Maternal and neonatal outcomes of COVID-19 in a high-risk pregnant cohort with and without HIV

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Background. The impact of SARS-CoV-2 infection in pregnant women living with HIV (PLHIV) has not been described previously.
Objectives. To describe the clinical presentation and outcomes of a cohort of women with high-risk pregnancies with confirmed COVID-19 to determine whether risk factors for disease severity and adverse outcomes of COVID-19 differed in pregnant women without HIV compared with PLHIV.
Methods. We prospectively enrolled pregnant women with COVID-19 attending the high-risk obstetric service at Tygerberg Hospital, Cape Town, South Africa, from 1 May to 31 July 2020, with follow-up until 31 October 2020. Women were considered high risk if they required specialist care for maternal, neonatal and/or anaesthetic conditions. Common maternal or obstetric conditions included hypertensive disorders, morbid obesity (body mass index (BMI) ≥40 kg/m²) and diabetes. Information on demographics, clinical features, and maternal and neonatal outcomes was collected and compared for PLHIV v. pregnant women without HIV.
Results. One hundred women (72 without HIV and 28 PLHIV) with high-risk pregnancies had laboratory-confirmed COVID-19. Among the 28 PLHIV, the median (interquartile range) CD4 count was 441 (317 - 603) cells/μL, and 19/26 (73%) were virologically suppressed. COVID-19 was diagnosed predominantly in the third trimester (81%). Obesity (BMI ≥30 in *n*=61/81; 75%) and hypertensive disorders were frequent comorbidities. Of the 100 women, 40% developed severe or critical COVID-19, 15% required intensive care unit admission and 6% needed invasive ventilation. Eight women died, 1 from advanced HIV disease complicated by bacteraemia and urosepsis. The crude maternal mortality rate was substantially higher in women with COVID-19 compared with all other deliveries at our institution during this period (8/91 (9%) v. 7/4 058 (0.2%); *p*<0.001). Neonatal outcomes were favourable. No significant differences in COVID-19 risk factors, disease severity, and maternal/neonatal outcome were noted for PLHIV v. those without HIV.
Conclusions. In this cohort of high-risk pregnant women, the impact of COVID-19 was severe, significantly increasing maternal mortality risk compared with baseline rates. Virally suppressed HIV infection was not associated with worse COVID-19 outcomes in pregnancy.

South Africa (SA) has the highest number of confirmed positive SARS-CoV-2 infections on the African continent, with 1 491 807 laboratory-confirmed COVID-19 cases and 47 899 COVID-related deaths recorded from the first case on 5 March 2020 until 13 February 2021.[1] Population cohort analysis data from Western Cape Province, SA, demonstrated a doubling of COVID-19 mortality risk in persons living with HIV.[2] Although more data confirming the interaction between COVID-19 and HIV are emerging globally,[3,4] there are limited data available for COVID-19 in pregnant women living with HIV (PLHIV).[5]

Infection rates for COVID-19 are higher in pregnant women than in adults of similar age in the general population.[6] Risk factors for severe COVID-19 are well described and are similar for pregnant women, including pre-existing comorbidities, advanced maternal age and obesity.[7-9] Immunological changes associated with pregnancy may also predispose pregnant women to severe viral infections, as observed during the 2009 influenza A (H1N1)

pandemic.[10,11] There is mounting evidence that pregnant women with COVID-19 have higher rates of intensive care unit (ICU) admission, invasive ventilation and mortality compared with non-pregnant individuals.[12] Whether concomitant HIV infection in pregnancy affects SARS-CoV-2 infection risk, disease severity and COVID-19 outcome is currently unknown.

Objectives

In this prospective observational cohort study, we describe women with high-risk pregnancies and confirmed COVID-19 presenting to a large referral hospital in Cape Town, SA. Our objectives were: (*i*) to describe the clinical presentation and outcomes of women with high-risk pregnancies diagnosed with COVID-19; (*ii*) to determine whether risk factors for severe disease and adverse outcomes of COVID-19, including the need for respiratory support, ICU admission and death, differed in pregnant women without HIV compared with PLHIV; and (*iii*) to compare the number of maternal

deaths, rates of multiple births, caesarean sections and stillbirths, and the number of low-birthweight (LBW) infants for COVID-19 pregnancies compared with all deliveries at our hospital during the study period.

