining 8359 patients with nationality recorded, 4498 (53.81%) were South African, 2666 (31.89%) were Zimbabwean, and 1195 (14.30%) were from other (predominantly African) countries. As the tertiary referral centre, CMJAH reported more miscarriages (1.66%, 141/8502), pre-term deliveries (24.39%, 2074/8502) and post-term deliveries (0.66%, 56/8502) than HCHC (0.44%, 15.34% and 0.13%, respectively). At HCHC, 6.43% (194/3018) of patients had no record of any antenatal care, compared to 4.13% (351/8502) at CMJAH, although 33.69% (2864/8502) of patients at

CMJAH had no information on whether or not they received antenatal care, since no antenatal clinic was recorded for them in the birth register. HCHC had a higher rate of babies born before arrival at the facility (BBA) compared to CMJAH (7.69% vs. 1.33%, respectively). Multiple gestation was more common at CMJAH, 2.95% compared to 0.46% at HCHC. At CMJAH, 50.47% of deliveries were via Caesarean section, 44.92% were normal vaginal deliveries (NVD), 1.29% were assisted vaginal deliveries, and 3.32% unknown. Conversely, at HCHC, most deliveries were NVD (98.34%), and the remainder were “unknown” where details of the delivery (including normal deliveries or instrument-assisted deliveries) was not recorded. Overall, of 11791 neonates, 5735 (48.64%) were female, 5696 (48.31%) were male, five (0.04%) were cases where the sex was atypical, and 355 (3.01%) did not have the neonate’s sex recorded.

600 *Table 3.1 Demographic and clinical characteristics of 11520 women and 11791 neonates who*
 601 *had a birth outcome between 1 July 2017 and 30 June 2018*

Maternal Variables	Total n (%) N = 11520	HCHC n (%) N = 3018 (26.20%)	CMJAH n (%) N = 8502 (73.80%)
Age at delivery			
<20 (adolescent)	762 (6.61%)	247 (8.18%)	515 (6.06%)
20-34	9117 (79.14%)	2543 (84.26%)	6574 (77.32%)
>34 (advanced maternal age)	1592 (13.82%)	214 (7.09%)	1378 (16.21%)
Missing/Unknown	49 (0.43%)	14 (0.46%)	35 (0.41%)
Race (CMJAH only)			
Black African	8306 (97.72%)	N/A	8306 (97.72%)
Coloured	56 (0.66%)		56 (0.66%)
Asian	31 (0.36%)		31 (0.36%)
White	72 (0.85%)		72 (0.85%)
Missing/Unknown	31 (0.36%)		31 (0.36%)
Nationality			
South African	4498 (39.05%)	52 (1.72%)	4446 (52.29%)
Zimbabwean	2666 (23.14%)	104 (3.45%)	2562 (30.13%)
Other ¹	1195 (10.37%)	29 (0.96%)	1166 (13.71%)
Missing/Unknown	3161 (27.44%)	2833 (93.87%)	328 (3.86%)
HIV Status			
Positive	3090 (26.82%)	891 (29.52%)	2199 (25.86%)
Negative	8225 (71.40%)	2106 (69.78%)	6119 (71.97%)
Missing/Unknown	205 (1.78%)	21 (0.70%)	184 (2.16%)
Parity			
0 (nulliparous)	3162 (27.45%)	745 (24.69%)	2417 (28.43%)
1-4	8191 (71.10%)	2237 (74.12%)	5954 (70.03%)
>4 (grande multipara)	103 (0.89%)	7 (0.23%)	96 (1.13%)
Missing/Unknown	64 (0.56%)	29 (0.96%)	35 (0.41%)
Gestational age at delivery			
<26 weeks (pre-viable – miscarriage)	154 (1.34%)	13 (0.43%)	141 (1.66%)
26-36 weeks (preterm)	2537 (22.02%)	463 (15.34%)	2074 (24.39%)
37-42 weeks (term)	8277 (71.85%)	2178 (72.17%)	6099 (71.74%)
>42 weeks (post-term)	60 (0.52%)	4 (0.13%)	56 (0.66%)
Missing/Unknown	492 (4.27%)	360 (11.93%)	132 (1.55%)
Any ANC in pregnancy			
Yes	8050 (69.88%)	2763 (91.55%)	5287 (62.19%)
No	545 (4.73%)	194 (6.43%)	351 (4.13%)
Missing/Unknown	2025 (25.39%)	61 (2.02%)	2864 (33.69%)
Born before arrival at facility (BBA)			
No	11059 (96.00%)	2707 (89.70%)	8352 (98.24%)
Yes	345 (2.99%)	232 (7.69%)	113 (1.33%)
Missing/Unknown	116 (1.01%)	79 (2.62%)	37 (0.44%)
Multiple gestation	265 (2.30%)	14 (0.46%)	251 (2.95%)
Mode of delivery			
NVD	6787 (58.92%)	2968 (98.34%)	3819 (44.92%)
Assisted VD	110 (0.95%)	0 (0.00%)	110 (1.29%)
Caesarean section	4291 (37.25%)	0 (0.00%)	4291 (50.47%)
Missing/Unknown	332 (2.88%)	50 (1.66%)	282 (3.32%)
Neonatal Variable	Total n (%) N = 11791	HCHC n (%) N = 3032 (25.71%)	CMJAH n (%) N = 8759 (74.29%)
Sex			
Female	5735 (48.64%)	1549 (51.09%)	4186 (47.79%)
Male	5696 (48.31%)	1450 (47.82%)	4246 (48.48%)
Atypical	5 (0.04%)	2 (0.07%)	3 (0.03%)
Missing/Unknown	355 (3.01%)	31 (1.02%)	324 (3.70%)

¹ Other nationalities included 37 countries, mostly African but also from Europe and Asia.

603

604 **Adverse maternal outcomes**605 **Hypertensive Disorders of Pregnancy**

606 Of 11520 deliveries, 935 (8.12%) were diagnosed with a hypertensive disorder of pregnancy
 607 (Table 3.2). As expected from a referral centre, the majority of these delivered at CMJAH
 608 (99.47%, 930/935). Most mothers with a hypertensive disorder were aged 20-34 years old
 609 (72.83%, 681/935), while those with advanced maternal age accounted for a further 21.82%
 610 (204/935); only 4.81% (45/935) were <20 years old. Among women with a hypertensive
 611 disorder, a comparatively low proportion were living with HIV (20.43%, 191/935). Almost
 612 30% of women with hypertensive disorders were nulliparous (29.52%, 276/935), and 2.03%
 613 (19/935) had diabetes.

614 Given the higher number of hypertensive cases seen at CMJAH, expected since this was a
 615 referral hospital, the odds of having a hypertensive disorder among mothers delivering at
 616 HCHC was significantly lower than CMJAH in the multivariable analysis (aOR 0.01, 95% CI
 617 0.01-0.04) (Table 3.3). Being an adolescent (<20 years) was significantly protective against
 618 having a hypertensive disorder in pregnancy (aOR 0.71, 95% CI 0.51-0.99). Conversely,
 619 advanced maternal age (>34 years) was a risk factor for hypertensive disorders (aOR 1.60, 95%
 620 CI 1.34-1.91). Of 3090 WLHIV, 191 (6.18%) had hypertensive disorders. The odds of
 621 hypertensive disorders were significantly lower among WLHIV than those who were HIV-
 622 negative, with very similar odds ratios and confidence intervals in both models (aOR 0.69, 95%
 623 CI 0.58-0.82). Nulliparous women (parity=0) and women with diabetes also had a significantly
 624 increased risk of hypertensive disorders (aOR 1.18, 95% CI 1.00-1.39 and aOR 1.67, 95% CI
 625 1.00-2.79, respectively). While having cardiac disease was a significant risk factor in the
 626 univariate model (OR 2.51, 95% CI 1.30-4.83), this effect did not persist in the multivariable

627 model. Previous miscarriage and multiple gestation were not significantly associated with
 628 hypertensive disorders.

629 *Table 3.2 Prevalence of maternal outcomes*

Outcome	Hypertensive disorder n (%)	Prolonged labour n (%)	Haemorrhage n (%)
N	935 (8.12%)	618 (5.36%)	447 (3.88%)
Birth site			
CMJAH	930 (99.47%)	610 (98.71%)	391 (87.47%)
HCHC	5 (0.53%)	8 (1.29%)	56 (12.53%)
Age			
<20 (adolescent)	45 (4.81%)	72 (11.65%)	18 (4.03%)
20-34	681 (72.83%)	496 (80.26%)	345 (77.18%)
>34 (advanced maternal age)	204 (21.82%)	48 (7.77%)	81 (18.12%)
Missing/Unknown	5 (0.53%)	2 (0.32%)	3 (0.67%)
HIV			
Negative	718 (76.79%)	490 (79.29%)	303 (67.79%)
Positive	191 (20.43%)	122 (19.74%)	128 (28.64%)
Missing/Unknown	26 (2.78%)	6 (0.97%)	16 (3.58%)
Hypertensive disorder			
No		590 (95.47%)	414 (92.62%)
Yes		28 (4.53%)	33 (7.38%)
Diabetes			
No	916 (97.97%)	615 (99.51%)	447 (100%)
Yes	19 (2.03%)	3 (0.49%)	0 (0%)
Cardiac disease			
No	924 (98.82%)	618 (100%)	444 (99.33%)
Yes	11 (1.18%)	0 (0%)	3 (0.67%)
Parity			
0 (Nulliparous)	276 (29.52%)	316 (51.13%)	104 (23.27%)
1-4	640 (68.45%)	298 (48.22%)	336 (75.17%)
5+ (Grande multipara)	17 (1.82%)	2 (0.32%)	4 (0.89%)
Missing/Unknown	2 (0.21%)	2 (0.32%)	3 (0.67%)
Previous miscarriage			
No	910 (97.33%)	612 (99.03%)	435 (97.32%)
Yes	25 (2.67%)	6 (0.97%)	12 (2.68%)
Born before arrival (BBA)			
No	928 (99.25%)	618 (100%)	438 (97.99%)
Yes	3 (0.32%)	0 (0%)	3 (0.67%)
Missing/Unknown	4 (0.43%)	0 (0%)	6 (1.34%)
Mode of delivery			
Normal vaginal delivery (NVD)	392 (41.93%)	217 (35.11%)	217 (48.55%)
Assisted vaginal delivery	13 (1.39%)	18 (2.91%)	1 (0.22%)
Caesarean section	501 (53.58%)	376 (60.84%)	221 (49.44%)

Outcome	Hypertensive disorder n (%)	Prolonged labour n (%)	Haemorrhage n (%)
N	935 (8.12%)	618 (5.36%)	447 (3.88%)
Missing/Unknown	29 (3.1%)	7 (1.13%)	8 (1.79%)
Multiple gestation			
No	912 (97.54%)	615 (99.51%)	434 (97.09%)
Yes	23 (2.46%)	3 (0.49%)	13 (2.91%)
Gestational age at birth			
<26 weeks (pre-viable – miscarriage)	38 (4.06%)	0 (0%)	14 (3.13%)
26-36 weeks (preterm)	354 (37.86%)	72 (11.65%)	186 (41.61%)
37-42 weeks (term)	529 (56.58%)	540 (87.38%)	236 (52.8%)
>42 weeks (post-term)	4 (0.43%)	3 (0.49%)	5 (1.12%)
Missing/Unknown	10 (1.07%)	3 (0.49%)	6 (1.34%)
Birth weight			
<2500 g (low birth weight)	342 (36.58%)	25 (4.05%)	133 (29.75%)
2500-4499 g (normal)	550 (58.82%)	549 (88.83%)	301 (67.34%)
≥4500 g (macrosomia)	6 (0.64%)	8 (1.29%)	1 (0.22%)
Missing/Unknown	37 (3.96%)	36 (5.83%)	12 (2.68%)
Congenital anomaly			
No	915 (97.86%)	606 (98.06%)	439 (98.21%)
Yes	20 (2.14%)	12 (1.94%)	8 (1.79%)
Retained placenta			
No	924 (98.82%)	614 (99.35%)	434 (97.09%)
Yes	11 (1.18%)	4 (0.65%)	13 (2.91%)
Prolonged labour			
No	907 (97.01%)		432 (96.64%)
Yes	28 (2.99%)		15 (3.36%)
Lacerations			
No	728 (77.86%)	444 (71.84%)	323 (72.26%)
Yes	207 (22.14%)	174 (28.16%)	124 (27.74%)
Haemorrhage			
No	902 (96.47%)	603 (97.57%)	
Yes	33 (3.53%)	15 (2.43%)	

630

631 **Prolonged Labour**

632 Of the 618 cases of prolonged labour (5.36%), 610 cases occurred at CMJAH (98.71%), while
633 8 (1.29%) occurred at HCHC (Table 3.2). There were 496 (80.26%) cases of prolonged labour
634 among those aged 20-34 years old; while 72 occurred in adolescents (11.65%) and only 48
635 cases (7.77%) occurred in those of advanced maternal age. Nulliparous women accounted for
636 just over half (51.13%, 316/618) of prolonged labour cases, while just under half (48.22%,

298/618) had 1-4 previous deliveries. Only six women had a previous miscarriage (0.97%). Most of the cases of prolonged labour delivered by Caesarean section (60.84%, 376/618), 35.11% (217/618) were delivered by NVD, and 2.91% (18/618) by assisted vaginal delivery. There were only three (0.49%) cases of multiple pregnancies among women with prolonged labour. Of women with prolonged labour, most pregnancies resulted in term deliveries (87.38%, 540/618), and most babies had a normal birth weight (88.83%, 549/618).

