UNIVERSITY OF THE WITWATERSRAND

Faculty of Health Sciences

A RETROSPECTIVE REVIEW OF THE CASE RECORDS OF COVID-19 DISEASE IN PREGNANT WOMEN IN A TERTIARY HOSPITAL

MSc (Medicine) Dissertation

Obstetrics and Gynaecology

Dr Shastra Avendra Bhoora

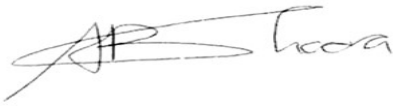
Student number: 0001382X

Supervisor: Professor Lawrence Chauke

Submitted to the University of the Witwatersrand in fulfilment of the requirements for the degree of Master of Science in Medicine (Obstetrics and Gynaecology).

DECLARATION

I, Dr Shastra Avendra Bhoora, student number 0001382X, declare that the dissertation I am submitting for examination for the masters in science degree is my own original work. The dissertation has not been submitted to any other academic institution.

Signed: 

Date: 24 November 2022

DEDICATION

This research dissertation is dedicated to my husband and son, who have been unwavering in their support and forgiving with their time. They continue to believe in me and encourage me to thrive.

PRESENTATIONS

March 2022

Presented at the 39th Perinatal Priorities Conference, Eastern Cape

March 2022

Research findings presented at the first CMJAH Inaugural Research Day

PUBLICATIONS

August 2022

Accepted for publication by the South African Medical Journal

Reference SAMJ 16552

ABSTRACT

Keywords: COVID-19, severity of disease, maternal and fetal outcomes, tertiary setting

Introduction and background: Coronavirus disease 2019 (COVID-19) remains a global communicable disease that is rapidly evolving. There are varying reports regarding the prevalence, profiles and outcomes of pregnant women with COVID-19. Limited information is available for developing country settings where disease profiles are different from high income countries. This study was conducted to describe the prevalence, profile and clinical outcomes of pregnant women admitted with a diagnosis of COVID-19 in a tertiary facility in Gauteng, South Africa.

Methods: The study was a retrospective review of maternal records over a six-month period during the first wave of the pandemic in the Gauteng province. The study group included all pregnant women who tested positive for COVID-19. Data captured included demographic, medical history, obstetric history, clinical findings and laboratory variables. This information was captured from paper-based clinical files onto a REDCap® database using dedicated data-collection sheets. On completion of the data capturing, the information was then exported into Microsoft Excel. Statistics analysed were mostly descriptive and analysis included medians with 95% confidence intervals where applicable. Ethical clearance for the study was granted by the WITS HREC (M201169).

Results: The study group included 204 pregnant women. The majority (97%) (n=198) were African with a median age of 31 years (IQR 26-35). Recorded BMI suggested 34% (n=44) were overweight and 51% (n=64) were obese. Co-morbidities were present in 41% (n=84) and more than one co-morbidity was present in 6% (n=13). HIV 33% (67/204) was the most common co-morbidity and viral loads were suppressed in 69% (40/58) and the median CD4 count was 405cells/ul (IQR 185-686). The caesarean section rate was 60% (105) mostly due to obstetric reasons and not COVID-19 indicated. There were 74 (36%) preterm deliveries and 8 (4%) of stillbirths. The median birth weight was 2940g (IQR 2450-3320g). Fifty-six (27%) patients presented with symptoms. Symptoms found predominantly were: cough 9% (n=18),

dyspnoea 6% (n=12) and headache 4% (n=8) however, the majority 77% (n=148) of the women were asymptomatic. MEOWS scores were used to triage disease profiles among those pregnant women who were symptomatic. MEOWS score of 0 means stable and a score of greater than 6 refers to critical illness. Five patients (3.9%) had recordable oxygen saturation below 94% (90-93%). Only 1 of the 5 (0.2%) was admitted into the ICU and was discharged alive. Thirty-three (63%) patients were critically ill (MEOWS >6), with 21(10%) admitted to the ICU and 3(1.5%) died from COVID-19, making the CRF 1.5%. Twenty-eight patients (13.7%) had pre-eclampsia and 61% (20/33) had a MEOWS score > 6. Pre-eclampsia was found to be significantly associated with severe COVID-19 disease ($p<0.0001$) and a higher BMI resulted in a greater MEOW score $p=0.012$, in contrast, patients with HIV had lower MEOWS scores ($p=0.025$).

Conclusion:

We found a high percentage of asymptomatic infections among pregnant. There was a low CFR amongst ICU admissions and not a single case of known neonatal transmission. There was a strong association of BMI and COVID-19 disease but low rates of severity of disease among those who were HIV positive and virally suppressed. Preeclampsia was significantly associated with severe COVID-19 disease and warrant greater caution. Future research into the interactions between HIV and COVID-19 in pregnancy as well as the use of scoring systems, like the MEOWS score, in COVID-19 in pregnancy are needed.

ACKNOWLEDGEMENTS

I am grateful to the guidance and motivation provided to me by my supervisor Professor Chauke. He was instrumental in the conception of the study and has been supportive and patient during all steps of the research journey.

There are many who have been contributory in the production of this research and I would like to acknowledge them all:

- Dr Jarrod Zamparini has been the greatest technical support. Dr Zamparini has always been available to assist with access to REDCap®, data collection, data analysis and data interpretation.
- I would like to thank Dr Balie, Dr Odell, Dr Murray and Dr Mall for assisting with the data capturing.
- Thato Ratsuma has kept an accurate record of all patients admitted into the COVID ward and has made these details available to me despite the challenges experienced with the safe keeping of the records.
- Sister Beverley Letsoalo who allowed me access to her office and computer. She was also encouraging and helpful during stressful times. Her kindness is unmeasured.
- Dr Nyakoe Robert has assisted with bench marking and the formatting of the thesis.
- Ms Rogene Beukes for being gracious with her time and for the technical support.

I am eternally indebted to the patients who graciously agreed to participate in the study and to all my colleagues who under extreme pressures of clinical work assisted to counsel patients and capture the relevant data.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AIDS	Acquired immunodeficiency Syndrome
ALT	Alanine aminotransferase
BAME	Black and minority ethnicity
BMI	Body mass index
CFR	Case-fatality rate
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPAP	Continuous positive airway pressure
CRP	C - reactive protein
DRC	Democratic Republic of the Congo
EBOV	Ebola haemorrhagic fever
FBC	Full blood count
FRC	Functional Residual Capacity
GA	Gestational age
H1N1	H1 haemagglutinin N1 Neuraminidase hemagglutinin
HIV	Human immunodeficiency virus
HS-Trop T	High sensitivity troponin test
ICU	Intensive Care Unit
INOSS	International network of obstetric survey systems

LDH	Lactate dehydrogenase
MEOWS	Modified Obstetric Early Warning Score
MERS	Middle East Respiratory Syndrome
MUAC	Mid-upper arm circumference
NCCEMD	National Committee on Confidential enquiries into Maternal Deaths
NHS	National Health System
PCT	Procalcitonin
ProBNP	Pro hormone B-type natriuretic peptide
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT-PCR	Reverse-transcriptase polymerase chain reaction
SARS	Severe Acute Respiratory Syndrome
sFlt-1/PIGF	Soluble fms-like tyro-sine kinase-1 to placental growth factor
TB	Tuberculosis
TPHA	Treponema pallidum haemagglutinin assay
U&E	Urea and electrolytes
USA	United States of America
UtAPI	Uterine artery pulsatility index
ZA	Neuraminidase

DEFINITIONS

BMI	Body mass index calculated in kg/m^2
D-dimer	A fragment produced during degradation of a clot. D stands for domain and dimer indicates two identical domains
Hypoxaemia	A below normal level of oxygen in the blood
INTERCOVID	A large, multi-national, prospective study assessing the effect of COVID-19 in pregnancy worldwide Maternal death a death of a women while pregnant or within 42 days of delivery
Maternal near-miss	an event in which a pregnant woman comes close to death but does not die and survives a complication in pregnancy, intrapartum and 42 days post delivery
ProBNP	Hormone release by the heart in response to changes in heart pressure
Adolescent pregnancy	Pregnancy in women 10-19 years old

1 LITERATURE REVIEW:

1.1 Introduction

The novel coronavirus infection first identified in China in December 2019 has stemmed to become one of the most significant public health hazards in current times. [1–5] In the beginning, the novel virus was referred to as 2019-nCoV and then subsequently referred to as SARS-CoV-2. The disease process caused by SARS-CoV-2 is called COVID-19. [6]

COVID-19 diseases has been rapidly wide spreading and within a short period has found its way throughout the globe [7] .The World Health Organization declared COVID-19 a pandemic on March 11, 2020. [8] The South African government implemented a strict lockdown of the country to help curb the spread of the virus in March 2020. SARS-CoV-2 like previous corona viruses induces a respiratory infection that can progress hastily into severe pneumonia and can ultimately result in death in high-risk medical groups. [8] Epidemics from recent years of many emerging viral infections, particular the corona virus family, have had injurious consequences on pregnancies resulting in significant morbidity and mortality for both mother, fetus and neonate. COVID-19 was initially thought not to affect pregnant women more than the non-pregnant population but it is becoming more evident that pregnant women are experiencing more adverse outcomes as COVID-19 evolves.[9–12] Although it has been a steep learning curve these past months, much is still unknown.

1.2 SARS-CoV-2

Coronaviruses are enveloped non-segmented positive-sense RNA viruses. They belong to the family *Coronaviridae* and are widely spread among humans, other mammals, and birds and cause multi-system disease i.e. respiratory, enteric, hepatic, and neurologic diseases. Human disease is often mild and has been caused by six coronavirus species, four of which, namely: 229E, OC43, NL63, and HKU1 — are predominant and classically cause symptoms associated with the common cold in healthy individuals. *Coronaviridae* exhibit genetic diversity and novel coronaviruses are likely to occur sporadically in humans. Fatal illness was previously caused by two *Betacoronaviruses*, zoonotic in nature, namely: severe acute

respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV.).[2,13]

SARS-CoV-2 has unique features that differ from other *Betacoronaviruses* in that they bind effectively with human angiotensin converting enzyme-2 receptors as they exhibit mutations on the receptor-binding domain of a S protein and have O-linked glycans and polybasic furin cleavage sites.[14]

The first cases of SARS-CoV-2 were reported after the infected individuals had visited the Wuhan Huanan Seafood Wholesale Market prior to the onset of the disease. [15] It was unclear at first as to what or who the primary vector was and in January 2020 it became evident that droplet transmission from person-person contributed to the wide spread of disease. The initial clinical information reported SARS-CoV-2 cases as mild disease with only a small percentage of people displaying severe and even lethal disease.[4,5]

COVID-19 in pregnancy is diagnosed on history of a close contact, clinical manifestations, chest radiography, and directed tests, similar to the criteria of diagnosis for SARS -CoV-1 and MERS in pregnancy. Pregnant women are susceptible to respiratory disease owing to impaired cellular immunity and physiological changes. The major symptoms presented in pregnancy are nonspecific and feature a fever, cough, myalgia, and dyspnoea.[8]

1.3 Physiology of pregnancy

The increased severity of respiratory infections in pregnant women is thought to be related to normal physiologic changes that occur during pregnancy. The respiratory, circulatory, secretory, and immune systems, all undergo physiological alteration during pregnancy: heart rate and oxygen consumption increase, lung capacity decreases, and there is a shift away from cell-mediated immunity.