Methods
Study design
We conducted an observational cohort study of pregnant women with COVID-19 who were attending the high-risk obstetric service at Tygerberg Hospital (TBH), Cape Town, SA. We included women who presented to the service between 1 May and 31 July 2020. All pregnant women with laboratory-confirmed positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) results during these 3 months were prospectively and consecutively included. Women were followed up until 31 October 2020 to allow them all to deliver.

Participants
Pregnant women attending the high-risk obstetric care service were screened for symptoms and/or signs of COVID-19, or contact exposure. Only women who screened positive for symptoms had nasopharyngeal swab tests submitted for SARS-CoV-2 RT-PCR, as testing capacity was limited. We also included women whose symptoms and/or positive SARS-CoV-2 test result occurred within 7 days of delivery, as it was likely that they had contracted SARS-CoV-2 infection during pregnancy. All women who had symptoms and/or a positive test >7 days post partum were excluded.

Study setting
TBH is the largest public sector referral hospital in Cape Town. The obstetric service delivers >8 000 women a year and only manages high-risk pregnancies. The caesarean section rate (48%) and LBW rate (39%) at TBH are both high.[13] Common high-risk maternal or obstetric conditions include hypertensive disorders, morbid obesity (body mass index (BMI) ≥40 kg/m²) and diabetes.[14] According to SA referral guidelines, all women in the referral hospital's drainage area with a BMI ≥40 kg/m² have to be referred to the referral hospital and delivered in the hospital. HIV is not considered a high-risk factor in our setting. Testing for HIV is offered to all pregnant women at their first antenatal visit and is repeated at 32 weeks' gestation and at delivery, according to national guidelines.[15] With expanded access to diagnosis of and treatment for HIV, increasing numbers of women are initiated on combination antiretroviral therapy (cART) before falling pregnant.[16] Universal cART for all PLHIV was introduced in 2015.[16] Approximately 20% of all women who deliver at TBH are PLHIV, with an intrauterine HIV transmission rate of 0.82%.[17]

In preparation for the COVID-19 pandemic, a dedicated obstetric unit (separate ward, theatres and staff) was established for the care of pregnant women with suspected and confirmed COVID-19. This unit was staffed by senior obstetric trainees, nursing and midwifery teams who were supported by critical care consultants, obstetricians, and anaesthetic and neonatology staff. Where possible, healthy neonates were kept with their mothers to establish breastfeeding. In line with national protocols, SARS-CoV-2 RT-PCR testing was not performed for healthy neonates born to mothers with COVID-19. If a neonate required admission to any neonatal ward, SARS-CoV-2 testing was performed.

Data collection and classification
The obstetric trainee team and research midwife prospectively collected routine clinical data and laboratory outcomes on all pregnant women with confirmed COVID-19. Data included demographics, HIV information, COVID-19 symptoms, pregnancy complications, and birth and neonatal outcomes. Data on the number of deliveries, the route of delivery and maternal/neonatal outcome are routinely captured on an electronic birth register at TBH. Data for the patients with COVID-19 were collected using a secure online Research Electronic Data Capture (REDCap) data registry hosted by Stellenbosch University.[18,19] Ethical approval was obtained from the Stellenbosch University Health Research Ethics Committee (ref. no. N20/04/002_COVID-19).

BMI was corrected for the trimester when first weight measurements were taken, to adjust for expected weight gain during pregnancy as per provincial policy. If measured in the second trimester, 4 kg was deducted, and in the third trimester, 8 kg was deducted. A miscarriage was defined as the accidental loss of a fetus before 24 weeks' gestation.[20] COVID-19 severity (mild/moderate v. severe/critical) was classified using the National Institutes of Health criteria.[21] Mild or moderate illness was defined as symptomatic women not needing oxygen supplementation, while women with respiratory symptoms requiring oxygen supplementation were defined as having severe illness. Critical illness included respiratory failure, septic shock, and/or multiorgan dysfunction.