As expected, the odds of prolonged labour were significantly lower at HCHC than CMJAH: (aOR 0.04, 95% CI 0.02-0.09) (Table 3.3). Advanced maternal age (>34 years) was significantly protective against prolonged labour compared to those aged 20-34 years (aOR 0.62, 95% CI 0.46-0.86). Nulliparity was a significant risk factor (aOR 2.94, 95% CI 2.50-3.46) for prolonged labour, compared to women with 1-4 previous deliveries. Those with previous miscarriage had lower odds of prolonged labour (aOR 0.43, 95% CI 0.19-0.98) than those who did not. Compared to normal vaginal delivery, both assisted delivery (aOR 2.44, 95% CI 1.42-4.19) and Caesarean section (aOR 1.75, 95% CI 1.46-2.10) had higher odds of prolonged labour, though the temporality of this relationship could not be determined with the available data, making the association difficult to interpret. Significantly protective odds ratios against prolonged labour were seen in cases of multiple gestation vs. singleton pregnancy (aOR 0.27, 95% CI 0.08-0.84), preterm deliveries vs. term deliveries (aOR 0.65, 95% CI 0.49-0.86), and low birth weight vs. normal birth weight (aOR 0.27, 95% CI 0.17-0.41). Unknown gestational age had a significantly protective effect against prolonged labour compared to term deliveries (aOR 0.29, 95% CI 0.09-0.94), while unknown birth weight was a significant risk factor for prolonged labour (aOR 1.93, 95% CI 1.31-2.85). Of the 3090 WLHIV, 122 (3.95%) experienced prolonged labour; this association was significant in the univariate model (OR 0.65 95% CI 0.53-0.79) but not the multivariable model (aOR 0.92, 95% CI 0.74-1.14).

662 Diabetes, cardiac disease, and congenital anomalies were not significantly associated with
663 prolonged labour.

664 *Table 3.3 Risk factors for maternal outcomes*

Variable	Hypertensive Disorder n (%)		Prolonged labour n (%)		Haemorrhage n (%)	
	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)
Birth Site						
CMJAH	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)
HCHC	0.01 (0.01-0.03)	0.01 (0.01-0.04)	0.03 (0.02-0.07)	0.04 (0.02-0.09)	0.39 (0.30-0.52)	0.52 (0.38-0.72)
Age						
<20	0.78 (0.57-1.06)	0.71 (0.51-0.99)	1.81 (1.40-2.35)	1.28 (0.96-1.70)	0.62 (0.38-0.99)	0.67 (0.40-1.12)
20-34	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)
>34	1.82 (1.54-2.15)	1.60 (1.34-1.91)	0.54 (0.40-0.73)	0.62 (0.46-0.86)	1.36 (1.06-1.75)	1.18 (0.91-1.53)
Missing/Unknown	1.41 (0.56-3.56)	1.84 (0.67-5.02)	0.74 (0.18-3.05)	1.38 (0.31-6.08)	1.66 (0.51-5.36)	2.33 (0.68-7.90)
HIV						
Negative	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	
Positive	0.69 (0.58-0.81)	0.69 (0.58-0.82)	0.65 (0.53-0.79)	0.92 (0.74-1.14)	1.13 (0.92-1.40)	
Missing/Unknown	1.52 (1.00-2.31)	1.28 (0.84-1.97)	0.48 (0.21-1.08)	0.63 (0.27-1.46)	2.21 (1.31-3.73)	
Hypertensive disorder						
No			1 (base)	1 (base)	1 (base)	1 (base)
Yes			0.52 (0.36-0.77)	0.45 (0.30-0.66)	0.90 (0.63-1.29)	0.55 (0.38-0.79)
Diabetes						
No	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	
Yes	2.76 (1.66-4.57)	1.67 (1.00-2.79)	0.55 (0.18-1.76)	0.47 (0.15-1.52)	— ¹	—
Cardiac disease						
No	1 (base)	1 (base)	1 (base)		1 (base)	
Yes	2.51 (1.30-4.83)	1.77 (0.91-3.43)	— ²	—	1.28 (0.40-4.11)	
Parity						
0	1.13 (0.97-1.31)	1.18 (1.00-1.39)	2.94 (2.50-3.46)	2.62 (2.18-3.15)	0.80 (0.64-0.99)	0.80 (0.63-1.03)
1-4	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)
5+	2.33 (1.38-3.95)	1.45 (0.85-2.49)	0.52 (0.13-2.14)	0.62 (0.15-2.57)	0.94 (0.35-2.58)	0.69 (0.25-1.94)

Variable	Hypertensive Disorder n (%)		Prolonged labour n (%)		Haemorrhage n (%)	
	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)
Missing/Unknown	0.38 (0.09-1.56)	0.39 (0.09-1.76)	0.85 (0.21-3.51)	1.42 (0.33-6.21)	1.15 (0.36-3.68)	1.52 (0.45-5.09)
Previous miscarriage						
No	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	
Yes	1.43 (0.94-2.17)	0.95 (0.62-1.46)	0.48 (0.21-1.08)	0.43 (0.19-0.98)	1.41 (0.78-2.54)	
BBA*						
No					1 (base)	
Yes					0.21 (0.07-0.67)	
Missing/Unknown					1.32 (0.58-3.02)	
Mode of delivery*						
NVD			1 (base)	1 (base)	1 (base)	1 (base)
Assisted			5.92 (3.51-9.99)	2.44 (1.42-4.19)	0.28 (0.04-2.00)	0.23 (0.03-1.70)
Caesar			2.91 (2.45-3.45)	1.75 (1.46-2.10)	1.64 (1.36-1.99)	1.71 (1.30-2.26)
Missing/Unknown			0.65 (0.30-1.40)	0.53 (0.24-1.19)	0.75 (0.37-1.53)	0.68 (0.32-1.46)
Multiple gestation						
No	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	
Yes	1.08 (0.70-1.66)	0.82 (0.53-1.27)	0.20 (0.06-0.62)	0.27 (0.08-0.84)	1.29 (0.73-2.26)	
GA at birth*						
<26 weeks			— ³	—	3.41 (1.94-5.99)	3.46 (1.83-6.53)
26-36 weeks			0.42 (0.33-0.54)	0.65 (0.49-0.86)	2.70 (2.21-3.28)	2.51 (1.97-3.18)
37-42 weeks			1 (base)	1 (base)	1 (base)	1 (base)
>42 weeks			0.75 (0.24-2.42)	0.46 (0.14-1.51)	3.10 (1.23-7.81)	2.85 (1.12-7.24)
Missing/Unknown			0.09 (0.03-0.27)	0.29 (0.09-0.94)	0.42 (0.19-0.95)	0.63 (0.27-1.47)
Birth weight*						
<2500 g			0.21 (0.14-0.31)	0.27 (0.17-0.41)	2.23 (1.80-2.75)	1.19 (0.91-1.56)
2500-4499 g			1 (base)	1 (base)	1 (base)	1 (base)
≥4500 g			3.01 (1.41-6.44)	2.06 (0.94-4.53)	0.61 (0.08-4.40)	0.54 (0.07-3.92)
Missing/Unknown			1.88 (1.32-2.68)	1.93 (1.31-2.85)	1.09 (0.60-1.96)	0.89 (0.48-1.66)

Variable	Hypertensive Disorder n (%)		Prolonged labour n (%)		Haemorrhage n (%)	
	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)
Congenital anomaly*						
No			1 (base)		1 (base)	
Yes			0.98 (0.54-1.75)		0.89 (0.44-1.82)	
Retained placenta*						
No					1 (base)	1 (base)
Yes					6.35 (3.43-11.75)	7.01 (3.65-13.49)
Prolonged labour*						
No					1 (base)	1 (base)
Yes					0.60 (0.36-1.02)	0.62 (0.36-1.05)
Lacerations*						
No					1 (base)	1 (base)
Yes					0.87 (0.70-1.07)	1.66 (1.25-2.21)

* Certain explanatory variables were not included in the models for outcome definitions, where that explanatory variable could not be a risk factor for that outcome.

¹ No cases of diabetes in those with haemorrhage – 98 observations not used.

² No cases of cardiac disease in those with prolonged labour – 61 observations not used.

³ No cases of GA <26 weeks in those with prolonged labour – 154 observations not used.

666 Maternal Haemorrhage

667 Of the 11520 mothers delivering in the study, 447 (3.88%) had a reported obstetric
 668 haemorrhage, including placenta praevia, abruption, and postpartum haemorrhage (Table 3.2).
 669 Those with haemorrhage delivered more often at CMJAH (87.47%, 391/447) than at HCHC
 670 (12.53%, 56/447). In nearly half of the cases of haemorrhage, delivery was by Caesarean
 671 section (49.44%, 221/447), compared to 48.55% (217/447) delivering by NVD. While 236
 672 cases of haemorrhage (52.8%) delivered at term, 41.61% (186/447) delivered preterm, a further
 673 3.13% (14/447) were pre-viable (miscarriages) and 1.12% (5/447) were post-term deliveries.
 674 Genital lacerations (grades 1, 2 and 3 vaginal tears and episiotomies) were present in 27.74%
 675 (124/447) of cases of haemorrhage, and retained placenta in 2.91% (13/447) of cases.

676 Since deliveries occurring at HCHC were less complex, those delivering there were less likely
 677 to experience haemorrhage than those delivering at CMJAH (aOR 0.52, 95% CI 0.38-0.72)
 678 (Table 3.3). While adolescent pregnancy was significantly associated with haemorrhage in the
 679 univariate analysis (OR 0.62, 95% CI 0.38-0.99), this effect did not persist in the multivariable
 680 model. Mothers who were hypertensive had significantly lower odds of developing of maternal
 681 haemorrhage than those who were not hypertensive (aOR 0.55, 95% CI 0.38-0.79). Mothers
 682 delivering by Caesarean section had a significantly higher odds of developing haemorrhage
 683 than those delivering by NVD (aOR 1.71, 95% CI 1.30-2.26). Pre-viable deliveries (aOR 3.46,
 684 95% CI 1.83-6.53), preterm deliveries (aOR 2.51, 95% CI 1.97-3.18) and post-term deliveries
 685 (>42 weeks) (aOR 2.85, 95% CI 1.12-7.24) were significantly associated with haemorrhage
 686 compared to term deliveries. Retained placenta was significantly associated with haemorrhage,
 687 with an adjusted odds ratio of 7.01 (95% CI 3.65-13.49). The odds of haemorrhage among
 688 those who experienced genital lacerations was higher than those without lacerations (aOR 1.66,
 689 95% CI 1.25-2.21). The proportion of WLHIV experiencing haemorrhage was 4.14%
 690 (128/3090) (OR 1.13, 95% CI 0.92-1.40). Cardiac disease, parity, previous miscarriage, BBA,

multiple gestation, birth weight, congenital anomaly, and prolonged labour were not significantly associated with maternal haemorrhage in this dataset.