The maternal respiratory system in particular undergoes physiological and anatomical changes as a result of uterine quiescence induced by the effects of progesterone and upward displacement of the diaphragm caused by the growing uterus.[16,17] The elevated diaphragm and decreased compliance of chest wall, eventually lead to a reduction in functional residual capacity (FRC) by 30%. The decline in FRC renders the mother prone to hypoxaemia, subsequently compensated by increased tidal volume and hyperventilation. Pregnant women

are more likely to contract COVID-19 as a result of SARS-CoV-2 being in the air as compared to non-pregnant people.[18]. In addition, changes of nasal mucosa occur and are mediated by progesterone during pregnancy. The upper respiratory tract changes in a way that it will not be able to clear SARS-CoV-2 effectively owing to adhesive properties of the virus. [18] The hypoxic respiratory failure in women after infection with a respiratory infection is further complicated by the increase in metabolic rate and oxygen consumption (seen with the cardiovascular changes), the decrease in FRC and ventilation-perfusion mismatch. Furthermore, pregnancy is considered to be a supressed immunological state to tolerate the development of the allogeneic fetus.[18,19]

1.4 Past viral outbreaks

Earlier pandemics of many emergent viral respiratory and viral haemorrhagic infections have classically resulted in poor obstetric outcomes. These disturbing outcomes have included maternal morbidity and mortality, maternal-fetal transmission of the virus, intrauterine fetal loss, perinatal infections and neonatal death.[19] Data on pregnant women infected with COVID- 19 is still emerging and remains sparse. The limited data analysed thus far in the current pandemic suggests that COVID-19 outcomes for the mother appear more favourable compared to Influenza A (H1N1) (2009), SARS and MERS. This is further illustrated by the case fatality rate of 25% for MERS, 18% for SARS and 0% for COVID-19 in the initial months of the pandemic. [19]

Influenza:

Influenza A, B, and C viruses belong to the family *Orthomyxoviridae.* They are characterized by segmented, negative-strand RNA genomes and are dependent on RNA polymerase for replication. Influenza A known as an entity of the H1N1 virus, is further categorized by the subtype of surface glycoproteins, namely the hemagglutinin (HA) and the neuraminidase (NA). [17]

Influenza A pandemics were experienced in 1918, 1957 and 2009. [20] Pregnant women and those in the postpartum period were found to have severe illness and an increase in mortality when compared to the non-pregnant general population. [21] The pandemics of 1918 and

1957 reported large numbers of pregnant women dying from influenza. In 2009 it became more evident that pregnant women were frequently hospitalised for severe acute respiratory syndromes. A systematic review of influenza or influenza-like illness in the first trimester from 2013, suggested that the presence of influenza infection was associated with an increased risk of congenital abnormalities, including cleft lip, neural tube defects, hydrocephaly, and congenital heart defects. [22] Pyrexia was found to be a common clinical complication of influenza and a risk factor for certain birth defects and other adverse infant outcomes. [23] Antipyretics could attenuate the hyperthermia induced by the influenza infection and limit the consequence of birth defects and adverse infant outcomes.[23] Increased severity of disease caused by influenza necessitates the routine administration of the inactivated form of the influenza vaccine.

Severe Acute Respiratory Syndrome

Severe Acute Respiratory Syndrome is caused by coronavirus SARS-CoV-1[19] It is transmitted through person-to-person contact, respiratory droplets, environment contamination and possibly sewage. The SARS epidemic occurred over nine months from November 2002 to July 2003. Greater than 8000 people in 26 different countries were affected and claimed the lives of 774 people. Twelve pregnant women were reported to contract the virus and three women died which translated into a 25% case fatality rate. Miscarriages were prevalent in the first trimester and intrauterine growth restriction and preterm birth occurred in the second and third trimesters of pregnancy. Three out of the four preterm deliveries were induced deliveries that were conducted for maternal conditions. Vertical transmission was not found in any of the infants. Clinical outcomes of pregnant women that contracted SARS-CoV-1 were worse that non pregnant women in the population.[19]

Middle East Respiratory Syndrome

Middle East Respiratory Syndrome also causes a severe acute respiratory syndrome and was first reported in 2012, from Saudi Arabia. Soon after it was detected, MERS spread to more than 27 countries within and beyond the Arabian Peninsula. Human infection was suggested

to come from camels and bats. Poor infection control and preventative measures were identified as reasons for outbreaks of MERS. Eleven pregnant women were affected by MERS. This disease also revealed alarming results of maternal death, premature delivery, neonatal intensive care unit admissions and perinatal deaths. No vertical transmission of MERS was reported [19].

Zika Virus

Zika virus belongs to the Flavivirus genus, family to dengue virus, West Nile virus and yellow fever virus. The virus was found in the rhesus macaque monkey and this was the first vector identified for human transmission. As the virus spread, it became more evident that it may have been spread by a genus of mosquito, the *Aedes* species, and aggressive biters. Hetero sexual transmission has also been confirmed from the presence of viral RNA found in semen and vaginal secretions. Zika virus was first identified in 1947 in Uganda and since then transmission has been sporadic, occurring mainly in Africa and South Asia. Significant outbreaks were later reported in 2007 in the South Pacific, in 2013 in the French Polynesia and in 2015 Zika virus was found in South America and the United States of America. In 2016, 2246 cases were reported in the USA. Twenty percent of the infected population were symptomatic. Symptoms were non-specific and included fever of sudden onset, joint pain, conjunctivitis and a red maculopapular rash. Guillain-Barre syndrome often occurred following the febrile illness. All pregnant women that experience vague symptoms or who had a possible exposure were tested for the Zika virus. The greatest congenital complication was an increase in cases of microcephaly confirming congenital infection and fetal affectation. Prenatal counselling has become imperative in reducing fetal risks associated with Zika virus[24].

Ebola virus

Ebola haemorrhagic fever, EBOV, belongs to the virus family Filoviridae, genus *Ebolavirus*, and was first discovered in 1976 near the Ebola River of the Democratic Republic of the Congo (DRC). It is not very clear how at first human infection occurs but fruit-bats and primates (non-human) have been thought to initially spread the disease. The virus is highly

contagious, resulting from contact with the bodily fluids of infected-symptomatic persons. EBOV outbreaks have been confined to sub- Saharan Africa and the epidemic of EBOV of 2014-2016 was devastating, claiming 11000 lives. More than 5000 of these infections occur in women of reproductive age. The case fatality rate ranged from an alarming 25-90 percent and was the highest in fetuses and neonates. Other obstetric complications that were reported included spontaneous miscarriage, intrauterine fetal death and vaginal bleeding. [25]

HIV

Human Immunodeficiency virus is a RNA virus, whose genetic and mechanical properties promote viral replication and integration into a healthy human T-cell during initial cellular infection. Acquired Immune Deficiency Syndrome (AIDS) is the disease caused by HIV types 1and 2 was first recognized as a new entity in 1981(origin of HIV-Sharp). Since, it has burdened the world and the magnitude of the HIV pandemic remains exponentially high in low to middle income countries.[26] Close to eight million people are living with HIV in South Africa, making up more than 20% of HIV infections globally. Biological, social, behavioural, cultural and economic injustices result in the unreasonable and disproportionate rates of HIV among women, particularly young and adolescent women. Women of reproductive age comprise more than half of all people living with HIV infection worldwide and it was estimated in 2017 that more than 1.5 million women with HIV will give birth annually. The consequences of HIV vary depending on the use of antiretroviral therapy. Pregnant women on highly active antiretroviral therapy are less likely to be infected with tuberculosis and other severe opportunistic infections. Pregnant women not on HAART experience TB and anaemia more frequently and with greater complication. Fetal outcomes result in significant intrauterine growth restriction. Perinatal concerns revolve around vertical transmission and horizontal transmission. The presence of HIV is confirmed in both placental tissue and breast

Milk.[25,27–30]

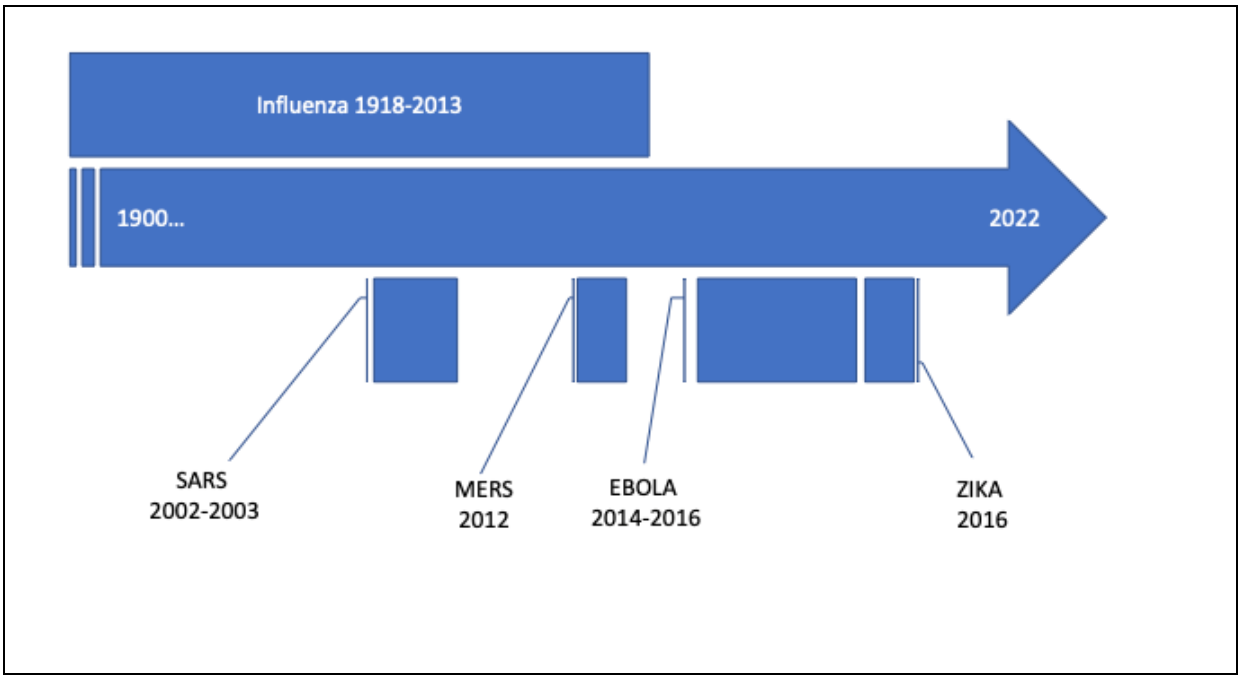


Figure 1: Graphic representation of previous viral outbreaks

1.5 COVID-19 in pregnancy

Prevalence of disease

A living systematic review and meta-analysis of 26 studies and 11 432 women of coronavirus disease in pregnancy reports most recent data: that the overall rate of COVID-19 diagnosis in pregnancy is 10% (95% CI 7% to 14%). These rates varied by the sampling procedure, which translated into a mean of 7% positivity rate among asymptomatic women and mean of 18% positivity amongst women that showed symptoms.[31] Sutton et al of Columbia University in New York described a 13.1% asymptomatic positivity rate and 1.9% symptomatic positivity rate among 215 pregnant women who were admitted into the labour ward for delivery. [32] The proposal in the South African setting prior to achieving universal testing was to advocate for judicious personal protective equipment to mitigate against infectious spread to both the patient and the healthcare worker during labour and delivery. [33]

Clinical manifestations of COVID-19 in pregnancy

Amongst pregnant women who were symptomatic for COVID-19, fever was the most prevalent symptom followed by cough and dyspnoea. [31,34] The INOSS, International network of obstetric survey systems based cohort study in South Africa reports that cough super ceded fever and dyspnoea. [35] When compared to non-pregnant women, the incidence of fever and cough did not differ significantly between the two groups (p=0.765). [36]

Severity of disease has been experienced amongst high risk groups. Pre-existing comorbid conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension and cancers have been associated with an elevated case-fatality rate (CFR). [37] South Africa has a high prevalence of non-communicable disease processes, namely, hypertension 26.9% and diabetes 11.3%. A case series of the first 100 COVID-19 affected patients at Charlotte Maxeke Johannesburg Academic Hospital, in Johannesburg, illustrated that hypertension and diabetes were evident in 31 patients (31%) and 18 patients (18%) respectively. HIV is another challenging healthcare entity in the country and 11 patients (11%) were affected. [38] Hypertension was the commonest comorbidity amongst pregnant women investigated in the Ekurhuleni district in South Africa, followed by diabetes and obesity. [39] Among the pregnant women who died in Ekurhuleni over a six month period, 6 women (100%) had hypertension and 3 women (50%) tested positive for HIV. [40]

Pregnancy and neonatal outcomes

During the first half of 2020, 11308 pregnancies were identified during a systematic literature review. Of pregnancies delivered and reported, 98% of women (10 437/10 597) survived until delivery or until hospital discharge and 96% (1375/1428) of women delivered a live fetus. The frequent mode of delivery was by caesarean section (70% 612/871). Fetal outcomes included: 20 spontaneous miscarriages, 17 elective abortions, 14 stillbirths, and 2 ectopic pregnancies, however the overall survival was 99% (1155/1163) of fetuses/neonates. [41]

Severity of disease in pregnancy

The majority of COVID-19 cases in pregnancy are mild to moderate in severity (79% 1583/1999). [41] Those pregnant women who suffer severe disease have a greater risk of ICU admission and potential death than non-pregnant women. [42]