Statistical analysis
Descriptive analysis was conducted reporting counts and proportions. Non-parametric data were described using medians and interquartile ranges (IQRs). Pregnant women with COVID-19 were analysed by HIV status. Mild or moderate COVID-19 was compared with severe or critical COVID-19. Student's t-test or the Mann-Whitney U-test was used for comparing continuous data, and the χ^2 test or Fisher's exact test was used for comparing categorical data. A p-value <0.05 was considered statistically significant.

Results
SARS-CoV-2 laboratory testing of high-risk pregnant women
SARS-CoV-2 RT-PCR testing was performed in 275 women attending the high-risk obstetric service between 1 May and 31 July 2020. COVID-19 was confirmed in 103/275 women (37%), of whom 3 were excluded because their COVID-19 symptoms started >7 days post partum. The final cohort of 100 pregnant women was followed up until 31 October 2020 to allow all of them to deliver.

Pre-existing medical and obstetric conditions in women with COVID-19
Seventy-two of the 100 pregnant women with COVID-19 were HIV-uninfected and 28 were PLHIV (Table 1). Twenty-seven of 28 PLHIV (96%) were receiving cART at the time of delivery. CD4 counts were available for 21/28 women (75%) (median (IQR) 441 (317 - 603) cells/μL), and 19/26 (73%) were virologically suppressed (HIV viral load <50 copies/mL). For the 7 PLHIV with a detectable HIV viral load, the median (IQR) viral load was 361 (104 - 461) copies/mL. The viral load was not available for 2 women. PLHIV were more likely to be older and multiparous compared with women without HIV. Obesity was a frequent comorbidity (weights available for 81/100), with 25/81 (31%) obese and 36/81 (44%) morbidly obese women; no difference was observed between PLHIV and women without HIV. Pre-existing chronic hypertension and diabetes mellitus were present in 22/100 and 6/100 women, respectively, and 9/100 women had a previous or current diagnosis of tuberculosis.