Maternal Death

Only five maternal deaths were noted in the birth registers (45 per 100 000 live births) (Table 3.4). All the maternal deaths occurred at CMJAH; two (40.00%) were WLHIV and three (60.00%) had unknown HIV status. None had diabetes, previous miscarriages, or prolonged labour, and none of their neonates were born before arrival at the facility. Case 1 was a 28-year-old woman, with two previous deliveries. It is not known whether she attended antenatal care in the index pregnancy, nor whether the vaginal delivery was assisted. Complications recorded include severe pre-eclampsia, HELLP Syndrome, and intracranial haemorrhage. The pregnancy ended in a miscarriage at a gestational age of 24 weeks. Case 2 was a 33-year-old WLHIV, with a parity of two and a known cardiac condition (exact condition not specified in the birth register), but no recorded diagnosis of a hypertensive disorder. The index pregnancy was “unbooked” (she did not attend antenatal care). A Caesarean section was performed at 33 weeks of gestational age, complicated by pulmonary embolism. Case 3 was a 41-year-old WLHIV, and a grande multipara with six previous deliveries. She attended antenatal care and there was no recorded history of a hypertensive or cardiac disorder but “liver failure” and “jaundice” were recorded in the notes. The pregnancy resulted in a miscarriage, delivered NVD at 25 weeks. Case 4 was lacking all information on age, parity, HIV status, antenatal care history, or known comorbidities. She delivered a stillborn infant at 34 weeks by forceps delivery. The birth was complicated by severe pre-eclampsia and placental abruption. Case 5 was 33 years old, with no HIV status recorded. She had three previous deliveries; in this pregnancy she did not attend antenatal care and had an NVD at 33 weeks, complicated by severe pre-eclampsia. In summary, this comprises three cases related to hypertensive disease,

one related to a cardiac condition complicated by pulmonary embolism, and one related to liver failure.

Table 3.4 Demographic and clinical characteristics of 5 women who died while pregnant from 1 July 2017-30 June 2018

Variable	Case 1	Case 2	Case 3	Case 4	Case 5
Maternal age at birth	20-34	20-34	>34	Missing/ Unknown	20-34
Birth site	CMJAH	CMJAH	CMJAH	CMJAH	CMJAH
HIV status	Missing/ Unknown	Positive	Positive	Missing/ Unknown	Missing/ Unknown
Hypertensive disorder of pregnancy	Yes	No	No	Yes	Yes
Diabetes	No	No	No	No	No
Cardiac disorder	No	Yes	No	No	No
Parity	1-4	1-4	5+	Missing/ Unknown	1-4
Previous miscarriage	No	No	No	No	No
Any antenatal care in pregnancy	Missing/ Unknown	No	Yes	Missing/ Unknown	No
Born before arrival (BBA)	No	No	No	No	No
Mode of delivery	Vaginal, type unspecified	Caesarean section	Normal vaginal delivery	Assisted vaginal delivery	Normal vaginal delivery
Gestational age at birth	<26W	26-36W	<26W	26-36W	26-36W
Maternal haemorrhage	No	No	No	Yes	No
Prolonged labour	No	No	No	No	No

Adverse neonatal outcomes

Preterm Birth

Among the 11791 neonates included in the study, 24.32% (2868/11791) were born preterm (<37 weeks gestation) (Table 3.5). Of these, majority (83.16%, 2385/2868) were delivered at CMJAH, and only 17.69% (476/2868) at HCHC. Of the preterm deliveries at HCHC, the median gestational age was 35 weeks (IQR 34-36), while at CMJAH, the median gestational age among preterm deliveries was 34 weeks (IQR 30-36). Most cases of preterm birth (76.6%,

2197/2868) were to mothers aged 20-34 years, while 15.45% (443/2868) had mothers aged over 34 years and 7.6% (218/2868) were born to adolescent mothers. Of the preterm neonates, 29.6% (849/2868) were born to WLHIV. Preterm neonates were mainly born to mothers with 1-4 previous deliveries (69.49%, 1993/2868), while 29.01% (832/2868) were their mothers' first child. Of the preterm neonates, 14.23% (408/2868) were born to mothers with a hypertensive disorder, 7.39% (212/2868) were born in a pregnancy complicated by haemorrhage, and 12.13% (348/2868) were one of a multiple gestation.

Babies born at HCHC had a statistically significant reduced odds of being born preterm compared to those born at CMJAH (aOR 0.65, 95% CI 0.58-0.73) (Table 3.6), as expected since CMJAH is a tertiary referral hospital. Adolescent pregnancy was a significant risk factor for preterm birth (aOR 1.38, 95% CI 1.15-1.66). Of the 3167 babies born to WLHIV, 849 (26.81%) were born preterm. WLHIV and those with unknown HIV status were significantly more likely to have preterm births than HIV-negative mothers (aOR 1.34, 95% CI 1.21-1.48 and aOR 2.51, 95% CI 1.87-3.37 respectively). Neonates born to mothers diagnosed with hypertensive disorders had a significantly raised odds for preterm birth compared to mothers who had no hypertensive disorders (aOR 2.39, 95% CI 2.07-2.75). Nulliparity was also slightly more likely to result in preterm birth compared to mothers with 1-4 previous deliveries (aOR 1.12, 95% CI 1.02-1.23). Multiple gestation pregnancies were much more likely to deliver preterm than singleton pregnancies (aOR 6.37, 95% CI 5.28-7.68). Both placental abruption (aOR 3.46, 95% CI 1.76-6.77) and obstetric haemorrhage (aOR 2.43, 95% CI 1.98-3.00) were significant risk factors for preterm birth. Cardiac disease showed a significant association with preterm birth in the univariate model (OR 1.72, 95% CI 1.02-2.89) but not in the multivariable model. Diabetes, previous miscarriage, and congenital anomaly were not significantly associated with preterm delivery.

756 *Table 3.5 Prevalence of neonatal outcomes*

Variable	Preterm Birth n (%)	LBW/IUGR n (%)	Stillbirth n (%)	Congenital anomaly n (%)
N	2868 (24.32%)	2065 (17.51%)	354 (3.00%)	238 (2.02%)
Birth site				
CMJAH	2,385 (83.16%)	1,810 (87.65%)	323 (91.24%)	215 (90.34%)
HCHC	483 (16.84%)	255 (12.35%)	31 (8.76%)	23 (9.66%)
Age				
<20	218 (7.6%)	126 (6.1%)	19 (5.37%)	19 (7.98%)
20-34	2,197 (76.6%)	1,569 (75.98%)	279 (78.81%)	172 (72.27%)
>34	443 (15.45%)	364 (17.63%)	53 (14.97%)	46 (19.33%)
Missing/Unknown	10 (0.35%)	6 (0.29%)	3 (0.85%)	1 (0.42%)
HIV				
Negative	1,930 (67.29%)	1,308 (63.34%)	218 (61.58%)	163 (68.49%)
Positive	849 (29.6%)	684 (33.12%)	96 (27.12%)	70 (29.41%)
Missing/Unknown	89 (3.1%)	73 (3.54%)	40 (11.3%)	5 (2.1%)
Hypertensive disorder				
No	2,460 (85.77%)	1,713 (82.95%)	285 (80.51%)	218 (91.6%)
Yes	408 (14.23%)	352 (17.05%)	69 (19.49%)	20 (8.40%)
Diabetes				
No	2,844 (99.16%)	2,056 (99.56%)	349 (98.59%)	234 (98.32%)
Yes	24 (0.84%)	9 (0.44%)	5 (1.41%)	4 (1.68%)
Cardiac disease				
No	2,846 (99.23%)	2,048 (99.18%)	352 (99.44%)	236 (99.16%)
Yes	22 (0.77%)	17 (0.82%)	2 (0.56%)	2 (0.84%)
Parity				
0	832 (29.01%)	605 (29.3%)	99 (27.97%)	68 (28.57%)
1-4	1,993 (69.49%)	1,430 (69.25%)	247 (69.77%)	168 (70.59%)
5+	33 (1.15%)	23 (1.11%)	4 (1.13%)	1 (0.42%)
Missing/Unknown	10 (0.35%)	7 (0.34%)	4 (1.13%)	1 (0.42%)
Previous miscarriage				
No	2,803 (97.73%)	2,023 (97.97%)	347 (98.02%)	236 (99.16%)
Yes	65 (2.27%)	42 (2.03%)	7 (1.98%)	2 (0.84%)
BBA				
No	2,766 (96.44%)	1,986 (96.17%)	316 (89.27%)	235 (98.74%)
Yes	79 (2.75%)	75 (3.63%)	34 (9.60%)	2 (0.84%)
Missing/Unknown	23 (0.80%)	4 (0.19%)	4 (1.13%)	1 (0.42%)
Mode of delivery				
NVD	1,480 (51.6%)	1,000 (48.43%)	249 (70.34%)	110 (46.22%)
Assisted	22 (0.77%)	10 (0.48%)	4 (1.13%)	0 (0%)
Caesar	1,272 (44.35%)	986 (47.75%)	67 (18.93%)	125 (52.52%)
Missing/Unknown	94 (3.28%)	69 (3.34%)	34 (9.6%)	3 (1.26%)
Multiple gestation				
No	2,520 (87.87%)	1,736 (84.07%)	326 (92.09%)	219 (92.02%)

Variable	Preterm Birth n (%)	LBW/IUGR n (%)	Stillbirth n (%)	Congenital anomaly n (%)
N	2868 (24.32%)	2065 (17.51%)	354 (3.00%)	238 (2.02%)
Yes	348 (12.13%)	329 (15.93%)	28 (7.91%)	19 (7.98%)
GA at birth				
<26 weeks	161 (5.61%)	139 (6.73%)	74 (20.9%)	6 (2.52%)
26-36 weeks	2,707 (94.39%)	1,394 (67.51%)	191 (53.95%)	68 (28.57%)
37-42 weeks	0 (0%)	468 (22.66%)	63 (17.8%)	157 (65.97%)
>42 weeks	0 (0%)	0 (0%)	1 (0.28%)	2 (0.84%)
Missing/Unknown	0 (0%)	64 (3.10%)	25 (7.06%)	5 (2.10%)
Birth weight				
<2500 g	1,536 (53.56%)	2,065 (100%)	277 (78.25%)	59 (24.79%)
2500-4499 g	1,229 (42.85%)	0 (0%)	63 (17.8%)	176 (73.95%)
≥4500 g	3 (0.10%)	0 (0%)	0 (0%)	2 (0.84%)
Missing/Unknown	100 (3.49%)	0 (0%)	14 (3.95%)	1 (0.42%)
Congenital anomaly				
No	2,794 (97.42%)	2,006 (97.14%)	334 (94.35%)	
Yes	74 (2.58%)	59 (2.86%)	20 (5.65%)	
Retained placenta				
No	2,840 (99.02%)	2,042 (98.89%)	340 (96.05%)	237 (99.58%)
Yes	28 (0.98%)	23 (1.11%)	14 (3.95%)	1 (0.42%)
Prolonged labour				
No	2,796 (97.49%)	2,040 (98.79%)	352 (99.44%)	226 (94.96%)
Yes	72 (2.51%)	25 (1.21%)	2 (0.56%)	12 (5.04%)
Lacerations				
No	2,300 (80.2%)	1,769 (85.67%)	314 (88.7%)	189 (79.41%)
Yes	568 (19.8%)	296 (14.33%)	40 (11.3%)	49 (20.59%)
Haemorrhage				
No	2,656 (92.61%)	1,922 (93.08%)	308 (87.01%)	230 (96.64%)
Yes	212 (7.39%)	143 (6.92%)	46 (12.99%)	8 (3.36%)
Abruption				
No	2,830 (98.68%)	2,039 (98.74%)	328 (92.66%)	238 (100%)
Yes	38 (1.32%)	26 (1.26%)	26 (7.34%)	0 (0%)

757

758 **Low Birth Weight**

759 There were a total of 2065/11791 low birth weight infants (17.51%) (Table 3.5), with 87.65%

760 (1810/2065) of cases at CMJAH and 12.35% (255/2065) of cases at HCHC. Just over three

761 quarters (75.98%, 1569/2065) of LBW neonates were born to mothers aged 20-34 years, while

762 mothers of advanced maternal age (>34 years) accounted for a relatively high proportion of

LBW neonates (17.63%, 364/2065). LBW infants were also disproportionately born to WLHIV, with 33.12% (684/2065) of cases in this group. Hypertensive mothers delivered 17.05% (352/2065) of LBW infants, while diabetic mothers only delivered 0.44% (9/2065). Parity among the preterm mothers was 0 in 29.3% (605/2065), 1-4 in 69.25% (1430/2065), and five or more in 1.11% (23/2065) of cases. Nearly three-quarters of LBW neonates were born prematurely: 6.73% (139/2065) at a pre-viable gestational age of <26 weeks, and 67.51% (1394/2065) premature but viable at 26-36 weeks. Multiple pregnancies also accounted for 15.93% (329/2065) of cases of LBW.