Early in the pandemic Brazilian authors coined the term: 'An invisible tragedy.' This emotive piece exemplified the high prevalence of COVID-19 related maternal deaths.[43] At the end of May 2020, 232 severe cases of COVID-19 and 36 COVID-19 related maternal deaths were reported by the Ministry of health. Brazil was acknowledged to be the leading country of COVID-19 related maternal deaths.[10] During the same time period, the Swedish reported poorer outcomes for pregnant women admitted to intensive care units (ICU), Iran and Mexico reported 6 maternal deaths each and five COVID-19 related deaths were reported by the United Kingdom.[9,10,44,45] South African analysis of COVID-19 in pregnancy presented a CFR of 6.3% (39/621), 29 (74%) of the 39 maternal deaths were due to COVID-19 disease.[35]

COVID-19 in South Africa

Healthcare systems in developed countries were hard hit during the pandemic with increasing infection and death rates. [46] This global experience raised fear and concerns among developing countries, like South Africa, where local disease like tuberculosis (TB) and HIV strain the current health care system [35 38,47]. Informal settlements are in close proximity to each other and potentially this could also be a huge risk for rapid droplet transmission of COVID-19.[48,49] Pregnant patients remain vulnerable and research in low-middle income countries remain limited. On proposal of this research project there were no known local publications. As the pandemic has evolved there has been data available for the public and private setting which reviewed 673 COVID-19 pregnant cases from 36 healthcare facilities during the first wave.[35] Ekurhuleni district describes the outcomes of 103 COVID-19 pregnant cases over a six-month period and found more than half their study population to be symptomatic for COVID-19[39]. Another study focused on neonatal findings, describing the maternal characteristics and neonatal outcomes of 111 COVID-19 pregnant cases over eight months, only 25% of neonates were admitted to the neonatal department with no or mild disease and the majority of COVID-19 positive pregnant mothers were asymptomatic

(80%).[39,48] A Tygerberg study reviewed 100 COVID-19 pregnant cases over a three month period and found 40% of their high risk pregnant study group to be critically ill.[50]
Each study was unique in their description, with regard to patient profiles and background settings and were placed in different provinces throughout the country. The overall consensus proposed was for more research in a South African setting.

2 JUSTIFICATION FOR RESEARCH:

It is inevitable that pandemics like COVID-19 evoke anxiety and uncertainty of what will unfold. It is a new disease and although much has been established the ongoing global research into the subject is currently robust and the findings are rapidly changing. At first pregnant women were not more affected than the general non-pregnant population but later reports have indicated that a percentage of pregnant women may appear to have more severe disease than the non-pregnant population, resulting in higher ICU admissions and higher mortality.[9, 42,44,45] It is with these uncertainties and contemplations in mind that this study has been conceived, in an endeavour to review and report on the profile and outcomes of pregnant patients that present to a tertiary institution in a LMIC, like South Africa.

3 AIMS AND OBJECTIVES

AIM OF THE STUDY

To establish the demographic and clinical profile of pregnant women diagnosed with COVID-19 at a tertiary institution over six months.

OBJECTIVES

1. Describe the demographics of pregnant women diagnosed with COVID-19 at CMJAH
2. To describe the clinical outcome of mothers and the babies delivered to COVID-19 positive mothers
3. To assess the demographic and clinical predictors of the severity of COVID-19 in the study population

4 METHODS

4.1 Study design

This was a retrospective descriptive review of clinical records of all pregnant women with reverse-transcriptase polymerase chain reaction (RT-PCR) - or antigen-confirmed COVID-19 admitted to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 6 March and 30 August 2020. All women who were pregnant irrespective of the gestational age where included in the study.

4.2 Study setting

CMJAH is a 1088-bedded central hospital located in Johannesburg, South Africa. The hospital services a large portion of the City of Johannesburg and serves as a referral site to multiple smaller hospitals and midwife-led obstetric units in the city. Approximately 9,500 deliveries occur annually and more than 30,000 women are seen at the several high risk antenatal clinics per year at the hospital. There are close to 23 medical facilities that refer high risk cases to CMJAH; three District hospitals, seven Regional hospitals, as well as 10 Midwife obstetric units and associated clinics. During the COVID-19 pandemic CMJAH was acknowledged as a leading COVID-19 hospital and received many moderate-severe case referrals from within the cluster, as well as from the private medical sector.

4.3. Sampling

All pregnant women with a diagnosis of COVID-19 during the study period were included**.**

4.4 Methodology

Pregnant patients diagnosed with COVID-19 were admitted into a designated ward within the obstetrics and gynaecology department at CMJAH. The names and hospital numbers of all pregnant women with COVID-19 were retrieved from the ward register. The ward clerk compiled a list of the COVID-19 positive cases that were admitted into the ward which assisted

in identifying the cases for review during the study period. This list was then used to access the maternal records and clinical notes from patient affairs and the records department at CMJAH. Once the available files were retrieved the data collection process was initiated.

Data captured included demographic, medical history, obstetric history, clinical findings and laboratory variables. This information was captured on discharge or death from paper-based clinical files onto a database, REDCap®, version 11.4.4, Vanderbilt University 2021, using dedicated data-collection sheets. On completion of the data capturing, the information was then exported into Microsoft Excel®, Version 16.5.4, Microsoft Corporation, Redmond, USA and subsequently analysed using Prism 9.3, GraphPad Software Inc., La Jolla, California.

Routine pregnancy-specific data was collected from clinical maternal records and included gestational age, number of fetuses, parity, gravidity, antenatal booking laboratory tests (HIV status, rapid plasma reagin (RPR) or treponema pallidum haemagglutinin assay (TPHA) for syphilis serology, Rhesus status, pregnancy outcome, mode of delivery and indication for caesarean delivery if done. The BMI and MUAC were recorded on admission. Obesity was defines as a BMI > 30kg/m^2 and a MUAC measured > 30.5 cm Data regarding birth weight and Apgar score was also collected. Neonates were tested for COVID-19 as per the Department of health protocol.

Women were assessed as symptomatic for COVID-19 based on the presence of one or more of respiratory symptoms (including cough, dyspnoea, sore throat and rhinitis), ageusia, anosmia, diarrhoea, fatigue, malaise, fever and myalgia. All women without symptoms were considered asymptomatic and assessed as being admitted for pregnancy-related reasons as opposed to COVID-19. Women who were admitted for pregnancy-related reasons and who also presented with symptoms were isolated and tested for COVID-19.

Clinical severity was analysed using the Modified Obstetric Early Warning Score (MEOWS), although not validated for COVID-19 this score has been used in multiple settings as a marker of severity in pregnant women with COVID-19.

Routine laboratory tests performed for all women included, a full blood count (FBC) and urea and electrolytes (U&E) for asymptomatic disease and a full COVID-19 screen of blood tests for those who presented with mild, moderate or severe disease. These tests were congruent with the adult cohort of COVID-19 infected individuals and included: C-Reactive Protein (CRP), D-Dimer, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), pro hormone B-type natriuretic peptide (ProBNP), high sensitivity troponin test (HS-Trop T), Ferritin levels,

differential count, and procalcitonin (PCT) in addition to the FBC and U&E. If women were found to be HIV positive a CD4 count and HIV viral load were done at the time of admission, as per national prevention of mother to child (PMTCT) guidelines.

4.5 Statistical Analysis

Statistics are mostly descriptive and are reported in table format. The analysis includes medians with 95% confidence intervals and standard deviations where applicable. Data were assessed for normality using the Shapiro-Wilk normality test and found to be non-normally distributed, and thus non-parametric statistical tests were used for all analyses including Mann-Whitney U, and Spearmen rank correlation.

A general linear model (GLM), with a Poisson distribution and log link function, was used to analyse the demographic and clinical predictors of COVID-19 severity, using the MEOW scores as a proxy for levels illness.

4.6 Ethical approval

All patient parameters and identifiers were kept confidential and only available to the researcher. Permission to conduct the study was obtained from the chief executive officer (CEO) of CMJAH.

Ethical approval for this study was obtained by the Wits Human Research Ethics Committee (HREC) (Medical clearance certificate M201169) and the Research Committee of CMJAH. The establishment of the CMJAH database was approved by the same committees. The study was registered with the National Health Research Database (NHRD).

5 Results

Recruitment of cases

There were a total of 895 patients captured on the CMJAH COVID-19 database over the six month study period, 527 were female and 44. 8% (236/527) of the female patients were pregnant. All non-pregnant female patients were excluded. Records were only available for 204 (86.4%) pregnant women. (Figure 1).

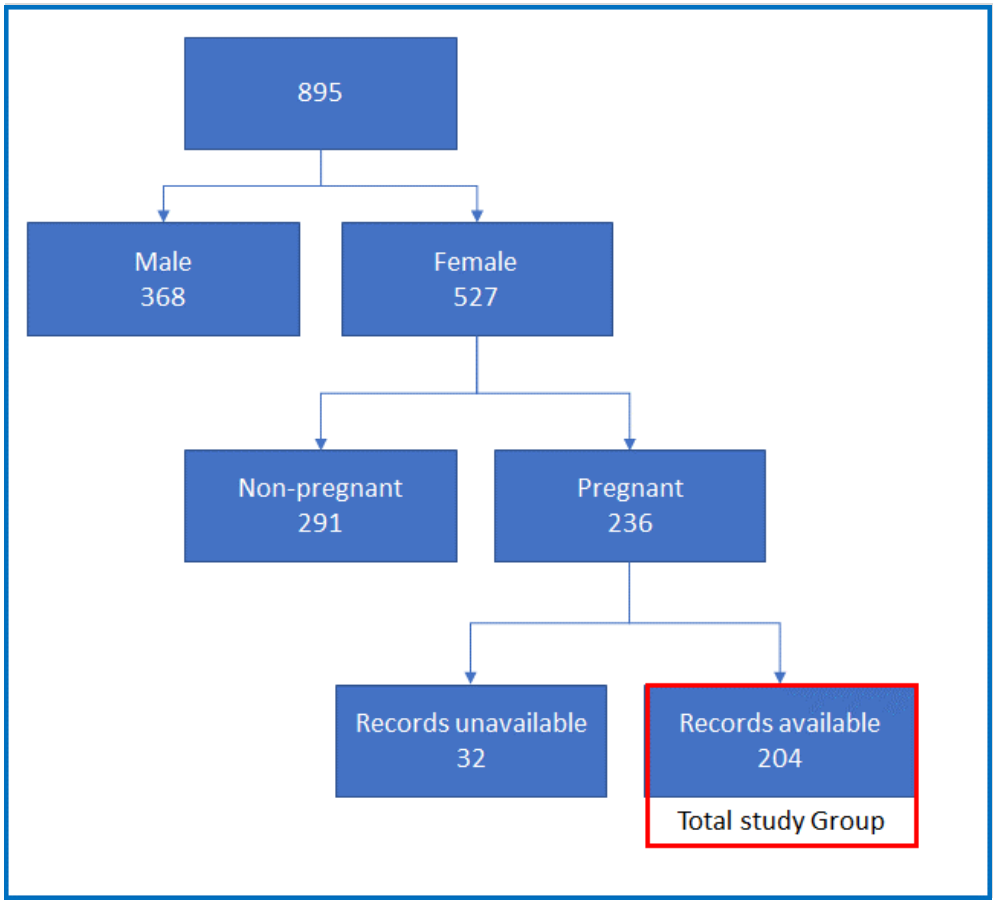


Figure 1

Flow chart showing the recruitment of study subjects for COVID-19 in pregnancy

Demographics

Most of the patients 198 (97%) were of black race. This is consistent with the demographics of the population served by my facility. The median age of the study population was 31 years (IQR 26 – 35) with the youngest and oldest aged 14 and 47 years respectively. There were 7 (3.4%) teenage pregnancies. Thirty-one patients (15%) were nulliparous and 27 (13%) were on their fifth or greater pregnancy. Median gestational age on admission for the pregnancies in my study was 37 weeks (IQR 30 – 39) with most patients 42% (n = 85) presenting at a gestational age of 38 weeks or greater. BMI could only be calculated for 128 patients because of missing data. A total of 44(34%) and 64 (51%) out of the 128 patients with weight recordings were overweight and obese respectively. This contrasts with data for mid-upper arm circumference (MUAC) which was available for 111 patients which only classified 28% (31/111) of the patients as overweight. The majority of the patients in our study had no previous comorbidity 5% (107/204) with 41% (84/204) affected by one comorbidity and 6% (n =13/204) with more than one comorbidity. The most common comorbidity recorded was HIV, with 33% (67/204) of the total patient study group being HIV positive. Of the HIV positive patients HIV viral loads were available for 58 patients with 69% (40/58) virologically suppressed according to national guidelines (VL < 50 copies/ml). CD4 counts were available for 43 patients with CD4 count above 200 cells/ul in 74% (32/43) of patients. Median CD4 count was 405 cells/ul (IQR185-686).