Table 1. Demographics, COVID-19 and pregnancy outcomes by HIV status

	All women (N=100)	Without HIV (N=72)	With HIV (N=28)	*p*-value
Demographics				
Age (years), median (IQR)	31 (27 - 37)	31 (27 - 36)	34 (28 - 39)	0.082
BMI (kg/m²),* *n* (%)				
<25 (normal weight)	8/81 (10)	6/59 (10)	2/22 (9)	0.603
≥25 - <30 (overweight)	12/81 (15)	9/59 (15)	3/22 (14)	0.554
≥30 - <40 (obese)	25/81 (31)	16/59 (27)	9/22 (41)	0.304
≥40 (morbidly obese)	36/81 (44)	28/59 (48)	8/22 (36)	0.334
Multiparous, *n* (%)	78 (78)	51 (71)	27 (96)	0.006
Twin pregnancy, *n* (%)	5 (5)	5 (7)	0 (0)	0.186
Chronic hypertension, *n* (%)	22 (22)	19 (26)	3 (11)	0.089
Gestational hypertension, *n* (%)	18 (18)	13 (18)	5 (18)	0.981
Pre-eclampsia, *n* (%)	24 (24)	18 (25)	6 (21)	0.733
Diabetes mellitus, *n* (%)	6 (6)	4 (6)	2 (7)	n/a
Gestational diabetes, *n* (%)	14 (14)	12 (17)	2 (7)	0.183
Asthma, *n* (%)	4 (4)	4 (6)	(0)	n/a
Tuberculosis (current and previous), *n* (%)	9 (9)	5 (7)	4 (14)	n/a
Anaemia,† *n* (%)	28 (28)	17 (24)	11 (39)	0.117
COVID-19				
Timing of infection, *n* (%)				
1st trimester	2 (2)	1 (1)	1 (4)	n/a
2nd trimester	17 (17)	13 (18)	4 (14)	0.451
3rd trimester	81 (81)	58 (81)	23 (82)	0.856
Delivery within 2 weeks of diagnosis, *n* (%)	50 (50)	33 (46)	17 (61)	0.181
Symptoms				
Cough, *n* (%)	77 (77)	56 (78)	21 (75)	0.767
Dyspnoea, *n* (%)	49 (49)	35 (49)	14 (50)	0.901
Fever, *n* (%)	36 (36)	26 (36)	10 (36)	0.970
Duration of symptoms (days), median (IQR)	3 (2 - 5)	3 (2 - 4)	3 (1 - 6)	n/a
Disease severity, *n* (%)				
Mild	60 (60)	43 (60)	17 (61)	0.928
Severe	29 (29)	20 (28)	9 (32)	0.666
Critical	11 (11)	9 (12)	2 (7)	n/a
Maximum respiratory support, *n* (%)				
Nasal prong oxygen	16/40 (40)	12/29 (42)	4/11 (36)	0.533
Face mask oxygen/non-rebreather mask	13/40 (33)	9/29 (31)	4/11 (36)	0.514
High-flow oxygen/nCPAP	5/40 (12)	3/29 (10)	2/11 (19)	0.422
Invasive ventilation	6/40 (15)	5/29 (17)	1/11 (9)	0.464
Treatments, *n* (%)				
Thromboprophylaxis	59 (59)	39 (54)	20 (71)	0.115
Dexamethasone‡	13 (13)	7 (10)	6 (22)	0.111
Hydrocortisone	3 (3)	3 (4)	0	n/a
Methylprednisolone	1 (1)	1 (1)	0	n/a
Antibiotics§	55 (55)	38 (53)	17 (61)	0.474
Complications				
Thromboembolism, *n* (%)	4 (4)	2 (3)	2 (2)	n/a
Acute kidney injury,¶ *n* (%)	3 (3)	2 (3)	1 (4)	n/a
ICU admission, *n* (%)	15 (15)	9 (13)	6 (21)	0.206
ICU stay (days), median (IQR)	4 (3 - 10)	5 (4 - 10)	3 (1 - 6)	0.271
Pregnancy outcomes, *n* (%)				
Caesarean section	49 (49)	30 (42)	19 (68)	0.019
Vaginal delivery with live birth	37 (37)	32 (44)	5 (18)	0.013
Stillbirth	5 (5)	3 (4)	2 (7)	n/a
Medical termination of pregnancy	1 (1)	1 (4)	0	n/a
Miscarriage	4 (4)	3 (4)	1 (4)	n/a
Mother died with fetus *in utero*	2 (2)	2 (3)	0	n/a
Unknown	2 (2)	2 (3)	0	n/a
Spontaneous preterm labour <37 weeks	4 (4)	3 (4)	1 (4)	n/a
Placental abruption	2 (2)	2 (3)	0	n/a
Maternal death	8 (8)	6 (8)	2 (7)	n/a

IQR = interquartile range; BMI = body mass index; nCPAP = nasal continuous positive airway pressure; ICU = intensive care unit; n/a = not applicable.
*Data only available for 81 women.
†Haemoglobin <11 g/dL.
‡For patients receiving oxygen therapy, dexamethasone was added as standard of care from 17 June 2020.
§Antibiotics (N=55): ceftriaxone *n*=44, ampicillin *n*=1, amoxicillin/clavulanic acid *n*=6, azithromycin *n*=1, cephazolin *n*=1.
¶Abrupt reduction in renal function based on an elevation of serum creatinine 2 - 3-fold from baseline.[29]

COVID-19 in 100 women with high-risk pregnancies

Fourteen women were managed as outpatients and 86 required hospital admission. Common symptoms included cough (77%), dyspnoea (49%) and fever (36%). Of the 86 admissions, 46 (53%) were for COVID-19-related illness, 23 (27%) for delivery, and 17 (20%) for other obstetric indications. The median hospital stay was 4 days (range 1 - 25). COVID-19 was diagnosed mainly in the third trimester (81%), and half of all women delivered within 2 weeks of infection onset.

Sixty women had mild/moderate COVID-19, 29 had severe disease and 11 had critical disease. Of the 11 women with critical disease, 6 were ventilated for respiratory failure and 1 collapsed and died in the ward prior to ICU admission. The remaining 4 did not require ventilation but presented with multiorgan dysfunction in addition to COVID-19 pneumonia: 1 with cardiomyopathy needing inotropic support, 1 with glucose instability requiring an insulin infusion, 1 with delirium, and 1 with bacteraemia and urosepsis.