In keeping with the referral pathway, infants delivered at HCHC had lower odds of LBW than those delivered at CMJAH (aOR 0.48, 95% CI 0.41-0.57) (Table 3.6). Advanced maternal age (>34 years) at time of birth was significantly associated with LBW (aOR 1.24, 95% CI 1.05-1.47), when compared to those aged 20-34 years. The proportion of LBW among babies born to WLHIV was 21.60% (684/3167). Both WLHIV and those with unknown HIV status were significantly more likely to deliver a LBW infant than those who were HIV-negative (aOR 1.61, 95% CI 1.41-1.83 and aOR 1.73, 95% CI 1.19-2.53, respectively). Women with hypertensive disorders were more likely to deliver a LBW infant (aOR 2.15, 95% CI 1.80-2.59). Conversely, infants born to mothers with diabetes had a lower risk of LBW compared to those whose mothers did not have diabetes (aOR 0.37, 95% CI 0.17-0.81). Nulliparity was a risk factor for LBW compared to infants born to mothers with 2-4 previous deliveries (aOR 1.32, 95% CI 1.14-1.52). Compared to term infants, pre-viable gestational age (aOR 87.17, 95% CI 54.53-139.34) and premature delivery (aOR 15.30, 95% CI 13.51-17.33) were both major significant risk factors for LBW. Multiple pregnancy was significantly associated with LBW (aOR 4.69, 95% CI 3.74-5.88). Cardiac disease, previous miscarriage, congenital anomaly, haemorrhage, and abruption were not significantly associated with LBW.

788 *Table 3.6 Risk factors for neonatal outcomes*

Variable	Preterm Birth n (%)		LBW n (%)		Stillbirth n (%)		Congenital anomaly n (%)	
	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)	Univariate OR (95% CI)	Multivariable aOR (95% CI)
Birth site								
CMJAH	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)
HCHC	0.51 (0.45-0.56)	0.65 (0.58-0.73)	0.35 (0.31-0.40)	0.48 (0.41-0.57)	0.27 (0.19-0.39)	0.27 (0.17-0.42)	0.30 (0.20-0.47)	0.31 (0.20-0.48)
Age								
<20	1.27 (1.08-1.50)	1.38 (1.15-1.66)	0.96 (0.79-1.17)	0.79 (0.61-1.02)	0.82 (0.51-1.31)		1.34 (0.83-2.16)	1.42 (0.88-2.31)
20-34	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)		1 (base)	1 (base)
>34	1.19 (1.06-1.34)	0.98 (0.86-1.12)	1.40 (1.23-1.59)	1.24 (1.05-1.47)	1.08 (0.80-1.45)		1.53 (1.10-2.12)	1.33 (0.95-1.86)
Missing/Unknown	0.83 (0.41-1.67)	0.73 (0.34-1.58)	0.69 (0.29-1.62)	0.49 (0.17-1.36)	2.11 (0.65-6.84)		1.11 (0.15-8.07)	1.08 (0.15-8.02)
HIV								
Negative	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)
Positive	1.23 (1.12-1.35)	1.34 (1.21-1.48)	1.50 (1.35-1.66)	1.61 (1.41-1.83)	1.18 (0.92-1.50)	0.81 (0.62-1.07)	1.14 (0.86-1.52)	1.16 (0.87-1.55)
Missing/Unknown	2.54 (1.92-3.35)	2.51 (1.87-3.37)	2.96 (2.21-3.96)	1.73 (1.19-2.53)	9.01 (6.22-13.05)	2.55 (1.58-4.12)	1.25 (0.51-3.09)	1.15 (0.46-2.85)
Hypertensive disorder								
No	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	
Yes	2.52 (2.20-2.89)	2.39 (2.07-2.76)	3.09 (2.68-3.55)	2.15 (1.80-2.59)	2.87 (2.19-3.76)	1.84 (1.33-2.57)	1.04 (0.65-1.65)	
Diabetes								
No	1 (base)		1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	
Yes	1.01 (0.64-1.60)		0.47 (0.24-0.94)	0.37 (0.17-0.81)	1.75 (0.71-4.32)	2.82 (0.94-8.51)	2.08 (0.76-5.72)	
Cardiac disease								
No	1 (base)	1 (base)	1 (base)		1 (base)		1 (base)	
Yes	1.72 (1.02-2.89)	1.54 (0.89-2.65)	1.79 (1.02-3.13)		1.08 (0.26-4.43)		1.62 (0.39-6.68)	

Variable	Preterm Birth n (%)		LBW n (%)		Stillbirth n (%)		Congenital anomaly n (%)	
	Univariate	Multivariable	Univariate	Multivariable	Univariate	Multivariable	Univariate	Multivariable
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Parity								
0	1.12 (1.02-1.23)	1.14 (1.02-1.27)	1.13 (1.02-1.25)	1.32 (1.14-1.52)	1.05 (0.83-1.33)		1.06 (0.80-1.41)	
1-4	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)		1 (base)	
5+	1.47 (0.97-2.23)	1.31 (0.84-2.03)	1.37 (0.86-2.18)	0.85 (0.47-1.51)	1.31 (0.48-3.58)		0.47 (0.07-3.40)	
Missing/Unknown	0.60 (0.30-1.17)	0.66 (0.32-1.36)	0.60 (0.27-1.32)	0.77 (0.30-2.02)	2.20 (0.79-6.11)		0.78 (0.11-5.64)	
Previous miscarriage								
No	1 (base)	1 (base)	1 (base)		1 (base)		1 (base)	1 (base)
Yes	1.26 (0.94-1.69)	1.24 (0.92-1.68)	1.08 (0.77-1.51)		1.03 (0.48-2.21)		0.43 (0.11-1.73)	0.35 (0.09-1.43)
BBA*								
No					1 (base)	1 (base)		
Yes					3.75 (2.59-5.43)	3.83 (2.10-6.97)		
Missing/Unknown					1.24 (0.46-3.39)	1.18 (0.35-3.97)		
Mode of delivery*								
NVD					1 (base)	1 (base)		
Assisted					0.98 (0.36-2.69)	1.24 (0.40-3.88)		
Caesar					0.40 (0.31-0.53)	0.20 (0.14-0.27)		
Missing/Unknown					2.98 (2.05-4.34)	0.81 (0.46-1.45)		
Multiple gestation								
No	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)
Yes	6.42 (5.34-7.70)	6.36 (5.27-7.66)	8.71 (7.27-10.45)	4.69 (3.74-5.88)	1.85 (1.24-2.75)	0.73 (0.47-1.14)	1.85 (1.15-2.98)	1.53 (0.94-2.47)
GA at birth*								
<26 weeks			106.60 (67.34-168.74)	87.17 (54.53-139.34)	112.07 (75.36-166.67)	11.03 (6.84-17.78)		
26-36 weeks			17.91 (15.89-20.19)	15.30 (13.51-17.33)	10.00 (7.50-13.34)	2.61 (1.84-3.70)		

Variable	Preterm Birth n (%)		LBW n (%)		Stillbirth n (%)		Congenital anomaly n (%)	
	Univariate	Multivariable	Univariate	Multivariable	Univariate	Multivariable	Univariate	Multivariable
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
37-42 weeks			1 (base)	1 (base)	1 (base)	1 (base)		
>42 weeks			— ¹	—	2.20 (0.30-16.09)	2.27 (0.30-17.36)		
Missing/Unknown			2.49 (1.88-3.29)	3.76 (2.79-5.07)	6.96 (4.34-11.17)	2.97 (1.59-5.54)		
Birth weight*								
<2500 g					22.66 (17.16-29.93)	10.56 (7.44-15.00)		
2500-4499 g					1 (base)	1 (base)		
≥4500 g					— ²	—		
Missing/Unknown					5.94 (3.30-10.70)	2.49 (1.21-5.15)		
Congenital anomaly								
No	1 (base)	1 (base)	1 (base)		1 (base)	1 (base)		
Yes	1.41 (1.07-1.87)	1.26 (0.94-1.68)	1.57 (1.16-2.11)		3.08 (1.92-4.93)	3.24 (1.81-5.80)		
Prolonged labour*								
No					1 (base)	1 (base)		
Yes					0.10 (0.02-0.40)	0.37 (0.09-1.53)		
Haemorrhage*								
No	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)	1 (base)		
Yes	2.79 (2.31-3.37)	2.44 (1.98-3.00)	2.21 (1.80-2.71)	1.23 (0.95-1.59)	3.98 (2.87-5.50)	3.57 (2.41-5.29)		
Abruption*								
No	1 (base)	1 (base)	1 (base)					
Yes	9.20 (4.90-17.30)	3.47 (1.77-6.80)	4.95 (2.85-8.59)					

* Certain explanatory variables were not included in the models for outcome definitions, where that explanatory variable could not be a risk factor for that outcome.

¹ No cases of GA >42 weeks in those with LBW – 61 observations not used.

² No cases of birth weight ≥4500 g in those with stillbirth – 50 observations not used.

792 Stillbirth

793 Of the total birth cohort of 11791 neonates, 354 were stillborn (3.00%) (Table 3.5). CMJAH
 794 had the most stillbirths (91.24%, 323/354). WLHIV delivered 27.12% (96/354) of stillborn
 795 infants; additionally, there was a relatively high percentage of unknown maternal HIV status
 796 among stillborn infants (11.3%, 40/354). Among the 354 stillborn neonates, 19.49% (69/354)
 797 had mothers who had a hypertensive disorder, 12.99% (46/354) had a mother with haemorrhage
 798 prior to, or during childbirth and 9.6% (34/354) were born before arrival at a health facility.
 799 Only 18.93% (67/354) of stillbirths were delivered by Caesarean section. Neonates born at a
 800 pre-viable gestational age accounted for 20.9% (74/354) of cases documented as stillbirths,
 801 which would be more accurately classified as miscarriages; over half were born between 26-
 802 36 weeks (53.95%, 191/354). The majority of stillbirths were LBW (78.25%, 277/354). Of the
 803 354 stillborn neonates, 5.65% (20/354) were diagnosed with at least one congenital anomaly:
 804 two had neural tube defects (one with anencephaly, and one with both spina bifida and
 805 hydrocephalus); two had hydrocephalus; one had both polydactyly and unspecified dysmorphic
 806 features; one had fetus papyraceus; one had ascites; one had trisomy 21; one had omphalocele;
 807 one had hydrocephalus, cleft palate, and polydactyly; nine had unspecified dysmorphic
 808 features; and one was listed as having a congenital anomaly with no further information
 809 recorded.

810

811 Stillbirths were less likely to occur at HCHC (aOR 0.27, 95% CI 0.17-0.42) compared to
 812 CMJAH (Table 3.6), as expected. There were 96 (3.03%) stillbirths among the 3167 infants
 813 born to WLHIV. Infants whose mothers had an unknown HIV status were significantly more
 814 likely to be stillborn (aOR 2.55, 95% CI 1.58-4.12). The presence of hypertensive disorders
 815 (aOR 1.84, 95% CI 1.33-2.57) and of haemorrhage (aOR 3.57, 95% CI 2.41-5.29) in the mother
 816 were both risk factors for stillbirth. Neonates born before arrival at the facility (BBA) were

much more likely to be stillborn than in-facility deliveries (aOR 3.83, 95% CI 2.10-6.97), while those born by Caesarean section were much less likely to be stillborn than those delivering by NVD (aOR 0.20, 95% CI 0.14-0.27). Preterm delivery at 26-36 weeks of gestation (aOR 2.61, 95% CI 1.84-3.70) and pre-viable delivery at <26 weeks (aOR 11.03, 95% CI 6.84-17.78) were both associated with stillbirth, although these would more accurately be classified as miscarriages in this population. Similarly, LBW was found to be a risk factor for stillbirth (aOR 10.56, 95% CI 7.44-15.00), along with congenital anomalies (aOR 3.24, 95% CI 1.81-5.80). Prolonged labour, multiple gestation, previous miscarriage, parity, cardiac disease, and maternal age were not associated with stillbirth.