Demographic data for both the asymptomatic and symptomatic groups are presented in table 5.1.

Table 5.1: Maternal demographic characteristics

Race	Total (n = 204)	Symptomatic (n = 56)	Asymptomatic (n = 148)	p
Black. n (%)	198 (97%)	52 (93%)	146 (99%)	0.049
White. n (%)	4 (2%)	4 (7%)	0 (0%)	
Indian. n (%)	2 (1%)	0 (0%)	2 (1%)	
Age				
Age (years), median (IQR)	31 (26 - 35)	32 (27 - 35)	30 (26 - 35)	0.640
Under 25 years old. n (%)	35 (17%)	8 (14%)	25 (17%)	0.098
25 - 29 years old. n (%)	47 (23%)	10 (18%)	37 (25%)	
30 - 35 years old. n (%)	77 (38%)	29 (52%)	48 (33%)	
Over 35 years old. n (%)	45 (22%)	9 (16%)	36 (25%)	
Gravidity				
Median (IQR)	3 (2 -4)	3 (2 - 4)	3 (2 - 4)	0.684
Nulliparous	31 (15%)	9 (16%)	23 (16%)	0.339
Grav 5+	27 (13%)	7 (13%)	20 (14%)	
Unknown	6 (3%)	3 (5%)	1 (1%)	
Gestational Age				
Median (IQR). weeks	37 (30 - 39)	36 (28 - 38)	7 (30 - 39)	0.217
GA <14. n (%)	11 (5%)	0 (0%)	11 (7%)	0.010
GA 14 – 22. n (%)	15 (7%)	4 (7%)	11 (7%)	
GA 23 – 27. n (%)	16 (8%)	10 (18%)	6 (4%)	
GA 28 – 31. n (%)	21 (10%)	5 (9%)	16 (11%)	
GA 32 – 37. n (%)	53 (26%)	19 (34%)	34 (23%)	
GA 38 – 40. n (%)	73 (36%)	15 (27%)	58 (39%)	
GA 41+. n (%)	12 (6%)	2 (4%)	10 (7%)	
Missing. n (%)	3 (1%)	1 (2%)	2 (1%)	
Physical Characteristics				
Weight (kg). median (IQR)	77 (66.8 – 90.5). n = 143	85 (76 - 97). n = 35	75 (66 - 87). n = 108	0.005
Height (cm). median (IQR)	159 (156 - 165). n = 129	160 (156 - 165). n = 30	159 (156 - 165). n = 99	0.822
BMI (kg/m2). median (IQR)	29.8 (26.7– 36.1). n = 128	33 (28,6 - 37). n = 30	29,3 (26,4 - 34,5). n = 99	0.040
BMI Underweight (<18). n (%)	0 (0%)	0 (0%)	0 (0%)	0.334
BMI Normal (18 - 24.9). n (%)	21 (16%)	3 (10%)	18 (18%)	
BMI Overweight (25 - 29.9). n (%)	44 (34%)	7 (23%)	37 (37%)	
BMI Obese Class I (30 - 34.9). n (%)	29 (23%)	9 (30%)	20 (20%)	

BMI Obese Class 2 (35 - 39.9). n (%)	19 (15%)	6 (20%)	13 (13%)	
BMI Obese Class 3 (>=40). n (%)	16 (13%)	5 (17%)	11 (11%)	
MUAC (cm), median (IQR)	30 (27 - 33). n = 111	31 (29 - 34). n = 32	29 (27 - 33). n = 79	0.099
MUAC Underweight (<23). n (%)	3 (3%)	1 (3%)	2 (3%)	0.605
Normal (23-32). n (%)	77 (69%)	20 (63%)	57 (72%)	
MUAC Overweight (>=33). n (%)	31 (28%)	11 (34%)	20 (25%)	
Comorbidities				
Patients with no pre-existing comorbidities. n (%)	107 (53%)	32 (57%)	75 (51%)	0.620
Patients with one comorbidity. n (%)	84 (41%)	20 (36%)	64 (43%)	
Patients with two comorbidities. n (%)	13 (6%)	4 (7%)	9 (6%)	
Asthma. n (%)	4 (2%)	2 (4%)	2 (1%)	0.303
Chronic Kidney Disease. n (%)	1 (0.5%)	0 (0%)	1 (1%)	>0.999
Chronic Lung Disease (incl TB). n (%)	1 (0.5%)	1 (2%)	0 (0%)	>0.999
Diabetes Mellitus. n (%)	10 (5%)	3 (5%)	7 (5%)	>0.999
Epilepsy. n (%)	1 (0.5%)	1 (2%)	0 (0%)	>0.999
Hypertension. n (%)	17 (8%)	3 (5%)	14 (9%)	0.411
HIV. n (%)	67 (33%)	15 (27%)	52 (35%)	0.317
HIV Viral Load (n = 58)				
HIV Viral Load <= 50copies/ml. n (%)	40 (69%)	11 (79%)	29 (66%)	0.513
HIV Viral Load > 50copies/ml. n (%)	18 (31%)	3 (21%)	15 (34%)	
CD4 (n = 43)				
Median (IQR)	405 (185 - 686)	369 (283 - 661)	417 (185 - 710)	0.816
CD4 count =< 200cells/ul. n (%)	11 (26%)	2 (18%)	9 (28%)	0.698
CD4 count > 200cells/ul. n (%)	32 (74%)	9 (82%)	23 (72%)	

Symptoms

One-hundred and forty-eight patients 73 % (n=148) were asymptomatic at the time of admission and were admitted for obstetric reasons and not due to COVID-19. The remaining 56 patients (27%) were symptomatic. The most predominant symptoms presented were cough 32% (n = 18), dyspnoea 21% (n = 12) and headache 14% (n = 8). Six patients had a fever (temperature greater than 37.8^{o}C) recorded during admission and 5 patients were hypoxaemic, with oxygen saturation below 94%(90-93%). Only 1 of the 5 (0.2%) was admitted into the ICU and was discharged alive. However, oxygen saturation was only recorded in 128 (n=204)

patients as the unit protocol did not include standard monitoring of saturation prior to the pandemic (Table 5.2)

Severity of disease

We used the Modified Early Obstetric Warning System (MEOWS) score to classify severity of disease, with 63% of patients (n=128) considered stable (MEOWS score = 0) and 16% (n=33) critically ill (MEOWS score ≥ 6). There were 16% (23/148) of asymptomatic patients that had a MEOWS score > 6. (Table 5.2)

High care and Critical Care unit admissions

Twenty-one patients (10%) (21/204) required admission to an intensive care unit (ICU). Of those patients who had a MEOWS score of > 6 (n=33), 64% (21/33) were admitted into an ICU with critical illness. Eleven (52%) of the 21 ICU admissions required ventilatory support of which 38% (8/21) received continuous positive airway pressure. ICU admissions were associated with elevated respiratory rates (p=0.002) but not associated with derangement of other vital signs. There was no relationship found between HIV status and ICU admission (p=0.22). Three patients (14%) (3/21) died during their hospital stay, all of whom had severe COVID-19 and required admission to ICU. (Table 5.2) Only 1 patient who died was HIV positive and died in ICU in early pregnancy. The other 2 patients both presented with features of severe pre-eclampsia, one of which died from severe postpartum haemorrhage, post caesarean delivery requiring a lifesaving hysterectomy, the baby did well. No cause of the PPH was found at relook laparotomy and therefore thought to be one of the complications of COVID-19. Only a few records had COVID-19 treatment captured. Corticosteroids were given to 9% (5/204) of patients, 23% (13/204) received antibiotics, 41% (23/204) received low molecular heparin and other medication was prescribed to 73% (41/204). The average length of stay for all patients in the study was 6 days and the median length of stay was 4 days (IQR 2-8).

Table 5.2 COVID-19 symptoms and severity of disease

Symptoms	Symptomatic	Asymptomatic	p	Normal range
Total	56 (27%)	148 (73%)		
Symptom Breakdown				
Cough	18 (9%)			
Diarrhoea	1 (0.5%)			
Dyspnoea	12 (6%)			
Fatigue	0 (0%)			
Fever	6 (3%)			
Headache	8 (4%)			
Malaise	2 (1%)			
Myalgia	4 (2%)			
Rhinitis	1 (0.5%)			
Sore Throat	6 (3%)			
Vomiting	2 (1%)			
Other Symptoms	12 (6%)			
Anosmia	1 (0.5%)			
Ageusia	1 (0.5%)			
Vitals, Median (IQR)				
Temperature. C (n = 199)	36.5 (36.4 – 36.8). n = 53	36.4 (36.3 – 36.6). n = 144	0.035	36.1-37.5
Respiratory Rate. bpm (n = 197)	18 (18 - 20). n = 54	18 (18 - 20). n = 141	0.012	12-20
Pulse Rate. bpm (n = 203)	93 (86.5 - 109). n = 55	92 (84 - 100). n = 146	0.059	61-100
Oxygen saturation. % (n = 128)	96 (94 - 97). n = 38	97 (96 - 98). n = 89	0.001	>95
Systolic Blood Pressure. mmHg (n = 203)	122 (114 - 139). n = 55	130 (119 - 145). n = 146	0.013	90-140
Diastolic blood pressure. mmHg (n = 203)	77 (69 - 92). n = 55	82 (73 - 90). n = 146	0.145	60-90
MEOWS				
0. n (%)	37 (66%)	91 (61%)	0.435	0.435
1 – 3. n (%)	3 (5%)	20 (14%)		
4 – 5. n (%)	6 (11%)	14 (9%)		
>=6. n (%)	10 (18%)	23 (16%)		
ICU admissions				
Total ICU admissions	21(10%)			
NIV-CPAP	8(4%)			
Invasive ventilation	11(5%)			
Deaths	3(1.5%)			

Laboratory results

Routine COVID-19 blood tests were performed on most patients, especially those who presented with symptoms. The median ranges and 95% confidence intervals of the blood results were available for the groups studied. A Mann-Whitney U test was used to elicit any relationship between deranged blood results and severity of illness and all parameters where found to be insignificant (Table 5.3). Comparison of blood results between those women who were symptomatic and those women who were asymptomatic, showed that conjugated bilirubin (umol/l) was the only statistical difference (p=0.05) (Table 5.4).

Table 5.3 Laboratory investigations of COVID-19 infected pregnant women

	Number of patients with results	Median	95% CI	Normal range
White Cell Count (x10^9/l)	160	8.185 (6.133 – 11.39)	7.28 – 9.3	3.9-12.6
Haemoglobin (g/dl)	166	11.95 (10.4 – 13.03)	11.6 – 12.3	11.6-16.4
Platelets (x10^9/l)	162	221 (179 - 284)	210 - 244	150-400
Neutrophil count (x10^9/l)	29	15.77 (4.635 – 71.3)	6.76 – 70.1	1.6
Lymphocyte count (x10^9/l)	29	2.59 (1.525 - 18,9)	1.59 – 18.2	8.3
C-reactive protein (mg/l)	89	41 (10 - 107)	19 - 62	<10
Procalcitonin (ng/ml)	68	0.095 (0.05 – 0.415)	0.06 – 0.15	<0.5
Beta-d-glucan (pg/ml)	15	62 (31 - 120)	31 - 120	<60
Sodium (mmol/l)	161	138 (136 - 140)	137 - 138	136-145
Potassium (mmol/l)	161	4.4 (4 – 4.7)	4.2 – 4.5	3.5-5.1
Urea (mmol/l)	161	2.4 (1.9 – 3.1)	2.2 – 2.6	2.1-7.1
Creatinine (umol/l)	159	59 (51 - 70)	57 - 61	49-90
D-dimers (mg/l)	63	0.92 (0.61 – 1.79)	0.75 – 1.22	0.0-0.2
Ferritin (ng/ml)	46	66 (35.5 – 96.75)	45 - 83	13-150
hs Troponin T (ng/l)	54	4 (2 – 9.75)	3 - 5	<3
LDH (U/l)	48	292 (226.5 – 379.3)	251 - 343	100-190
Total protein (g/l)	74	65 (59 - 68)	63 - 66	60-78
Albumin (g/l)	76	33 (29 - 36)	31 - 35	35-52
Total bilirubin (umol/l)	76	5 (4 - 8)	4 - 6	5-21
Conjugated bilirubin (umol/l)	76	2 (2 - 3,75)	2 - 3	0-3
Alanine transaminase (U/l)	112	14 (10 - 21)	12 - 16	7-35
Aspartate transaminase (U/l)	111	25 (19 - 32)	22 - 28	13-35
Alkaline phosphatase (U/l)	79	118 (86 - 165)	109 - 142	42-98
Gamma-glutamyl transferase (U/l)	76	17 (9.25 – 46.25)	13 - 31	<40
Interleukin 6 (pg/ml)	3	134.6 (3.7 - 271)	3.7 - 271	<7.0