Of the 30/40 women in the severe/critical disease categories whose weight was documented, all were either overweight (3/30; 10%), obese (9/30; 30%) or morbidly obese (18/30; 60%). No difference in proportions was observed between PLHIV with mild/moderate disease compared with PLHIV with severe/critical disease (n=17/60 (28%) v. 11/40 (28%); p=0.928). Dyspnoea was more common in the severe or critical disease group compared with mild or moderate disease (33/40 (83%) v. 16/60 (27%); p=0.001).

Women with severe/critical disease were also more likely to need other supportive treatment including anticoagulation (32/40; 80%), dexamethasone (13/40; 33%) and broad-spectrum antibiotics (29/40; 73%). Fifteen women required admission to the ICU or the maternity critical care unit, 12 primarily for respiratory support and 3 for non-COVID-19-related conditions (diabetic ketoacidosis, a caesarean hysterectomy, and severe pre-eclampsia).

No differences between PLHIV and women without HIV were found with regard to the timing of infection, type and duration of symptoms, disease severity, need for respiratory support, other medical treatment, or complications. Pregnancy outcomes for the 100 women (5 twin pregnancies) included 91 live births, 5 stillbirths, 4 miscarriages, 2 women who died with the fetus *in utero* and 1 medical termination of pregnancy. The 2 women who died with the fetus *in utero* died from complications of COVID-19. The medical termination was for severe preterm pre-eclampsia. There were 3 first-trimester miscarriages, and 1 at 19 weeks due to diabetic ketoacidosis. One baby was stillborn to a mother who defaulted her cART, 2 stillbirths were associated with severe pre-eclampsia, 1 was due to a placental abruption without associated pre-eclampsia, and the 5th was in a woman who had severe hypoxia related to COVID-19. Birth outcomes were unknown for 2 women who were lost to follow-up. No differences were observed for pregnancy outcomes in terms of HIV status, except for a higher caesarean section rate in older, multiparous PLHIV, where 9/19 (47%) had a history of two previous caesarean sections.

Maternal mortality

Eight women in this cohort died, of whom 2 were PLHIV. One woman died from advanced HIV and 7 from complications related to COVID-19 (Table 2). The woman with advanced HIV had a CD4 count of 14 cells/µL and had defaulted her cART in 2018. She had not received any antenatal care and delivered a macerated fetus weighing 1 131 g. She was diagnosed with *Escherichia coli* septicaemia, cultured in both blood and urine samples, and died 8 days later from urosepsis and acute renal failure. Her GeneXpert test for tuberculosis was also positive. The other PLHIV had a suppressed viral load and no clinical indications of advanced HIV disease.

Weight and height measurements were available for 6 of the 7 women whose deaths were directly related to COVID-19. One woman was overweight, and the others were all obese. Five women had chronic hypertension, and 2 of these women developed severe pre-eclampsia. Two women had pregnancies complicated by type 2 diabetes mellitus. Two women died with the fetus *in situ*. One woman had a caesarean section for severe pre-eclampsia and developed COVID-19 symptoms post partum. Four women needed a caesarean section delivery to improve respiratory function. One neonate was delivered close to term and 2 were delivered preterm. One woman who was delivered to improve her respiratory function had a neonatal death related to intrauterine hypoxia.

Neonatal outcomes

Among the 91 liveborn neonates (66 in women without HIV and 25 in PLHIV), the median (IQR) gestational age at delivery was 38 (36 - 39) weeks (Table 3). Twenty-seven infants (30%) were preterm and 25 (28%) were LBW. Of the 91 liveborn neonates, 76 (84%) remained with their mother and 15 (16%) were admitted to a neonatal ward; the median (IQR) gestational age of admitted infants was 34 (26 - 38) weeks. Reasons for admission included diagnoses of respiratory distress syndrome in 9, transient tachypnoea of the newborn in 2, congenital pneumonia in 2, jaundice, hypoglycaemia, and 1 neonate with an imperforate anus who required surgery. Of these 15 admitted neonates, 14 required respiratory support, including invasive ventilation in 1, nasal continuous positive airway pressure ventilation in 12 and nasal cannula oxygen in 1. The neonatal stay ranged from 5 to 30 days. A SARS-CoV-2 test was negative in 13/15 admitted neonates within 72 hours after birth (invalid in 1 and not done in another). No differences in neonatal birthweight or outcome were observed between neonates born to women without HIV v. PLHIV. The neonatal outcomes of the mothers who died of COVID-19 were poor. There were 4 intrauterine fetal deaths and 1 early neonatal loss in a neonate who had no respiratory effort at birth. There were 2 preterm deliveries, one at 32 weeks' gestation with a 1 945 g neonate and another at 26 weeks with a neonate weighing 750 g (Table 2). The outcome for the 91 liveborn neonates was excellent except for the neonate described above whose mother also died.