Congenital Anomalies

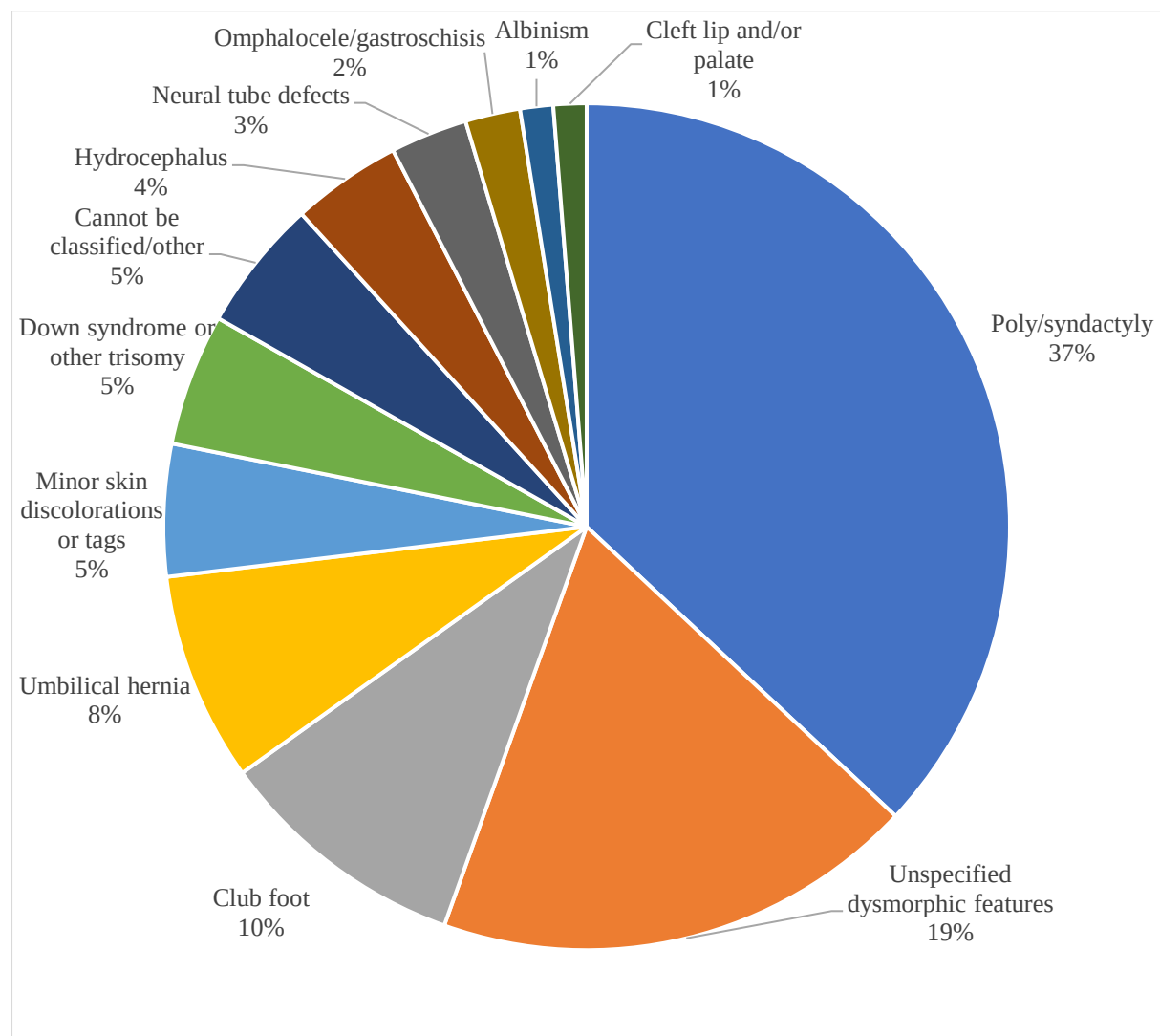
Among 11791 neonates, 238 cases of congenital anomalies (1.76%) were detected prior to discharge. The different types of anomalies and their frequencies are shown in Table 3.7 and Figure 3.1.

Table 3.7 Types of congenital anomalies found among 11791 neonates

Anomaly type	Number	Percent
Poly/syndactyly	88	36.97
Unspecified dysmorphic features	44	18.49
Club foot	23	9.66
Umbilical hernia	19	7.98
Minor skin discolorations or tags	12	5.04
Down syndrome or other trisomy	12	5.04
Cannot be classified/other	12	5.04
Hydrocephalus	10	4.20
Neural tube defects	7	2.94
Omphalocele/gastroschisis	5	2.10
Albinism	3	1.26
Cleft lip and/or palate	3	1.26
Total	238	100

Polydactyly and syndactyly were the most common anomalies reported (36.97%, 88/238). Commonly detected major structural anomalies included club foot (9.66%, 23/238); trisomies including Down syndrome (5.04%, 12/238); hydrocephalus (4.20%, 10/238); and neural tube defects (2.94%, 7/238). In 18.49% (44/238) of cases, “dysmorphic features” were recorded without a specific diagnosis.

Figure 3.1 Distribution of types of congenital anomalies.



Of the 238 cases of congenital anomaly, 90.34% (215/238) delivered at CMJAH (Table 3.5). Just under a fifth of cases of congenital anomalies (19.33%, 46/238) were born to mothers older

than 34 years, while 78.81% (172/238) were born to mothers aged 20-34 and 7.98% (19/238) were born to adolescent mothers. Similarly, 7.98% (19/238) were part of a multiple pregnancy.

Infants born at HCHC were significantly less likely to be diagnosed with a congenital anomaly than those born at CMJAH (aOR 0.30, 95% CI 0.20-0.47) (Table 3.6). In the univariate model, neonates born to mothers of advanced maternal age were significantly more likely to be diagnosed with a congenital anomaly (OR 1.53, 95% CI 1.10-2.12), however this did not persist in the multivariable model. Similarly, a positive association was found with multiple pregnancy in the univariate model (OR 1.85, 95% CI 1.15-2.98), but the adjusted odds ratio was not significant. In 3167 infants born to WLHIV, 2.2% (70/3167) were diagnosed with a congenital anomaly (OR 1.14, 95% CI 0.86-1.52). None of the other factors considered for this model were found to be significant; these were hypertensive disorder, diabetes, cardiac disease, parity, and previous miscarriage.

Chapter 4 Discussion

Study Findings

This study assessed the prevalence and risk factors of maternal and infant outcomes at birth, using birth registers, in inner city Johannesburg, South Africa. The population under study was mostly young, and over a quarter of mothers were presenting in their first pregnancy. The proportion of non-South African patients was high, reflecting what is known about the population of the inner-city of Johannesburg (6). The percentage of WLHIV (26.82%) is in line with other recent studies in the area (13). The percentage of missing HIV status was concerningly high (1.78%); considering HIV status as a risk factor for various negative outcomes, as well as the importance of early treatment during pregnancy, this challenge needs specific attention.

Hypertensive disorders were found in 935 (8.12%) participants. This is lower than the finding by Balkus et al. in the MTN 042B study reported in 2021, which found a prevalence of “any hypertension” of 13.2% at the same two facilities (7). However, the total prevalence of pregnancy-induced hypertension, pre-eclampsia, and eclampsia was 10.2% in that population, which is closer to the prevalence reported here; this may indicate that the staff completing the birth register more selectively report pregnancy-induced hypertensive disorders rather than any hypertensive disorder. Significant risk factors found in this study for hypertensive disorders included advanced maternal age (>34 years old at birth), diabetes, and nulliparity. These risk factors were also present in the systematic review and meta-analysis conducted by Bartsch et al. (23). However, multiple pregnancy, which was listed as a risk factor in that paper, was not found to be a risk factor in this study. HIV seemed to protect against hypertensive disorders, an association which persisted in the multivariable model. Existing research on the association of hypertensive disorders with HIV is not clear; however, a similar finding of lower prevalence of hypertensive disorders among HIV-negative mothers was found by Balkus et al. (7). In that

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population, the prevalence of hypertension-related complications was 11.2% among mothers who were HIV-negative compared to 7.5% among WLHIV ($p<0.001$). This finding may be a result of a hitherto unknown mediating factor of HIV on hypertensive disorders of pregnancy. WLHIV, including those well controlled on ART, tend to have lower weight gain compared to HIV-negative women and this may also differ between regimens, for example women on efavirenz-based ART have lower weight gain during pregnancy than those on DTG-based ART (24). Since being overweight is a risk factor for hypertensive disorders (25), HIV-related lower weight gain may be the mechanism for reduced risk of hypertensive disorders among WLHIV. The relationship of HIV and weight bears further study (24).

In this study, 447 (3.88%) women experienced haemorrhage. This is higher than the 2.6% reported by Balkus et al. at the same sites in 2021 (7). However, in that study, haemorrhage was restricted to postpartum; here, both antepartum and postpartum are included. Associated risk factors in this study included preterm birth, post-term birth, delivery by Caesarean section, retained placenta, and genital lacerations. Mothers diagnosed with a hypertensive disorder of pregnancy were significantly less likely to experience maternal haemorrhage. This finding is not supported in existing literature; hypertensive disorders are associated with placental disease that may actually lead to haemorrhage (26), and the thrombocytopaenia found in severe pre-eclampsia complicated by HELLP syndrome (**h**aemolysis, **e**levated **l**iver enzymes, and **l**ow **p**latelets) can interfere with clotting (27). In our study, it is likely that women with known gestational hypertensive disorder may be booked for elective Caesarean section, so would be at lower risk of experiencing haemorrhage. This may be reflected in the finding that Caesarean section was significantly associated with haemorrhage, although it is worth noting that antepartum causes of haemorrhage would also be indications for delivery by emergency Caesarean section. Since the birth register does not capture the temporal relationship between

the onset of haemorrhage and the decision to perform a Caesarean section, the temporality of the exposure and the outcome cannot be determined. Similarly, both pre-viable birth (gestational age <26 weeks at birth) and preterm birth (26-36 weeks) were significantly associated with haemorrhage, but since some causes of haemorrhage can predispose to preterm delivery, its status as a risk factor should be interpreted with caution. Our data showed post-term birth (>42 weeks) as a risk factor for haemorrhage. Ende et al. also reported diabetes, race, and placental abruption as additional risk factors for haemorrhage (28), but these were not included in this analysis for several reasons. While diabetes is an emerging risk factor for haemorrhage, possibly owing to its effect on vasculature and perfusion and therefore warranting further research on the association, none of the women in our study with haemorrhage had diabetes. As a result, diabetes could not be included in the model. Race could not be analysed due to non-random missingness (only captured at one site), and abruption was not considered a risk factor but rather as part of the definition of haemorrhage. Ende also reported genital tract trauma (including lacerations) and retained placenta as definite risk factors for haemorrhage, findings which are reflected in this study.

Prolonged labour was present in 618 (5.36%) cases. This is in line with global estimates of prevalence of 2.00-8.00% (29). Nulliparous women were more likely to experience prolonged labour, while the following were protective: advanced maternal age, and as expected preterm and low birth weight birth. Women with hypertensive disorders were less likely to experience prolonged labour, which may be because elective Caesarean sections bypass the phases of labour that are likely to be prolonged. This reasoning seems contradictory to the finding that Caesarean section was associated with prolonged labour, but this may be because prolonged labour itself can be an indication for emergency Caesarean section. The same caveat applies to the finding that mothers who underwent assisted delivery were much more likely to experience

prolonged labour. While it is necessary to include both modes of delivery in the model to control for their effect, the inability to determine temporality means that their interpretation as risk factors for prolonged labour should be made with caution. Unknown birth weight was positively associated with prolonged labour, although this may reflect challenges with recording data in case of difficult deliveries. Lastly, a handful of significant associations with prolonged labour should be interpreted with caution given very small numbers of cases and wide confidence intervals. These are: previous miscarriage (only 6 cases in those with prolonged labour); multiple gestation (3 cases) and unknown gestational age (3 cases).