Table 5.4: Comparison of blood results between symptomatic and asymptomatic pregnant women

	Total, Median (IQR)	Symptomatic, Median (IQR)	Asymptomatic, Median (IQR)	p
White Cell Count (x10^9/l)	8.185 (6.133 – 11.39). n = 160	7.19 (5.395 – 11.32). n=42	8.36 (6.65 – 11.47). n=117	0.1877
Haemoglobin (g/dl)	11.95 (10.4 – 13.03). n = 166	11.9 (10.88 – 13.23). n=42	12 (10.1 - 13). n=123	0.5715
Platelets (x10^9/l)	221 (179 - 284). n = 162	237.5 (176.5 – 286.3). n=42	221 (179 - 284). n=119	0.8098
Neutrophil count (x10^9/l)	15.77 (4.635 – 71.3). n = 29	4.89 (2.443 – 8.298). n=8	6.505 (4.468 – 9.108), n=20	0.2806
Lymphocyte count (x10^9/l)	2.59 (1.525 – 18.9). n = 29	1.91 (1.613 – 2.495). n=8	12.4 (1.435 – 19.98). n=20	0.2584
C-reactive protein (mg/l)	41 (10 - 107), n = 89	26.5 (10 – 105.3). n=28	44.5 (10.25 – 117.3). n=60	0.8989
Procalcitonin (ng/ml)	0.095 (0.05 – 0.415). n = 68	0.1 (0.07 – 0.56). n=23	0.085 (0.04 – 0.3625). n=44	0.2533
Beta-d-glucan (pg/ml)	62 (31 - 120). n = 15	112 (48.25 – 204.3). n=4	52 (30.75 - 117). n=10	0.1948
Sodium (mmol/l)	138 (136 - 140). n = 161	137 (135 - 140). n=42	138 (136 - 139). n=118	0.3176
Potassium (mmol/l)	4,4 (4 - 4,7). n = 161	4.4 (4.1 – 4.725). n=42	4.4 (4 – 4.7). n=118	0.9884
Urea (mmol/l)	2.4 (1.9 – 3.1). n = 161	2.3 (1.7 – 3.225). n=42	2.4 (2 – 3.1). n=118	0.5126
Creatinine (umol/l)	59 (51 - 70). n = 159	58 (52 – 70.5). n=41	60 (51 – 70.5). n=117	0.9158
D-dimers (mg/l)	0.92 (0.61 – 1.79). n = 63	0.82 (0.63 – 1.59). n=23	1.02 (0.5575 – 1.835). n=40	0.6074
Ferritin (ng/ml)	66 (35.5 – 96.75). n = 46	74 (36 - 169). n=17	59 (33 - 88). n=29	0.3011
hs Troponin T (ng/l)	4 (2 – 9.75). n = 54	4 (3 - 5). n=19	4 (2 – 13.25). n=34	0.863
LDH (U/l)	292 (226.5 – 379.3). n = 48	320 (252.5 – 398.5). n=17	275 (220.8 – 363.5), n=30	0.2411
Total protein (g/l)	65 (59 - 68). n = 74	64 (55.5 – 67.5). n=25	65 (59.5 – 68.75). n=48	0.4784
Albumin (g/l)	33 (29 - 36). n = 76	33 (27.75 – 36.25). n=26	32 (29 - 35). n=49	0.8919
Total bilirubin (umol/l)	5 (4 - 8). n = 76	6 (5 - 10). n=25	4.5 (4 – 7.25). n=50	0.051
Conjugated bilirubin (umol/l)	2 (2 - 3,75). n = 76	3 (2 - 5). n=25	2 (2 - 3). n=50	0.0463
Alanine transaminase (U/l)	14 (10 - 21). n = 112	15.5 (8.75 – 28.25). n=30	14 (10 – 19.5). n=81	0.5818
Aspartate transaminase (U/l)	25 (19 - 32). n = 111	26.5 (17 - 40). n=30	24 (19.25 - 31). n=80	0.6872
Alkaline phosphatase (U/l)	118 (86 - 165). n = 79	114 (89.5 – 158.8). n=26	127.5 (83.75 – 165.8). n=52	0.8641

Gamma-glutamyl transferase (U/l)	17 (9.25 – 46.25). n = 76	22.5 (12.75 – 60.75). n=26	15 (7.5 - 41). n=49	0.1072
Interleukin 6 (pg/ml)	134.6 (3.7 - 271). n = 3	134.6 (3.7 - 271). n = 3	0	N/A

Pregnancy Outcomes

There were 5 twin pregnancies (2%) in our study and no triplets or higher order pregnancies. Twenty three patients (n = 11%) remained undelivered at the end of their admission and there were 159 deliveries (78%) of live infants (n=165). There were 8 stillbirths (4%), 6 miscarriages (3%) and 5 ectopic pregnancies (3%) (Table 5.5). Three (38%) (3/8) of the stillbirths occurred between a gestational age (GA) of 23-27 weeks, 50%(4/8) stillbirths occurred between a GA of 28-31 weeks and 13% (1/8) stillbirth occurred between a GA of 32-37 weeks. One stillbirth occurred in ICU after the mother was diagnosed with an inferior vena cava thrombosis. Three patients who had stillbirths were unbooked for antenatal care and 3 of which were HIV positive. One patient tested positive for syphilis and presented with an intrauterine death. Three placental histology reports sent from the stillbirth deliveries were available and all suggested features of chorio-amnionitis.

Mode of delivery and fetal birth weights

One-hundred and five (60%) patients were delivered via caesarean section mostly due to a previous caesarean section (n = 41, 33%) or fetal distress (n = 33, 27%) respectively. Eighty-one patients (77%) who had a caesarean section were asymptomatic for COVID-19 and 23% (24/105) were symptomatic for COVID-19. Of the seventy-one (35%) patients who delivered vaginally, 69% (49/71) were asymptomatic for COVID-19 and 31% (22/71) were symptomatic for COVID-19. No patients were delivered via caesarean section for COVID-19 indications. Of those patients who experienced symptoms of COVID-19, 22 (48%) and 24 (52%) delivered vaginally and by caesarean section respectively. Those who had symptoms suggested of COVID-19 had no impact on the route of delivery and the p value was not significant (p=0.29) (Table 5.5). Twenty-three (11%) patients of the entire study group were undelivered, 22% (5/23) patients were discharged from hospital between a GA of 14-22 weeks,30% (7/23) patients were discharged between a GA of 23-27 weeks, 17% (4/23) patients were discharged between a GA of 28-31 weeks, 13% (3/23) patients were discharged at a GA of 32-37 weeks and 9%(2/23) were discharged at a GA between 38-40 weeks. Unfortunately, gestational age at discharge was missing for 2 patients. Median birth weight for the live births was 2940g (IQR

2450 – 3320g) with 19 /176 infants (11%) under 2000g at the time of delivery. Median gestational age for the miscarriages and stillbirths was 18 and 28 weeks respectively (Table 5.5).

Table 5.5: Pregnancy and delivery outcomes

	Total (n = 204)	Symptomatic (n = 56)	Asymptomatic (n = 148)	p
Number of foetuses				
Multi-gestation. n (%)	5 (2%)	0 (0%)	5 (3%)	0.326
Pregnancy outcome				
Live birth. n (%)	159 (78%)	38 (68%)	121 (82%)	0.039
Ectopic. n (%)	5 (2.5%)	0 (0%)	5 (3%)	
Miscarriage. n (%)	6 (3%)	0 (0%)	6 (4%)	
TOP. n (%)	2 (1%)	0 (0%)	2 (1%)	
Molar. n (%)	1 (0.5%)	0 (0%)	1 (1%)	
Stillbirth. n (%)	8 (4%)	4 (7%)	4 (3%)	
Undelivered. n (%)	23 (11%)	14 (25%)	9 (6%)	
Mode of delivery				
Vaginal Delivery. n (%)	71 (40%)	22 (48%)	49 (38%)	0.294
Caesarean Section. n (%)	105 (60%)	24 (52%)	81 (62%)	
Indication for Caesarean Section				
Abruptio Placentae. n (%)	5 (4%)	0 (0%)	5 (5%)	
Cephalopelvic Disproportion. n (%)	6 (5%)	1 (4%)	5 (5%)	
Fetal distress. n (%)	33 (27%)	12 (48%)	21 (21%)	
Malpresentation. n (%)	4 (3%)	0 (0%)	4 (4%)	
No progress. n (%)	9 (7%)	3 (12%)	6 (6%)	
Previous Caesarean Section. n (%)	41 (33%)	5 (20%)	36 (37%)	
Preeclampsia. n (%)	9 (7%)	2 (8%)	7 (7%)	
Failed IOL. n (%)	5 (4%)	0 (0%)	5 (5%)	
Other. n (%)	11 (9%)	2 (8%)	9 (9%)	
Note: 23 patients (22%) had more than 1 indication for CS				
Birth weight				
Birth weight (grams). median (IQR)	2940 (2450 - 3320)	2810 (2450 - 3170)	2940 (2423 - 3320)	0.818
Birth weight <1000g. n (%)	2 (1%)	0 (0%)	2 (2%)	
Birth weight 1000 - 1499g. n (%)	3 (2%)	0 (0%)	3 (2%)	

Birth weight 1500 - 1999g. n (%)	14 (8%)	1 (3%)	13 (10%)	
Birth weight 2000 - 2499g. n (%)	21 (12%)	8 (21%)	13 (10%)	
Birth weight 2500 - 2999g. n (%)	43 (25%)	10 (26%)	33 (26%)	
Birth weight 3000 - 3499g. n (%)	46 (27%)	9 (24%)	37 (29%)	
Birth weight 3500 - 3999g. n (%)	26 (15%)	6 (16%)	20 (16%)	
Birth weight >4000g. n (%)	3 (2%)	0 (0%)	3 (2%)	
Birth weight Missing. n (%)	6 (4%)	4 (11%)	2 (2%)	

Comparative statistics

Patients with co-morbidities were not more symptomatic than those that had no co-morbidities (p=0.43). BMI was compared to MEOWS and showed no correlation (p=0.13). HIV specifically was not associated with more symptoms (p=0.32). A strong correlation was found between pre-eclampsia and COVID-19 disease. Pre-eclampsia however and COVID-19 severity co-existed significantly with a p-value of p = < 0.0001.It is unclear as to which disease process, COVID-19 or pre-eclampsia, initiated the severity of illness.

A generalised linear model (GLM) analysis showed that BMI, Hypertension and HIV status were significant predictors of MEOWS scores (Table 5.6). A higher BMI generally resulted in a greater MEOW score (Figure 3). The estimate from the analysis showed that a unit increase in BMI increased the log odds of a higher MEOWS score by 0,026 (Table 5.6). Patients with a hypertension had greater MEOW scores (Figure 4), and having hypertension increased the log odds of a greater MEOW score by 0.824 (Table 5.6). In contrast, patients with HIV had lower MEOW scores (Figure 5); being HIV positive reduced the MEOW score by -0.643 (Table 5.6).

Table 5.6. Statistical output of a GLM for predictors (variables) of the severity (severe vs moderate) of COVID-19 symptoms in pregnant women.

Significant outcomes are shown in bold.

Variable	Estimate	P value
Age	0.010	0.366
BMI	**0.026**	**0.012**
Number of comorbidities	0.054	0.825
Hypertension	**0.824**	**0.006**
Diabetes	-0.629	0.130
HIV	**-0.643**	**0.025**
>1 Symptom	0.035	0.878

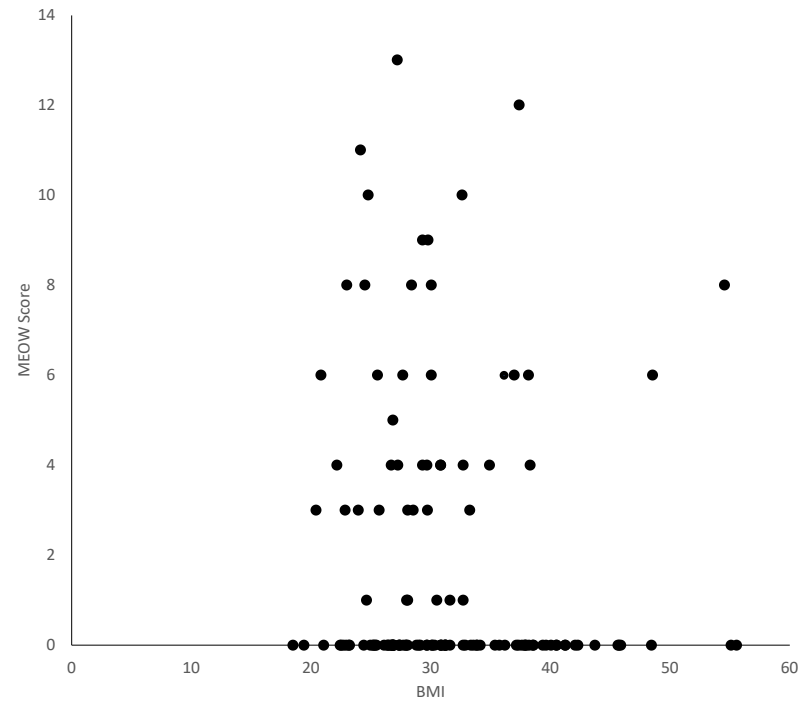


Figure 3

The relationship between BMI and MEOW scores.

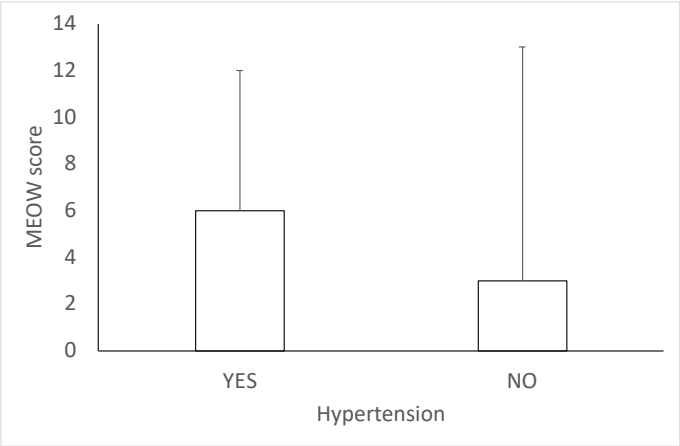


Figure 4

MEOW scores in patients that were (YES) or not (NO) hypertensive. The graph shows the and 3rd interquartile and maximum score (whiskers). The median, 1st interquartile and minimum score were all zero and do not appear in the graph.

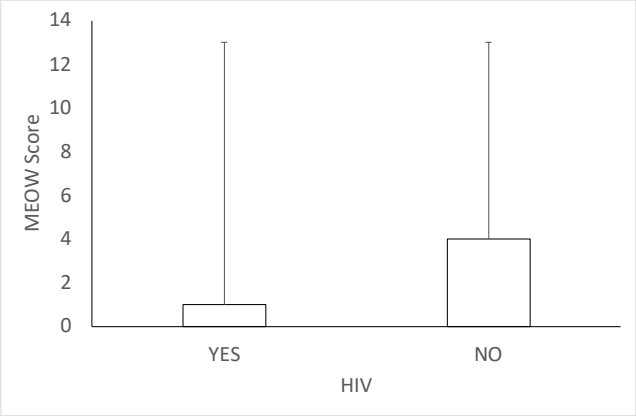


Figure 5

MEOW scores in patients that were (YES) or not (NO) HIV positive.

The graph shows the 3rd interquartile and maximum score (whiskers). The median, 1st interquartile and minimum score were all zero and do not appear in the graph.

6 DISCUSSION

Globally concerns regarding pregnant women infected with the corona virus remain pertinent and prompted the review of COVID-19 disease in pregnant women admitted into our institution.

COVID-19 Findings

In this study we report on 204 pregnant women who tested positive for COVID-19 with an overall mortality rate of 1.5%. This rate is lower than that seen in a large South African study (6.3%)[35] but similar to that seen in the INTERCOVID study (1.6%)[42], both of which were conducted during the same time frame. We note a higher mortality rate, however, when compared to similar studies from the United States (0.15%)[51] and the United Kingdom (0.7%)[52]. The three women who died in our study group required ICU admission, two of which presented with severe features of pre-eclampsia which we anticipate contributed to their deaths. We believe that the higher mortality rate in our setting when compared to the USA and UK owes to the vastly different medical background between developed and developing countries. Furthermore late access to basic medical care and limited access to ICU may also played a role.

Pregnant women who were asymptomatic at the time of admission accounted for 73% of our study group, similar to findings from the SAOSS study but contrasting to the data from the UK where 63% of women were symptomatic. Of those pregnant women who were symptomatic in our study, cough was the commonest finding and congruent with other South African studies.[35,39] Many institutions in South Africa adopted routine screening for all admitted patients from early in the pandemic and this could explain the higher rate of asymptomatic COVID-19 cases. Another observation during the time frame studied was that new cases in South Africa peaked at 13.994 per day compared to the UK who reported half the number of cases per day, 6201 cases per day, which may indicate a higher level of community spread in South Africa.[53-55]

According to the MEOWS score, 63%, of our patients were classified as stable, 5 pregnant women (2.5%) with milder disease were hypoxaemic and 16 pregnant women (8.1%) presented with tachypnoea. There was a significant association between tachypnoea and ICU admission amongst our study group, however when using the MEOWS score the majority of pregnant women were classifies as stable or having mild disease. A higher BMI in our study resulted in

a greater MEOWS score which was similar to Sattar et al, who reported a '5-10% higher risk for COVID-19 hospitalisation per every kg/m^2 higher BMI.'[60]We found an association between hypertension and higher MEOWS scores but HIV was associated with lower MEOWS scores. The use of the MEOWS scoring system has not been validated for COVID-19, however, the scoring system is recommended for use in COVID-19 by the ISIDOG as well as a number of NHS trusts in the UK as it is easy to use and has the ability to detect subtle changes early. The National committee on Confidential Enquires into Maternal Deaths, South Africa, also advocate for the use of a similar tool and has been incorporated in the latest version of the maternity record, although, it is limited to the postpartum period.[56] Future research is needed on the use of scoring systems to triage pregnant women who test positive for COVID-19.

COVID-19 Associations

We noted that a significant number of women in our study group were considered obese by body mass index, 51% with BMI greater than 30kg/m^2 were obese and 34% with a BMI between 25kg/m^2 – 30kg/m^2 were overweight. This number is higher than the South Africa (36%) estimated rates of obesity in pregnancy.[57] A link between obesity and COVID-19 is evident in the literature; The INTERCOVID study reported on 48.6% of pregnant women with COVID-19 who were obese compared to 40.2% pregnant women who did not have COVID-19.[42] Our institution is a tertiary, academic centre and is an established referral site for high risk/complicated pregnancies and pregnant women with a high BMI may have additional comorbidities and are therefore referred to our institution for specialist and sub-specialist intervention.

We report 7 (3.5%) adolescent pregnancies in our study group with the youngest being 14 years old at the time of delivery, highlighting the global and national burden of adolescent pregnancy, not spared by the COVID-19 pandemic. South African data reveals 9% of women age 15-17 years have born children and this rate increases to 16% if the age range includes 15-19 year old women.[58] Between April 2020 to March 2021, adolescent pregnancies increased by 60% in Gauteng, proposing a unique pandemic in its own, with lack of access to contraception during COVID-19 regulated lockdowns.[59] Approximately 12 million women aged 15-19 bear children in developing countries.[60] Reassuring for this adolescent age group among our study group; was that none experienced severe COVID-19 disease and there were no ICU admissions and no deaths.

HIV prevalence in our study group was 33% (n=67), similar to the SAOSS[35] study and in keeping with the national prevalence of 30%, however only 69% in our study were virologically surpressed.[35,61] Despite being in keeping with the rate of HIV viral suppression in national estimates, the rate of viral suppression of 69% in our study is concerning given South Africa's aim to reach the UNAIDS target of 95% viral suppression by 2030. [62]

Nonetheless, we were reassured by the fact that only one HIV positive women died (1.5%) with no difference in mortality between our HIV positive and HIV negative women (1.5% vs 1.4%, p=0.964). Furthermore there was no difference in severity of disease, lower MEOWS scores were significant among those who had HIV p=0.025. There were no increased ICU admission rate in the HIV positive group compared to the HIV negative group (6% vs 12%, p=0.22). These findings are similar to a non-pregnant cohort (men and women included) of HIV positive patients from our hospital.[63]

Significant in our study was the association of pre-eclampsia and severity of COVID-19 disease. Other studies have also found an association with pre-eclampsia and COVID-19 but after correcting for variables did not find pre-eclampsia to be associated with severe disease. [64] It is unclear whether this was a "preeclampsia-like syndrome" induced by COVID-19, as reported by Mendoza et al, or de novo preeclampsia.[65] Our facility does not have access to sFlt-1/PlGF testing and uterine artery doppler indices were not recorded in the clinical records of the pregnant women included in our study.

Pregnancy findings

The caesarean section delivery rate in our study was 60%, one third of pregnant women underwent CS due to due to previous caesarean delivery and pregnant women had a CS for COVID-19 related indications. Whilst the rate of Caesarean section in our cohort is higher than the South African rate of 28.6% and far higher than the "ideal rate" of 10 – 15% recommended by the WHO, we believe the high number of Caesarean deliveries is likely due to the level of care provided by our institution as a referral centre for the province.[56,66] Furthermore, in keeping with our setting as a referral centre for high-risk pregnancies we report a higher rate of preterm deliveries (39%) than that seen in other studies. Similarly, we report 12 miscarriages (5.9%) and 8 (3.9%) stillbirths, rates not increased when compared to pre-pandemic studies, although it is unclear if COVID-19 had any effect on these outcomes. [67,68]

In our study the majority 97% of pregnant women were of African/Black ethnicity, a majority group expected for this setting in Sub-Saharan Africa. Other South African studies during the same time frame also report an African/Black ethnic majority, 85.2% and 90% [35,39]. Data from the USA and UK have shown worse outcomes amongst pregnant women of BAME (Black Asian Minority Ethnicity) as well as increased rates of infection when compared to pregnant women of white ethnicity [42, 53]. We found 2% of the patients reviewed in our study were white race and all symptomatic for COVID-19. Internationally this is attributed to a number of factors, including differences in socioeconomic status, however South African data on differences amongst racial groups is limited. Notably the proportion of black patients in this cohort was significantly higher than in two previously published cohorts of patients with COVID-19 from our centre (99% vs 79%[63] and 84%[69]), even when corrected for age (99% vs 85%).

Antenatal booking rates were 85% amongst pregnant women admitted into our institution. This was much lower than the booking rate of 96% found amongst another health district in the same province of the country.[39] This culture could be attributed to fear of contracting COVID-19 in our institution as it was chosen as a designated COVID-19 isolation and treatment site early in the pandemic.

The majority of pregnant women in our study (78%) were in the third trimester of pregnancy. Those who were in earlier gestational ages and who remained undelivered were not followed up. Neonatal outcome might correlate with timing of viral load/exposure during pregnancy and severity of maternal outcome so more data is needed on COVID-19 exposure in early pregnancy and maternity outcomes.[70]

7 CONCLUSION

Our study describes pregnancy and neonatal outcomes in over 200 cases during the first wave of the corona virus pandemic in a South African setting. We found a high percentage of asymptomatic infections among pregnant. There was a low CFR amongst ICU admissions and not a single case of known neonatal transmission. There was a strong association of BMI and COVID-19 disease but low rates of severity of disease among those who were HIV positive and virally suppressed. Preeclampsia was significantly associated with severe COVID-19 disease and warrant greater caution. Pre-term deliveries and early pregnancy loss mimicked other studies of high numbers but caesarean deliveries did not, with rates being lower than expected for the pandemic-era. COVID-19 disease in pregnancy is a continuously evolving entity and our study provides valuable insight into the profiles of pregnant women with COVID-19, especially in a LMIC setting. Future research into the interactions between HIV and COVID-19 in pregnancy as well as the use of scoring systems, like the MEOWS score, in COVID-19 in pregnancy are needed.

8 LIMITATIONS

The biggest limiting factor was missing records owing to the retrospective nature of the study and incomplete data capturing. Data such as oxygen saturation and COVID-19 specific laboratory tests were not performed on all patients, especially those with asymptomatic disease. We were also unable to follow-up on pregnant women discharged from our institution undelivered and therefore outcome data is not available in these pregnant women who were lost to follow up.