The number of cases of maternal death (five cases in 11520 deliveries, or 45 per 100 000 live births) is much lower than the nationally reported maternal mortality rate of 88 per 100 000 live births (30). This is encouraging given the SDG goal to reduce maternal mortality (4). However, the small number of outcomes meant that we could not use a regression model for this outcome. Data for exposure variables were often missing, likely reflecting the hurried nature of record-keeping in emergency situations. There is also the possibility that maternal deaths may occur in the post-natal wards or even after discharge in the days after delivery, beyond the period during which the birth register would have been captured this information. This would mean that the true number of maternal deaths in this population would have been underestimated, as maternal deaths are defined as any death occurring in the mother up to 42 days after pregnancy (30). While these data cannot be used to draw firm conclusions about the risk factors for maternal death in inner-city Johannesburg, suggestions may be made for further research. Notably, the higher prevalence of hypertensive disorders (three out of five cases; 60.00%) aligns with evidence that this remains an important cause of maternal death (31), and focus should remain on this issue. A case-control study design may be more appropriate for research on this rare outcome, such as the one conducted in Uganda in 2016 (32). The findings

from that study also list hypertensive obstetric disorders as one of the main important direct causes of maternal death, along with puerperal sepsis, haemorrhage, and abortion-related complications (32). A similar study in the inner-city of Johannesburg may help find the most important causes of maternal death in this population. Cross-referencing birth register information with data from maternal death registries may also help supplement research into this important obstetric outcome.

Preterm birth at under 36 completed weeks of gestation, was the most common neonatal complication, with 2868 cases (24.32%) among the 11791 neonates. The percentage is higher than the 20.7% seen in the same clinics by Balkus et al. in 2021 (7). However, since the Balkus study extracted data directly from maternity case records, it may have less reporting error than cases reported in the birth register. That said, only 1888 cases were reviewed by Balkus over an eight-week period, compared to 11520 in this study over the course of a year, which may mean a reduced risk of a time-related bias in this analysis. This is important given emerging evidence that the seasonal effects of high temperature may increase adverse outcomes in pregnancy (33). The high incidence of preterm birth reflects the importance of the condition globally as one of the leading causes of neonatal morbidity and mortality (34). Significant risk factors that are similar to the scoping review of causes of preterm birth by Mabrouk et al. in 2022 (35) included adolescent pregnancy, WLHIV and those with unknown HIV status, and hypertensive disorders. HIV and ART remain a risk factor for prematurity, particularly significant in high-burden countries such as South Africa (35). Risk factors that did not coincide were nulliparity, multiple gestation, maternal haemorrhage, and abruption; multiple gestation, however, may also be considered a known risk factor for preterm birth (34). For the latter two, antepartum haemorrhage may be an indication for preterm induction of labour or emergency Caesarean section, hence it may be because of the treatment of these conditions that

a neonate is delivered prematurely rather than as a direct result of the condition itself. As with all other complications, preterm birth was significantly less likely to occur at HCHC. Given that the median gestational age for preterm deliveries at HCHC was 35 weeks, it may indicate a shortcoming in the process of referring preterm deliveries to CMJAH. It is possible that these cases presented in later stages of labour where referral was unfeasible, but this cannot be determined with certainty using the current dataset.

Low birth weight was reported in 2065 neonates (17.51%), which closely correlates with the prevalence of 17.4% found by Balkus et al. at these same sites in 2021 (7). LBW was significantly associated with advanced maternal age, maternal HIV infection, nulliparity, multiple gestation, and prematurity. Prematurity is known to be associated with LBW and is an important step in the pathway from prematurity to adverse outcomes, which may also be associated with multiple gestation (34). Risk factors for the related condition, IUGR, in Africa include HIV and gestational hypertension, as found in the scoping review by Accrombessi et al. in 2018 (36). However, IUGR assessment relies on accurate gestational age assessment recorded in the birth register. Where gestational ageing (such as in our study) is less accurate and not determined by early ultrasound, LBW may serve as a proxy for IUGR. Maternal HIV and hypertensive disorders of pregnancy were both found to be risk factors for LBW in our study. However, the latter finding must be interpreted with care in our dataset, as mothers experiencing a hypertensive disorder may have been more likely to undergo induction of labour or emergency Caesarean section, either of which could lead to the delivery of a preterm, LBW infant. This leads to the same challenge with interpretation seen with preterm birth. Diabetes seemed to be protective against LBW, but this should be offset against the fact that diabetes has an increased risk of macrosomia (37), which was not considered in this analysis.

The stillbirth incidence in the cohort was 3.00% (n=354), which is close to the 3.3% reported in 2021 by Balkus et al. (7). Hypertensive disorders, LBW, congenital anomaly, and haemorrhage were risk factors found in this population that are known from the literature (38,39). The finding that BBA and unknown HIV status were associated with stillbirth corresponds with the report by Gumede et al. in 2017 in Johannesburg, where lack of antenatal care was associated with stillbirth (12). Prematurity was also found to be associated with stillbirth in our study, although it is worth noting that neonates in the pre-viable gestational age category (<26 weeks) may be more accurately classified as miscarriages. A negative association was found between stillbirth and Caesarean section; since foetal hypoxia during labour can both cause stillbirths (38) and serve as an indication for emergency Caesarean section, thereby confounding the association, this finding should be interpreted with caution.

Congenital anomalies were found in 238 pregnancies (2.02%). This is very similar to the prevalence found by Balkus et al. of 2.1% (7). Minor anomalies like polydactyly and umbilical hernia predominated. However, many cases of congenital anomaly are not diagnosed fully and are recorded as dysmorphic features without being specified further; this reflects the birth register's status as a record of the mother and neonate in the delivery room, with no confirmatory diagnostic procedures recorded. Future research should track the neonates recorded with unspecified dysmorphic features to find their eventual diagnosis. Congenital anomalies were much more prevalent at CMJAH than HCHC, as expected from a referral centre. The high number of severe congenital anomalies among stillbirths also highlights the importance of careful examination of stillborn neonates. None of the risk factors under analysis were found to be significant; this may reflect the fact that many known risk factors for congenital anomalies are socio-economic and environmental factors such as income, exposure to pollutants, or substance use (40), which are not recorded in the birth register. Future

researchers in the area may need to consider cross-referencing birth register data with demographic data to explore these risk factors. This is also important in the context of drug exposures, which are not recorded in the birth register either; cross-referencing with dispensing databases or HIV treatment systems may be indicated as well.

As expected, the prevalence of adverse outcomes was higher at CMJAH than HCHC, due to CMJAH being a tertiary referral hospital, while HCHC is a primary midwife obstetric unit (MOU). Overall, the referral structure results in CMJAH managing a higher number of complicated cases, with associated risk for bias. The fact that cases may also have been referred to CMJAH from outside of the inner-city complicates the interpretation of the data as applying to the inner-city as a whole; however since the majority of mothers in the cohort do report an inner-city address, it should still be broadly applicable. All multivariable models contained birth site to control for this effect, even though it was not a risk factor for the outcomes under consideration. It is also not possible to determine from the birth register how accurate or consistent the application of referral criteria from the CHC to the hospital was; therefore we couldn't determine whether cases were managed at the appropriate facility, or whether in some circumstances women presented too late to be referred safely.

Only 39.50% of patients delivering in the cohort were recorded as being from South Africa. This is similar to other recent studies; for example, in 2022 Sawry et al. found that 46.2% of women presenting for antenatal care in the inner-city were from Zimbabwe, compared to 50.6% of South Africans (41). However, the fact that nationality information is missing to a high degree in these two sites' birth registers (27.4% missing at CMJAH and 93.9% missing at HCHC) reflects insufficiencies in record-keeping around nationality, which makes research on the effect of nationality on health outcomes more difficult. The perceived risk of stigma and

discrimination against foreign nationals in the South African healthcare system might mean that foreign mothers are less likely to volunteer their nationality (42). While legislation is in place to protect the healthcare rights of migrants, foreigners seeking healthcare in South Africa may still experience instances of stigma and discrimination while accessing health facilities (42). The high proportion of non-South African patients delivering in the inner-city therefore presents a unique challenge to obstetric health services. More dedicated research around the health implications of migration in the inner-city is required.

Strengths

The large size of the dataset (11520 pregnancies with 11791 neonates) means that even small differences were detectable to a statistically significant level. The population under study has limited data available in the literature for birth outcomes – data are available for larger aggregates, but the inner-city of Johannesburg itself is under-researched. This study therefore provides valuable insight that would otherwise not have been available. The study represents a complete birth cohort for one entire year at the two facilities; this means that conclusions drawn from this dataset are robust against seasonal or temporal variations in birth outcomes. This highlights the importance of the birth register and its careful completion, as it is a valuable tool for quantifying exposures and outcomes in the population. It also makes a strong case for a future electronic birth register and its regular review as a source of data on maternal and newborn outcomes.

Limitations

The study was constrained by the variables routinely captured in the birth register. It is therefore not possible to choose desired exposure and outcome variables *a priori* as part of study design. Only those that are already routinely used for monitoring and reporting at the sites are available.

1086 It is also unclear for example whether strict diagnostic criteria were used to distinguish between
1087 chronic and pregnancy-induced hypertension, or between conventional and severe pre-
1088 eclampsia. All four these categories were combined into one single category for this analysis:
1089 hypertensive disorders of pregnancy. Maternal files were not reviewed as part of this analysis,
1090 therefore all outcome definitions could not be corroborated, and were reliant on the birth
1091 register for accurate reporting, as well as limited to complications apparent in the labour ward.
1092 Another limitation is that the two sites used two different formats of birth register. This means
1093 that certain variables are only available at one site or are captured differently. For example,
1094 pre- and post-natal complications are captured in a free-text column at CMJAH, whereas at
1095 HCHC there are individual columns for a limited number of specific outcomes (such as
1096 prolonged labour and post-partum haemorrhage). The birth register itself is often poorly
1097 completed, as staff capacity in labour wards is frequently limited, and the birth register is often
1098 completed post-hoc using information from the patient's file. Some out-of-range or discrepant
1099 information could not be corrected based on just the birth register. For example, three cases of
1100 preterm birth were listed as having a birthweight over 4500g; it is very unlikely that a preterm
1101 neonate would have such a high birth weight, indicating that this is likely the result of incorrect
1102 capture of either the gestational age or birthweight. There is therefore a risk of bias, as data
1103 may be systematically incorrect or missing rather than at random (e.g. the records for
1104 complicated cases, or those born before arrival, may be recorded more poorly than
1105 straightforward cases, which may cause underestimation of exposures or outcomes in such
1106 groups). Another limitation is the possible underestimation of prevalence of congenital
1107 anomalies. Only anomalies that are present and externally visible at birth such as cleft lip or
1108 palate, polydactyly etc., are captured in the birth register. Anomalies that become apparent later
1109 in life, such as non-life-threatening cardiac defects or enzyme deficiencies, are not retroactively
1110 added to the birth register. Hence the ascertainment of these later anomalies was not possible

1111 using this dataset. Furthermore, some cases of anomalies were not clearly diagnosed at birth,
1112 with the register reflecting generic terms such as “gross abnormalities” or “dysmorphic
1113 features;” while this may reflect the difficulty in diagnosing anomalies in the delivery room, it
1114 does still mean that classifying anomalies based on the register is challenging. The same issue
1115 applies to maternal deaths, since maternal deaths occurring after the mother leaves the labour
1116 ward may not be captured in the birth register. Another challenge is that some variables were
1117 disproportionately missing at one site. Nationality was missing for 94% of deliveries at HCHC
1118 as the routine capturing of nationality information was not implemented there until late in the
1119 study period. Race was not captured in the HCHC birth register at all. Conversely, at CMJAH
1120 the name of the booking clinic was missing in 33.7% of cases, which means that it was not
1121 known whether the mother received antenatal care or not. Whether or not the mother received
1122 any antenatal care or not could therefore not be used as a risk factor or covariate. These had to
1123 be excluded from the models to avoid systematic bias, which means conclusions could not be
1124 drawn about them. The lack of details on medication exposures, notably ART, means it was
1125 not possible to evaluate this important pregnancy exposure, as well as other socio-economic
1126 and environmental exposures such as maternal nutritional status, pollution exposure, and use
1127 of alcohol or recreational drugs. There is also the two-week period in October at CMJAH where
1128 birth register volumes were missing, and data could not be abstracted from them. While this
1129 constitutes non-random missing data, it is unlikely that there is some systematic way that the
1130 deliveries in that time period differs from the rest of the database, especially since it would
1131 account for less than 4% of deliveries for the year. The cross-sectional nature of the study
1132 means that temporality could not be determined; for example to assess whether haemorrhage
1133 led to a Caesarean section or the caesarean section resulted in haemorrhage, limiting the ability
1134 to interpret the association between risk factors and outcomes. This is important in the context
1135 of childbirth, since interventions to halt labour (such as the use of tocolysis in prematurity) or

expedite delivery (by emergency Caesarean section) may confound the effect of gestational age or labour duration on adverse outcomes. While the two facilities should generally be representative of the inner-city population, CMJAH accepts referrals of complicated cases from other regions; therefore, the applicability of the findings in this study to the inner-city may be limited, although $\frac{3}{4}$ patients included reported inner-city addresses. Data from other inner-city facilities was not included, an additional limitation.