9 STRENGTHS

At submission, this thesis reflects the largest cohort of pregnant women studied in South Africa. Our study was the first to include the MEOWS score to identify severity of COVID-19 disease in pregnancy, highlighting the possible importance of scoring systems in risk stratification and triage of COVID-19 in pregnancy. Additionally we have been able to report on outcomes of COVID-19 in adolescents who were pregnant. The single-centre nature of our cohort is also a strength in that all women received the same standard of care and treatment protocols, reducing confounding factors related to mortality and ICU admission.

10 REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727–33. http://doi: 10.1056/NEJMoa2001017 Accessed July 2020

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; http://doi.org/ 10.1016/S0140-6736(20)30183-5 accessed July 2020

3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; http://doi.org 10.1016/S0140-6736(20)30211-7 accessed July 2020

4. European Centre for Disease Prevention and Control (ECDC). Rapid risk assessment: Cluster of pneumonia cases caused by a novel coronavirus, Wuhan, China. European Centre for Disease Prevention and Control. 2020. https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-clusterpneumonia-cases-caused-novel-coronavirus-wuhan

5. She J, Jiang J, Ye L, Hu L, Bai C, Song Y. 2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies. Clin Transl Med. 2020; http://DOI: 10.1186/s40169-020-00271-z accessed July 2020

6. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. World Health Organization. 2020. http://doi.org/10.1186/s40169-020-00271-z accessed July 2020

7. WHO. Coronavirus disease 2019 Situation Report 51 11th March 2020. World Health Organization. 2020. http://doi.org/ 10.1001/jama.2020.2633 accessed July 2020

8. Mei Y, Luo D, Wei S, Liao X, Pan Y, Yang X, et al. Obstetric Management of COVID-19 in Pregnant Women. Front Microbiol [Internet]. 2020 May 26 [cited 2020 Jul 25];11:1186. Available from: https://www.frontiersin.org/article/10.3389/fmicb.2020.01186/full Accessed August 2020

9. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, Seferovic MD, Aski SK, Arian SE, et al. Maternal death due to COVID-19. Am J Obstet Gynecol. 2020; http://doi.org/ 10.1016/j.ajog.2020.04.030 Accessed August 2020

10. Takemoto MLS, Menezes M de O, Andreucci CB, Nakamura-Pereira M, Amorim MMR, Katz L, et al. The tragedy of COVID-19 in Brazil: 124 maternal deaths and counting. Int J Gynecol Obstet [Internet]. 2020 Jul 29 [cited 2020 Aug 11];ijgo.13300. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ijgo.13300 accessed August 2020

11. Webb SAR, Pettilä V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med. 2009 Nov 12;361(20):1925–34. http://doi.org/ 10.1056/NEJMoa0908481 accessed August 2020

12. Data on COVID-19 during Pregnancy | CDC [Internet]. [cited 2020 Aug 11]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/specialpopulations/pregnancy-data-on-covid-19.html accessed August 2020

13. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;

http://doi.org/10.1056/NEJMoa2001017 accessed July 2020

14. Samudrala PK, Kumar P, Choudhary K, Thakur N, Wadekar GS, Dayaramani R, et al. Virology, pathogenesis, diagnosis and in-line treatment of COVID-19. Eur J Pharmacol. 2020 Sep 15;883:173375. http://doi.org/10.1016/j.ejphar.2020.173375 accessed October 2020
15. European Centre for Disease Prevention and Control. Cluster of pneumonia cases caused by novel coronavirus [Internet]. 2020. Available from: https://www.who.int/health-topics/coronavirus.Accessed October 2020
16. Schwartz DA, Hyg M. An Analysis of 38 Pregnant Women With COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2 Maternal Coronavirus Infections and Pregnancy Outcomes. http:// doi: 10.5858/arpa.2020-0901SA accessed December 2021
17. Bouvier NM, Palese P. The biology of influenza viruses. Vaccine [Internet]. 2008 Sep 12 [cited 2020 Jul 26];26(SUPPL. 4):D49. Available from: /pmc/articles/PMC3074182/?report=abstract http:// doi:10.1016/j.vaccine.2008.07.039 accessed July 2020
18. Zhao X, Jiang Y, Zhao Y, Xi H, Liu C, Qu F, et al. Analysis of the susceptibility to COVID-19 in pregnancy and recommendations on potential drug screening [Internet]. Vol. 39, European Journal of Clinical Microbiology and Infectious Diseases. Springer; [cited 2020 Jul 26]. p. 1209–20. Available from: /pmc/articles/PMC7178925/?report=abstract http://doi.org/10.1007/s10096-020-03897-6 accessed July 2020
19. Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med. 2020;799–805.

20. Seasonal influenza and pregnancy - UpToDate [Internet]. [cited 2020 Jul 26]. Available from: https://www.uptodate.com/contents/seasonal-influenza-and-pregnancy Accessed July 2020

21. FREEMAN DW, BARNO A. Deaths from Asian influenza associated with pregnancy. Am J Obstet Gynecol [Internet]. 1959 Dec [cited 2020 Jul 26];78:1172–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13824729 http://doi.org/10.1016/0002-9378(59)90570-8 Accessed July 2020

22. Luteijn JM, Brown MJ, Dolk H. Influenza and congenital anomalies: A systematic review and meta-analysis. Hum Reprod [Internet]. 2014 [cited 2020 Aug 11];29(4):809–23. Available from: https://pubmed.ncbi.nlm.nih.gov/24365800/ http://doi.org/10.1093/humrep/det455 Accessed August 2020

23. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. Vol. 14, Emerging Infectious Diseases. Centers for Disease Control and Prevention (CDC); 2008. p. 95–100. http://doi.org/ 10.3201/eid1401.070667 Accessed July 2020

24. Kriebs JM. Zika virus and its impact on pregnancy. J Perinat Neonatal Nurs. 2016;30(4):280–3. http:doi.org/ 10.1097/JPN.0000000000000217 Accessed July 2020

25. Olgun NS. Viral Infections in Pregnancy: A Focus on Ebola Virus. Curr Pharm Des. 2018; http://doi.org/ 10.2174/1381612824666180130121946 Accessed July 2020

26. Woldesenbet Id S, Kufa-Chakezha T, Lombard Id C, Manda S, Cheyip M, Ayalew K, et al. Recent HIV infection among pregnant women in the 2017 antenatal sentinel cross-sectional survey, South Africa: Assay-based incidence measurement. Centers Dis Control Prev South Africa [Internet]. Available from: https://doi.org/10.1371/journal.pone.0249953 Accessed December 2020

27. Turan B, Stringer KL, Onono M, Bukusi EA, Weiser SD, Cohen CR, et al. Linkage to HIV care, postpartum depression, and HIV-related stigma in newly diagnosed pregnant women living with HIV in Kenya: A longitudinal observational study. BMC Pregnancy Childbirth. 2014; http://doi.org/ 10.1186/s12884-014-0400-4 Accessed August 2020

28. Cavarelli M, Scarlatti G. Human immunodeficiency virus type 1 mother-to-child transmission and prevention: successes and controversies. J Intern Med [Internet]. 2011 Dec 1 [cited 2020 Jul 26];270(6):561–79. Available from: http://doi.wiley.com/10.1111/j.1365-2796.2011.02458.x Accessed July 2020

29. Moodley J. Saving Mothers 2011-2013: Sixth report on confidential enquiries into maternal deaths in South Africa, Short report. Pretoria Dep Heal. 2014; http://doi.org/ 10.2337/dc14-S014 Accessed July 2020

30. Janini LM, Tanuri A, Schechter M, Peralta JM, Vicente ACP, Torre N Dela, et al. Horizontal and Vertical Transmission of Human Immunodeficiency Virus Type 1 Dual Infections Caused by Viruses of Subtypes B and C. J Infect Dis [Internet]. 1998 Jan [cited 2020 Jul 26];177(1):227–31. Available from: https://pubmed.ncbi.nlm.nih.gov/9419195/ http://doi.org/ 10.1086/517360 Accessed July 2020

31. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. BMJ. 2020;370. http://dx.doi.org/10.1136/bmj.m3320 Accessed December 2021

32. Breslin N, Baptiste C, Gyamfi-Bannerman C, Miller R, Martinez R, Bernstein K, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM [Internet]. 2020 May [cited 2020 Aug 24];2(2):100118. Available from: https://pubmed.ncbi.nlm.nih.gov/32292903/ http:// doi: 10.1016/j.ajogmf.2020.100118 Accessed August 2020

33. Adam S, Maswime S, Soma-Pillay P, Matjila M, Chauke L, Botha MH, et al. Judicious use of personal protective equipment to prevent the spread of COVID-19 in maternity units. S Afr J Obstet Gynaecol. 2020;26(1):2–3. http://10.7196/SAJOG.2020.v26i1.1605 Accessed December 2021

34. Khalil A, Kalafat E, Benlioglu C, O'Brien P, Morris E, Draycott T, et al. SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine [Internet]. 2020;25(December 2019):100446. Available from: https://doi.org/10.1016/j.eclinm.2020.100446 Accessed December 2021

35. Budhram S, Vannevel V, Botha T, Chauke L, Bhoora S, Balie GM, et al. Maternal characteristics and pregnancy outcomes of hospitalized pregnant women with SARS-CoV-2 infection in South Africa: An International Network of Obstetric Survey Systems-based cohort study. Int J Gynecol Obstet. 2021;155(3):455–65. http:// DOI: 10.1002/ijgo.13917 Accessed October 2021

36. Badr DA, Mattern J, Carlin A, Cordier AG, Maillart E, El Hachem L, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol. 2020;223(5):764–8. http://doi.org/10.16/j.ajog.2020.07.045 Accessed Decmber 2021

37. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708–20.

38. Zamparini J, Venturas J, Shaddock E, Edgar J, Naidoo V, Mahomed A, et al. Clinical Characteristics of the First 100 COVID-19 Patients Admitted to a Tertiary Hospital in Johannesburg, South Africa. Wits J Clin Med. 2020;2(2):51.

39. Basu JK, Chauke L, Magoro T. Clinical Features and Outcome of COVID-19 Infection Among Pregnant Women in in South Africa. SSRN Electron J. 2021;10(2):1–9.

40. Basu JK, Chauke L, Magoro T. Maternal mortality from COVID 19 among South African pregnant women. J Matern Neonatal Med [Internet]. 2021;0(0):1–3. Available from: https://doi.org/10.1080/14767058.2021.1902501

41. Pastick KA, Nicol MR, Smyth E, Zash R, Boulware DR, Rajasingham R, et al. A systematic review of treatment and outcomes of pregnant women with COVID-19-A call for clinical trials. Open Forum Infect Dis. 2020;7(9):1–8.

42. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and Neonatal Morbidity and Mortality among Pregnant Women with and without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr. 2021;175(8):817–26.

43. Nakamura-Pereira M, Amorim M, Pacagnella R, Takemoto M, Pemso F, Rezende-Filho et al. COVID_19 and Maternal Death in Brazil: An Invisible Tragedy. Rev Bras Ginecol Obstet 2020;42(8):445–447. DOI https://doi.org/ 10.1055/s-0040-1715138.

44. Collin J, Bystrom Emma, AnnaSara C, Ahrne M. Oublic Helath Agency of Sweden's Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. Acta Obstetricia et Gynecologica Scandinavica. 2020 Voulume 99 Issue 7 Pages 819-822 DOI 10.1111/aogs.13901 accessed Aug 2022

45. Lumbreras-Marquez, Campos-Zamora, Liza-diaz de Leon H, Farber M. Maternal mortality from COVID-19 in Mexico. Int J Gynecol Obstet 2020 10.1002/ijgo.13250

Accessed April 2022

46. The Impact of COVID-19 in South Africa | PDF | Debt | Credit [Internet]. [cited 2022 Jan 11]. Available from: https://www.scribd.com/document/457964637/The-Impactof-COVID-19-in-South-Africa#download

47. Johnson L, Dorrington R. Modelling the impact of HIV in South Africa's provinces: 2018 update. 2018;(August):1–69. Available from: https://thembisa.org/downloads

48. Devi Ramdin T, Marina Bandini R, Radomsky M, Avendra Bhoora S, Elizabeth Ballot D. Clinical Characteristics, Maternal and Neonatal Outcomes of COVID-19 Positive Pregnant Mothers at a Tertiary Hospital in Johannesburg, South Africa. J Pediatr Perinatol Child Heal. 2021;05(04):252–63.

49. Gibson L, Rush D. Novel Coronavirus in Cape Town Informal Settlements: Feasibility of Using Informal Dwelling Outlines to Identify High Risk Areas for COVID-19 Transmission From A Social Distancing Perspective. JMIR Public Heal Surveill [Internet]. 2020 Apr 1 [cited 2022 Jan 11];6(2). Available from: /pmc/articles/PMC7141253/

50. De Waard L, Langenegger E, Erasmus K, Van der Merwe T, Olivier SE, Du Toit N, et al. Maternal and neonatal outcomes of COVID-19 in a high-risk pregnant cohort with and without HIV. South African Med J. 2021;111(12):1174.

51. Zambrano LD. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 [cited 2021 Jan 21];69. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6944e3.htm

52. Vousden N, Bunch K, Morris E, Simpson N, Gale C, O'Brien P, et al. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS). PLOS ONE. 2021 May 5;16(5):e0251123.
53. Cases in the UK | Coronavirus in the UK [Internet]. [cited 2022 Feb 8]. Available from: https://coronavirus.data.gov.uk/details/cases
54. WEEKLY EPIDEMIOLOGICAL BRIEF [Internet]. NICD. [cited 2022 Feb 8]. Available from: https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/surveillance-reports/weekly-epidemiological-brief/
55. Ritchie H, Mathieu E, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E, et al. Coronavirus Pandemic (COVID-19). Our World in Data [Internet]. 2020 Mar 5 [cited 2022 Jun 27]; Available from: https://ourworldindata.org/covid-cases
56. National Committee on the Confidential Enquiries into Maternal Deaths. Saving Mothers 2017-2019: Seventh triennial report on confidential enquiries into maternal deaths in South Africa. Department of Health; 2020.
57. Basu JK, Jeketera CM, Basu D. Obesity and its outcomes among pregnant South African women. Int J Gynaecol Obstet. 2010 Aug;110(2):101–4.
58. FR337.pdf [Internet]. [cited 2022 Feb 2]. Available from: https://dhsprogram.com/pubs/pdf/FR337/FR337.pdf#page=103
59. Teen pregnancies in South Africa jump 60% during COVID-19 pandemic - South Africa [Internet]. ReliefWeb. [cited 2022 Feb 2]. Available from: https://reliefweb.int/report/south-africa/teen-pregnancies-south-africa-jump-60-during-covid-19-pandemic

60. Adolescent pregnancy [Internet]. [cited 2022 Feb 2]. Available from: https://www.who.int/news-room/fact-sheets/detail/adolescent-pregnancy
61. Woldesenbet SA, Lombard C, Manda S, Kufa T, Ayalew K, Cheyip M, et al. The 2019 National Antenatal Sentinel HIV Survey, South Africa [Internet]. National Department of Health; 2021 [cited 2022 Feb 2]. Available from: https://www.nicd.ac.za/wp-content/uploads/2021/11/Antenatal-survey-2019-report_FINAL_27April21.pdf
62. Abuogi LL, Humphrey JM, Mpody C, Yotebieng M, Murnane PM, Clouse K, et al. Achieving UNAIDS 90-90-90 targets for pregnant and postpartum women in sub-Saharan Africa: progress, gaps and research needs. J Virus Erad. 4(Suppl 2):33–9.
63. Venturas J, Zamparini J, Shaddock E, Stacey S, Murray L, Richards GA, et al. Comparison of outcomes in HIV-positive and HIV-negative patients with COVID-19. Journal of Infection. 2021 Aug;83(2):217–27.
64. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Inequalities in maternal health: National cohort study of ethnic variation in severe maternal morbidities. BMJ. 2009 Mar 21;338(7696):b542–b542.
65. Papageorghiou AT, Deruelle P, Gunier RB, Rauch S, García-May PK, Mhatre M, et al. Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study. Am J Obstet Gynecol. 2021;225(3):289.e1-289.e17.
66. Mendoza M, Garcia-Ruiz I, Maiz N, Rodo C, Garcia-Manau P, Serrano B, et al. Preeclampsia-like syndrome induced by severe COVID-19: a prospective observational study. Available from: https://doi.org/10.1111/1471-0528.16369
67. WHO | WHO statement on caesarean section rates [Internet]. WHO. World Health Organization; [cited 2022 Feb 7]. Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/cs-statement/en/

68. DeSisto CL, Wallace B, Simeone RM, Polen K, Ko JY, Meaney-Delman D, et al. Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization — United States, March 2020–September 2021. MMWR Morb Mortal Wkly Rep. 2021 Nov 26;70(47):1640–5.
69. Madhi SA, Briner C, Maswime S, Mose S, Mlandu P, Chawana R, et al. Causes of stillbirths among women from South Africa: a prospective, observational study. The Lancet Global Health. 2019 Apr;7(4):e503–12.
70. Zamparini J, Venturas J, Shaddock E, Edgar J, Naidoo V, Mahomed A, et al. Clinical Characteristics of the First 100 COVID-19 Patients Admitted to a Tertiary Hospital in Johannesburg, South Africa. WJCM. 2020;2(2):51.
71. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. American Journal of Obstetrics and Gynecology. 2004 Jul;191(1):292–7.

11 APPENDICES

11.1 Patient information and consent form

INFORMATION DOCUMENT FOR PARTICIPANTS
CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL COVID-19 DATABASE

Dear participant,

We are part of the team responsible for the treatment and management of patients with Coronavirus Disease 2019 (COVID-19) in the Department of Medicine at Charlotte Maxeke

Johannesburg Academic Hospital. COVID-19 is caused by a novel zoonotic coronavirus, SARSCoV2, which was first identified in the city of Wuhan in China. The virus has spread rapidly across the globe and to date has infected more than two million people. New information about this disease is being shared daily by clinicians and scientists across the world and it is this information that is allowing us to make progress in the fight against COVID-19.

Little is known about COVID-19 in the South African setting and it is for this reason that we have created the Charlotte Maxeke Johannesburg Academic Hospital COVID-19 Database. Through this database we hope to learn more about COVID-19 and how COVID-19 affects people in South Africa. We will only be able to do this though if patients like you help us by allowing us to enter information related to your admission into this database.

Procedures
If you agree, clinical information related to your background medical history, symptoms and signs on admission and discharge, laboratory results, treatment given, final diagnosis and other clinically relevant data will be stored on the database. This database will be maintained on software known as REDCap that is administered by the University of the Witwatersrand. The database will be password protected and the information will be stored, coded and anonymously handled by the research team.

What are the risks associated with participating in the study?
There are no direct risks to you participating in the study. Personal information will be stored on the database but will only be accessible by the database administrators (Dr Jarrod Zamparini and Dr Jacqui Venturas). Your personal information will not be shared with anyone unless they have received permission from the database administrators and an authorized human research ethics committee.

What is the benefit to you of participating in this study?
There is no direct benefit to you however results obtained from this database may allow us to improve knowledge related to COVID-19 and benefit society as a whole in the fight against this disease.

What if I have queries about the study?
If you are unsure or have queries about the study please contact Jarrod Zamparini on

0722781158 or email jarrod.zamparini@wits.ac.za OR shastra.bhoora@wits.ac.za, tel: 083 657 8561/011 488 3179.

Informed Consent
I, _____(participant name), acknowledge that I

have read and understand the informed consent document (or that I have been explained the contents in a language that I understand). I hereby agree to allow the information stated above to be stored on the Charlotte Maxeke Johannesburg Academic Hospital COVID-19 Database and give consent for this information to be shared, in anonymous form, through peer-reviewed scientific publications. I understand that I have the right to withdraw my consent at any time and I have the right to withdraw my information from the database at any time.

Participant Name: _____

Participant signature: _____

Witness Name: _____

Witness Signature: _____

11.2 Appendix Data Sheet

Demographics and History

Age	
Parity	
Gravidity	
Booked	Y
	N
Booking Hb	
BMI Height Weight MUAC	
RVD	Pos
	Neg
	Unknown
CD4	
Viral load	
ARVs	Y
	N
Regimen No.	A
	B
	DT

Race	African
	Coloured
	Indian
	White other
Gest age	At admission at delivery
# of foetuses	

COVID DATA

COVID		
Swab result		
Date		
Asymptomatic	Y or N	
Symptomatic: Symptoms	Y or N Cough SOB Fever Sore throat Myalgia Headache Travel history Location Contact Who	
Screening	Y	N
Outcome	COVID ward/ 197 Steroids Nasal prongs FMO2 Polymask HFNO2 Vitamins Clexane Prophylatic Therapeutic ICU admission HFNO2 Ventilation Inotropes RRT ECMO Other:	
Organ dysfunction	CNS Parameter CVS Parameter Resp Parameter Renal Parameter Liver Parameter Haematology Parameter	

Discharge to	Home Site

Test Results:							
WCC		Sodium		TP		pH	
Haemoglobin		Potassium		Albumin		pO_2	
Platelets		Urea		Bilirubin		pCO_2	
Neutrophils		Creatinine		Conj Bili.		BE	
Lymphocytes		D-dimer		ALT		HCO_3	
CRP		Ferritin		AST		Lactate	
PCT		Troponins		ALP		SO_2	
BDG		LDH		GGT		P/F Ratio	
Gene xpert		Blood cultures		PJP PCR		Blood cultures	
						Urine mcs	
CXR		ECG		CT Chest			

Treatment		
Therapy	Dose	Duration
Vit C		
Vit D		
ZINC		
Thiamine		
Augmentin		
Azithromycin		
Steroids		
Clexane		
Other:		

Medical	
Cardiac Specify:	
Diabetes: Pregestational Type 1 Type 2 Gestational Overt Meds	
Asthma	
Epilepsy	
Hypertension Chronic Pre-eclampsia HELLP Eclampsia Imminent Gestational Meds	
Aids Def Disease Specify:	
Smoking:	
Non Aids infxn	
Other	

Preg Cx	
Preterm Rupture of membranes Chorio-amnionitis	
Antepartum Haemorrhage Placenta previa Abruptio placentae Cervical lesion Vasa Previa Unknown origin	
Intra-Uterine Growth Restriction	
Anaemia	
Other	

Progress of Labour

1st stage:	2nd stage:	3rd stage:
Hrs:	Hrs:	Min:

Induction of labour (IOL)	Y N
Augmentation of labour (AOL)	Y N
Spontaneous Rupture of membranes (SROM)	Y N
Artificial Rupture of membranes (AROM)	Y N
Meconium Stained Liquor (MSL)	Thin Thick Clear
Perineum trauma	Y N

Blood loss NVD >500mls CS>1000mls	Y N
Blood Transfusion	Y N
Uterine Rupture	Y N
Hysterectomy	Y N
ICU	Y N
Death	

Modes of Delivery

Caesar: Indication	
Fetal Distress	
Cephalo-Pelvic Disproportion	
No Progress	
Malpresentation	
Placenta praevia	
Abruptio placenta	
Other	

Vaginal	Normal
	Vacuum
	Forceps

Sterilisation	Y
	N
	declined

Fetal Outcome

Alive		Y
		FSB
		MSB
Weight		
Apgar	1 min	
	5 min	
Prematurity		
COVID-19 Swab		
TU/NICU		
		Y
END		N

11.3 Ethics certificate

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

Office of the Deputy Vice-Chancellor (Research and Postgraduate Affairs

TO:	Dr SA Bhoora School of Clinical Medicine Department of Obstetrics and Gynaecology Medical School University E-mail: shastra.bhoora@gmail.com
CC:	Supervisor: Professor L Chauke <Lawrence.Chauke@wits.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2020/12/21
REF:	R14/49
PROTOCOL NO:	**M201169** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	A retrospective review of the case records of COVID-19 disease in pregnant women in a tertiary hospital

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

MSWorks2000\Ian\2007\Clearcon.wps

11.4 CMJAH CEO APPROVAL LETTER

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
Clinical Department

Enquiries: Ms. TT Mahlangu
Tel: (011) 488-3365
Email: Thandi.Mahlangu4@gauteng.gov.za

Physical Address: Room 2624,17 Jubilee, Parktown 2193 Postal Address: Private Bag x39, Johannesburg 2000

29 December 2020

Dear Prof. Bhoora (GP_202009_003)

STUDY TITTL: A Retrospective review of the cases records of COVID-19 Disease in pregnant women in tertiary hospital.

Department: O&G

No.	DOCUMENTS REQUIRED FOR STUDENT RESEARCH	TICK
1.	Covering letter from the APPLICANT/COMPANY	X
2.	Protocol	X
3.	Support letter from the Head of Department	X
4.	Ethics clearance certificate	
5.	NHRD Registration	
	DOCUMENTS REQUIRED FOR ANY 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: (Clinical) Ms TT Mahlangu **Signature:** _____ **Date:** 6/01/2020

Checked BY: Mr S. Zwane **Signature:** _____

RECEIVED CEO
0 -01- 2021
CMJAH