Conclusion

Maternal health remains one of the most important healthcare challenges in the world today. South Africa is facing difficulties in achieving the SDG targets for improving maternal and neonatal health, warranting an additional focus on these issues in the country. The population of the inner-city of Johannesburg is vulnerable to adverse health outcomes in general, as a result of many factors, including population density, a high proportion of migrants, and the presence of key populations like sex workers in the area. The birth register maintained at delivery facilities is a useful source of routine information on maternal outcomes. While it contains data on all deliveries, it has limited clinical information. Nevertheless, using the birth register, we were able to detect a higher-than-expected prevalence of haemorrhage and preterm birth, and a lower-than-expected prevalence of hypertensive disorders and maternal death. Prevalences of prolonged labour, LBW, stillbirth and congenital anomaly were within range of other studies. The most frequent risk factors found across all adverse outcomes in this study were adolescent pregnancy, advanced maternal age, nulliparity, hypertensive disorders, preterm delivery, HIV, multiple gestation, and haemorrhage. Since all of these risk factors are prevalent in the populations under study, as well as in South Africa and Africa as a whole, they merit focus for further, more in-depth research. It would be useful to explore whether the same associations exist in other populations, and whether potential interventions can protect against

1161 adverse outcomes. Therefore, the birth register remains an important source of data; completing
1162 it accurately and regularly reviewing its contents can help identify important problems and
1163 focus efforts on them accordingly. Collecting birth register data electronically, and being able
1164 to pool data from numerous different facilities, spanning different environments such as urban,
1165 peri-urban and rural, would increase the generalisability of the results and could assist with
1166 health system strengthening, tailored to need. Further studies of other types, such as case-
1167 control studies, may also help elucidate information about the rare but important outcomes in
1168 this population, such as maternal death; such studies may also benefit from augmentation of
1169 birth register data with other data on socio-economic and environmental exposures.

1170

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1326 Appendix A: Signed Plagiarism Declaration**PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS**

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Jean Gilbert le Roux (Student number: 544158) am a student registered for the degree of MSc Epidemiology & Biostatistics in the academic year 2024.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: 

Date: 08/07/2024

1328 **Appendix B: Summary of studies investigating risk factors for adverse maternal and**
 1329 **newborn outcomes**

First Author	Year	Population	Main Findings
Bartsch (23)	2015	Systematic review and meta-analysis of 25 356 588 pregnancies in 92 cohort studies	Risk factors for pre-eclampsia : • Prior pre-eclampsia (RR 8.4, 95% CI 7.1 – 9.9) • Chronic hypertension (RR 5.1, 95% CI 4.0 – 6.5) • Pregestational diabetes (RR 3.7, 95% CI 3.1 – 4.3) • Prior placental abruption (RR 2.0, 95% CI 1.4 – 2.7) • Obesity (RR 2.8, 95% CI 2.6 – 3.1) • Overweight (RR 2.1, 95% CI 2.0 – 2.2) • Use of assisted reproductive techniques (RR 1.8, 95% CI 1.6 – 2.1) • Chronic kidney disease (RR 1.8, 95% CI 1.5 – 2.1) • Prior stillbirth (RR 2.4, 95% CI 1.7 – 3.4) • Nulliparity (RR 2.1, 95% CI 1.9 – 2.4) • Maternal age > 35 years (RR 1.2, 95% CI 1.1 – 1.3) • Maternal age > 40 years (RR 1.5, 95% CI 1.2 – 2.0) • Antiphospholipid syndrome (RR 2.8, 95% CI 1.8 – 4.3) • Multiple gestation (RR 2.9, 95% CI 2.6 – 3.1)
Ende (28)	2021	Systemic review and meta-analysis of 27 studies of various types	Definite risk factors for atonic postpartum haemorrhage : • Asian race (OR 1.39, 95% CI 1.33-1.46) • Prior PPH (OR 2.25, 95% CI 1.02-4.96) • Diabetes (OR 1.22, 95% CI 1.08-1.39) • Prolonged labour (OR 1.76, 95% CI 1.53-2.03) • Genital tract trauma ◦ Perineal laceration (OR 1.67, 95% CI 1.28-2.18) ◦ Vaginal laceration (OR 2.19, 95% CI 1.13-4.24) ◦ Cervical laceration (OR 5.70, 95% CI 2.56-12.67)
Musaba (43)	2020	270 women with obstructed labour and 270 controls in women delivering in Eastern Uganda	Risk factors for prolonged labour : • Referral from a lower-tier facility (AOR 6.80, 95% CI: 4.20-11.00) • Nulliparity (AOR 2.15 95% CI: 1.26-3.66) • Herbal medicine use (AOR 2.72 95% CI: 1.49-4.96)

Accrombessi (36)	2018	Scoping review of 45 studies of various types, restricted to Africa	Risk factors for intrauterine growth restriction (IUGR): • Undernutrition (OR 2.28, 95% CI 1.59 – 3.25) • HIV (OR 1.86, 95% CI 1.38 – 2.50) • Malaria (OR 1.95, 95% CI 1.04 – 3.66) • Gestational hypertension (OR 2.61, 95% CI 2.42 – 2.82)
Say (31)	2014	WHO systematic analysis of 417 datasets from 115 countries	Common causes of maternal death: • Haemorrhage (27.1% of deaths, 95% UI 19.7% – 37.5%) • Hypertensive disorders (14.0%, 95% UI 11.1% - 17.4%) • Infection (10.7%, 95% UI 5.9% – 18.6%) • Abortion (7.9%, 95% UI 4.7% – 13.2%) • Embolism (3.2%, 95% UI 1.8% - 5.5%)
World Health Organisation (40)	2022	Worldwide (fact page)	Factors associated with congenital anomalies: • Parental genetic defects • Consanguineous parents • Socio-economic status • Advanced maternal age • Exposure to pollution or radiation • Nutritional deficiencies • Diabetes • Use of alcohol or drugs • Congenital infections
Mabrouk (35)	2022	Scoping review of 181 studies using “Sub-Saharan Africa” as a keyword	Risk factors for pre-term birth: • Previous history of pre-term birth • Underutilised antenatal care • Adolescent pregnancy • Advanced maternal age • Inter-pregnancy interval • Malaria • Premature rupture of membranes

			• HIV • Hypertension in pregnancy
Reinebrant (38)	2018	Systematic review of 85 reports from 50 countries	Common associations with stillbirths : • Antepartum haemorrhage • Congenital malformation • Disorders related to foetal growth • Hypoxic peripartum causes • Placental conditions • Infection

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1332 **Appendix C1: List of variables available in the CMJAH birth register**

1333

Record ID	Hb (Haemoglobin) (g/dL)
Event Name	Mode of delivery
Mothers race	Emergency caesar reason/indication
Mothers address (suburb, area, or region)	Does it mention lacerations, tears, or episiotomy? Or perineum intact?
Mothers nationality	Maternal status/complications post-natal
Mothers age	Was the mother referred or transferred somewhere?
Mothers parity	Estimated blood loss (mL)
Mothers gravidity	What was mothers preferred feeding method?
Number of miscarriages	Sex/gender
Number of abortions/TOPs	Infant status at birth - alive or not?
Gestational age - weeks /40	Infant outcome/complications
Gestational age - days	Was the infant referred or transferred somewhere?
Duration of labour - Hours	Apgar /10 - 1 minute
Duration of Labour - Minutes /60	Apgar /10 - 5 minutes
Antepartum complications/reason for referral	Apgar /10 - 10 minutes
RPR (Syphilis test)	Were any abnormalities noted? Check all that apply.
If RPR is positive, was any treatment for syphilis given?	Birth weight (BW/W/WT) or birth mass (BM/M) (g)
HIV	Birth length (L/BL/LT) (cm)
If HIV was positive, was any HIV treatment recorded?	Head circumference (O/HC) or occipito-frontal circumference (OF/OFC) (cm)
Was HIV treatment for the mom started in labour?	

1334

1335

1336 Appendix C2: List of variables in the HCHC birth register

File Number	Mother transferred out (TFO)?
Mothers nationality	Maternal death?
Mothers address (suburb, area, or region)	Gestational age at birth
Age	How many infants were born?
Gravidity	Gender
Parity	Alive (infant status)
RPR (Syphilis test) result	Apgar - 5 minutes
RPR treatment	Apgar - 10 minutes
HIV status	Resuscitate bagmask
On ART	Birth weight
HIV 1st test result	Head circumference
HIV re-test after 12 weeks result	Birth length
CD4 Count	Birth defects
Initiate ART	Live birth to HIV-positive woman
Birth before arrival (BBA)	Infant feeding method
Infant time of birth	Was EBF in 1 hour ticked, circled or marked?
Duration of active phase of labour	Admitted
Mode of delivery	Infant discharge
Perineum	Early neonatal death
Complications	Transfer out
Mother discharged?	If infant died, was transferred, or admitted, is a diagnosis recorded?

1337

1339

MATERNITY REGISTER:
KRAAMREGISTER:

TPH 1 (A) (81/500202)

Schedule "D"
 Skedule "D"

1340

Appendix E: Risk factors, directly corresponding variables, and proxy variables used for each outcome

Hypertensive disorders of pregnancy

Risk factors	Directly corresponding variable	Proxy variable
Prior pre-eclampsia	None	None
Chronic hypertension	None	None
Pregestational diabetes	None	Diabetes
Prior placental abruption	None	None
Obesity	None	Raised BMI*
Overweight	None	Raised BMI*
Assisted reproductive methods	None	None
CKD	None	None
Prior stillbirth	None	Poor obstetric history
Nulliparity	Parity	
Maternal age > 35/40	Maternal age at birth	
aPL	None	None
Multiple gestation	Multiple gestation	

*Removed because of lack of data

Maternal Haemorrhage

Risk factors	Directly corresponding variable	Proxy variable
Race	Race ¹	
Diabetes	Diabetes ²	
Abruption	Abruption ³	
Retained Placenta	None	Retained products of conception
Genital lacerations	Lacerations/tears/episiotomy	
Prolonged labour	Prolonged labour	

¹Race was removed because of non-random missingness

²No cases of haemorrhage had diabetes, hence it was removed from the model

³Abruption was included in the definition of haemorrhage and therefore not used as a risk factor

Prolonged labour

Risk factors	Directly corresponding variable	Proxy variable
Referral from lower tier facility	None	None
Nulliparity	Parity	
Use of herbal medicine in pregnancy	None	None

1351 Maternal Death

Risk factors	Directly corresponding variable	Proxy variable
Haemorrhage	Haemorrhage	
Hypertensive disorders	Hypertensive disorders of pregnancy	
Infection	None	
Abortion	Stillbirth; gestational age	
Embolism	None	None

1352

1353 LBW

Risk factors	Directly corresponding variable	Proxy variable
Undernutrition	None	
HIV	HIV	
Malaria	None	None
Gestational hypertension	None	Hypertensive disorders of pregnancy

1354

1355 Congenital anomaly

Risk factors	Directly corresponding variable	Proxy variable
Maternal genetic defect	None	None
Consanguineous parents	None	None
Socio-economic status	None	None
Advanced maternal age	Age	
Exposure to pollution or radiation	None	None
Nutritional deficiencies	None	None
Diabetes	Diabetes	
Use of drugs or alcohol	None	None
Congenital infections	None	None

1356

1357 Preterm delivery

Risk factors	Directly corresponding variable	Proxy variable
Previous history of pre-term birth	None	None
Underutilised antenatal care	None	None
Adolescent pregnancy	Maternal age	

Advanced maternal age	Maternal age	
Inter-pregnancy interval	None	None
Malaria	None	None
Premature rupture of membranes	None	None
HIV	HIV	
Hypertension in pregnancy	Hypertensive disorders of pregnancy	

1358

1359 [Stillbirth](#)

Risk factors	Directly corresponding variable	Proxy variable
Disorders related to foetal growth	None	None
Infection	None	None
Congenital malformation	Congenital anomaly	
Hypoxic peripartum	None	None
Placental conditions	None	None
Antepartum haemorrhage	None	Haemorrhage

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1361

1362 **Appendix F: Primary study human research ethics approval**

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

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Wits RHI Shandukani Research Centre
2nd Floor, Hillbrow Health Precinct
Corner Esselen Street & Klein Street
Hillbrow, Johannesburg
2001
Fax: 086 548 4889

Dear Dr Fairlie,

PROTOCOL: C1091006 - EPIDEMIOLOGY OF OBSTETRIC AND NEONATAL OUTCOMES IN SOUTH AFRICA

ETHICS REFERENCE NO: 180707

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial has been approved by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol/Expert Reviewer. Date of Meeting where trial was reviewed: 27 July 2018.

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. It is the responsibility of the Sponsor and Principal Investigator to ensure, where required, that relevant approvals are in place and compliance with the following is adhered to before a trial may begin:

- If trial is being conducted in Provincial Health facilities: Approval from the Hospital CEO / Clinic Manager / District Research Committee (whichever is applicable) be obtained.
- The study is submitted onto The National Health Research Database (NHRD).
- The relevant approvals are uploaded onto the NHRD system: Ethics Approval, SAHPRA Approval, Hospital CEO / Clinic Manager / District Research Committee Approval.

* A copy of the SAHPRA Approval and/or SAHPRA Notification letter must be submitted to the Ethics Secretariat Office for record purposes (IF SAHPRA APPROVAL / NOTIFICATION IS APPLICABLE).

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :

- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC-001 and SOP-IEC-005, Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study.

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* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the SAHPRA Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the South African Health Products Regulatory Authority and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING:

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE:

* The South African Department of Health, South African Health Products Regulatory Authority requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator(s) per fax: 011 274 9281 for our records (this is applicable with the initial Approval).

8.2 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

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9. WE AWAIT YOUR RESPONSES AS REQUESTED: Ensure to have these documents forwarded at the earliest for the HREC records.

* SAHPRA Approval letter and/or letter of Notification before the above study may commence / or where an Amendment may be implemented (IF SAHPRA APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* Copy of Independent Ethics Declaration Approval Form signed by the Principal Investigator. (this is applicable with the initial Approval).

* Kindly forward the above to the undersigned at fax: 011 274 9281 at your earliest convenience.

The above has been noted for the Ethics Committee information and records.

**KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA /
SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE**

Regards,



PROF CLEMENT PENNY

For and on behalf of the Human Research Ethics Committee: (Medical)

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1371 Appendix G1: Primary study approval documents (CMJAH)

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries: Ms. N. Mzila
Office of the Clinical Director
011 488 4812

Dear Dr. L. Fairlie

STUDY TITLE: Epidemiology of obstetrics and neonatal outcomes in South Africa.

DEPARTMENT: Obstetrics and Gynaecology

	DOCUMENTS REQUIRED FOR STUDENT RESEARCH	TICK
1.	Covering letter from the APPLICANT	X
2.	Research protocol	X
3.	Support letter from the Head of Department	X
4.	Ethics clearance certificate	
5.	NHRD Registration	
	DOCUMENTS REQUIRED FOR COMPANY RESEARCH	
1.	Covering letter from the APPLICANT/COMPANY	
2.	Research protocol	
3.	Support letter from the Head of Department	
4.	Ethics clearance certificate	
5.	Approval from the Department of Health	

CHECKED BY: Ms. N. Mzila

SIGNATURE: 

DATE: 06/09/2018

CHECKED BY: Splabale

SIGNATURE: 

DATE: 06/09/2018



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CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Office of the Head of Department: Obstetrics and Gynaecology

Enquiries: Dr L. Chauke

Tel: 011 488-3179

Fax: 011 643-2522

30 July 2018

Ms G. Bogoshi
CEO
Charlotte Maxeke Johannesburg Academic Hospital
Parktown
Johannesburg

Dear CEO

Re: Request to conduct research titled:

Permission to obtain: Research for the Maternal Case Records and Birth Register of patients who delivered at Charlotte Maxeke Johannesburg Academic Hospital between 01 Jul 2017 and 30 June 2018. Epidemiology of obstetric and neonatal outcomes in South Africa study: Dr Lee Fairlie.

The above matter refers. I have looked at the protocol and **satisfied to recommend** that he be granted permission to conduct the study as proposed. The candidate has also satisfied the requirements of the Wits Human Research Committee.

Thank you

Dr H. L. Chauke
Chief Specialist and Clinical Head
Department of Obstetrics and Gynaecology
Charlotte Maxeke Johannesburg Hospital
and the University of the Witwatersrand

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GAUTENG PROVINCE

HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email: Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
6th September 2018

Dear Dr. L. Fairlie

RE: Request to Access Maternal Case Records and Birth Registers of Patients Who Delivered At Charlotte Maxeke Johannesburg Academic Hospital between 01 July 2017 and 30th June 2018.

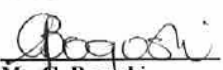
STUDY TITLE: Epidemiology of obstetrics and neonatal outcomes in South Africa.

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

~~Supported / not supported~~


Dr. M.I. Mofokeng
Clinical Director
DATE: 8/09/2018

Approved / not approved


Ms. G. Bogoshi
Chief Executive Officer
DATE: 07.09.2018

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1377 Appendix G2: Primary study approval documents (HCHC)

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA



JOHANNESBURG HEALTH DISTRICT

Faculty Of Health Sciences
Human Research Ethics Committee(Medical)
University of The Witwatersrand
Johannesburg, South Africa
cutlandc@rmpru.co.za

Enquiries: Dr EM Ohaju
Tel: 011 694 3888 Cell: 076 8831659
Email: Elizabeth.Ohaju@gauteng.gov.za

Hillbrow CHC: Administration Building
Cr Smith Str. & Klein Street
Private Bag X21, Johannesburg
South Africa, 2017

DRC Ref: 2018-11-016

NHRD Ref no: GP_201811_040

Dear: Dr Clare Cutland

Title: *Epidemiology of obstetric and neonatal outcomes in South Africa*

Your application for Research Approval refers.

The District Research Committee has reviewed your application. This letter serves as an in-principle approval to access the Districts Health facilities (mentioned below) for the above project subject to following conditions:

- The facility to be visited: **See Attached List**
- This facility will be visited from **29/01/2019 to 29/01/2020**
- The research can only commence after you submit an ethics clearance certificate from a recognized institution.
- You will report to the Facility Manager before initiating the study.

Region	Regional Health Manager	Contact No.	Cell phone
A (LA)	Nelly Shongwe	011 237 8010	082 467 9276
F(LA)	Oupa Montsioa	011 681 8130	082 467 9423
ABCEF	Ms Matlala	011 440 1259	082 307 0267
E (LA)	Vusi Mazibuko	011 582 1504	082 464 9547
D	Ms. Maria Mazibuko	011 674 1200	082 781 9919
D (L. A)	Busi Phiri	011 986 - 0164	082 467 9386

The following conditions must be observed:

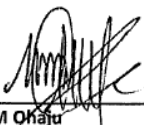
- Participants' rights and confidentiality will be maintained all the time.

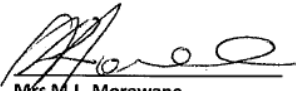
- The study will comply with **Publicly Financed Research and Development Act, 2008 (Act 51 of 2008) and its related Regulations.**
- You will submit a copy (electronic and hard copy) of your final report. In addition, you will submit a six-monthly progress report to the District Research Committee.
- Your supervisor and University of The Witwatersrand will ensure that these reports are being submitted timeously to the District Research Committee.
- The District must be acknowledged in all the reports/publications generated from the research and a copy of these reports/publications must be submitted to the District Research Committee.

We reserve our right to withdraw our recommendation, if you breach any of the conditions mentioned above.

Please feel free to contact us, if you have any further queries. On behalf of the District Research Committee, we would like to thank you for choosing our Johannesburg health district to conduct such an important study.

Regards,


 Dr E.M. Ohajo
 Chairperson: District Research Committee
 Johannesburg Health District
 Date 28/01/2019


 Mrs M.L. Morewane
 Chief Director
 Johannesburg Health District
 Date: 30/01/2019

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List of Facilities

17 ESSELEN STREET CLINIC
 80 ALBERT STREET CLINIC
 BEZVALLEY CLINIC
 CHIAWELO CHC
 CROWN GARDENS CLINIC
 DIEPKLOOF LA CLINIC
 DIEPKLOOF PROV CLINIC
 ELIAS MOTSOLEDI CLINIC
 GLENANDA CLINIC
 ITIRELENG CHC
 JABAVU/VUSABANTU CLINIC
 JEPPE CLINIC
 JOUBERT PARK CLINIC
 KIBLER PARK CLINIC
 KLIPSPRUIT WEST CLINIC
 LILLIAN NGOYI CHC
 MALVERN CLINIC
 MANDELA SISULU CLINIC
 MAYFAIR CLINIC
 MEADOWLANDS ZONE 2 PROV CLINIC
 MICHAEL MAPONYA PROV CLINIC
 MOFOLO CHC
 MOFOLO SOUTH CLINIC
 MOROKA CLINIC
 NALEDI PORTA CABIN
 NOKUPHILA CLINIC
 NOORDGESIG PROV CLINIC
 ORLANDO PROV CLINIC
 PROTEA GLEN CLINIC
 ROSETTENVILLE CLINIC

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SENAOANE CLINIC
SHANTY CLINIC
SINQOBILE CLINIC
SOUTH HILLS CLINIC
TLADI PROV CLINIC
YEOVILLE CLINIC
ZOLA CHC
ZONDI CLINIC
HILLBROW CHC

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1385 Appendix H: Nested secondary study human research ethics approval



R14/49 Dr Jean le Roux

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220310

NAME: Dr Jean le Roux
(Principal Investigator)
DEPARTMENT: School of Public Health
 Charlotte Maxeke Johannesburg Academic Hospital
 Hillbrow Community Healthcare Centre

PROJECT TITLE: *Prevalence and associated risk factors of adverse maternal and newborn outcomes in inner-city Johannesburg: a cross-sectional analysis of birth registers*

DATE CONSIDERED: 25/03/2022

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof L Fairlie and Dr S Sawry

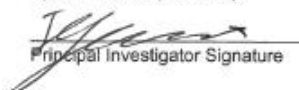
APPROVED BY: 
 Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 24/08/2022

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


 Principal Investigator Signature

29 SEP 2022
 Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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1388 Appendix I: Turnitin receipt and report



Digital Receipt

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Submission author:	Jean le Roux
Assignment title:	Draft submission (all, regardless of course/programme)
Submission title:	544158_msc_report_V1.7_20240228_clean.pdf
File name:	544158_msc_report_V1.7_20240228_clean.pdf
File size:	2.32M
Page count:	90
Word count:	22,036
Character count:	118,214
Submission date:	28-Feb-2024 08:28AM (UTC+0200)
Submission ID:	2306764677

Prevalence and associated risk factors of adverse maternal and newborn outcomes in inner-city Johannesburg: a cross-sectional analysis of birth registers



School of Public Health
Faculty of Health Sciences

Jean Gilbert le Roux
Student number: 544158

A research report submitted to the Faculty of Health Sciences in partial fulfillment of the requirements for the degree Master of Science in Epidemiology in the field of Epidemiology and Biostatistics

February 2024

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544158_msc_report_V1.7_20240228_clean.pdf

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Lee Fairlie

Date: 28/02/2024



Shobna Sawry

Date: 28/02/2024