Key obstetric indicators for pregnancies at TBH affected and unaffected by COVID-19 (1 May - 31 October 2020)

A total of 4 149 women with high-risk pregnancies were delivered at TBH during this time frame, 91 with COVID-19 (9 from the cohort delivered at other institutions) and 4 058 not included in the study cohort. No differences were observed in the rates of multiple pregnancy, caesarean section, stillbirth and live LBW infants, but the crude maternal mortality rate was substantially increased in women with COVID-19 compared with women without suspected COVID-19 (n=8/91 (8.8%) v. n=7/4 058 (0.2%); p<0.001) (Fig. 1).

Discussion

Our observational study is the first to assess the impact of laboratory-confirmed COVID-19 in a cohort of high-risk pregnant women from sub-Saharan Africa, including women living with HIV. Of the 28 PLHIV (a quarter of the total cohort), the majority were receiving cART and were virally suppressed. In this group of high-risk pregnancies with well-controlled HIV disease, we found no differences in COVID-19 risk factors, disease severity or outcomes for both mothers and their neonates, compared with COVID-19 pregnant women without HIV infection.

Table 2. COVID-19-associated deaths in pregnant women at Tygerberg Hospital (*N*=8)

Age (years)	Gravidity	Parity	BMI (kg/m²)	Other risk factors	Delivery	Neonatal outcome	Maternal outcome	Death
29	2	1	25	Advanced HIV Defaulted cART Chronic leg ulcer Active TB Urosepsis No antenatal care	Spontaneous vaginal delivery	Macerated stillborn, 1 131 g	Severe sepsis Renal failure	Day 7 postpartum
28	2	1	25	Chronic hypertension Superimposed pre-eclampsia	Emergency CS at 26 weeks for severe features of superimposed pre-eclampsia	Baby alive, 750 g Admitted to NICU No COVID symptoms	COVID symptoms 2 days postpartum Intubated and ventilated Multiorgan failure	Day 5 postpartum
37	2	1	48	Chronic hypertension Superimposed pre-eclampsia Type 2 DM Anaemia	CS at 30 weeks for deteriorating maternal condition related to COVID-19	Neonatal death, 1 500 g No respiratory effort 5-minute Apgar Failed resuscitation	Intubated and ventilated Acute renal injury Repeat laparotomy	Day 7 postpartum
35	5	4	39	Chronic hypertension Asthma	CS at 36 weeks for deteriorating maternal condition related to COVID-19	Intrauterine death, 2 685 g	Intubated and ventilated Multiorgan failure	Day 1 postpartum
38	6	5	40	Chronic hypertension	Undelivered	Intrauterine death at 27 weeks' gestation	Intubated and ventilated	Day 4 after admission
33	3	1	30	Chronic hypertension Anaemia PLHIV	CS at 37 weeks for deteriorating maternal condition related to COVID-19	Baby alive, 2 350 g No COVID symptoms	Repeat laparotomy day 2 postpartum Intubated and ventilated on day 7 2nd repeat laparotomy day 9	Day 9 postpartum
40	5	2	55	Gestational hypertension Type 2 DM Anaemia	Undelivered	Intrauterine death at 26 weeks' gestation	Cardiac arrest Possible thrombotic event	Day 4 after admission
28	3	2	Unknown	None	CS at 32 weeks for deteriorating maternal condition related to COVID-19	Baby alive, 1 945 g No COVID symptoms	Intubated and ventilated Severe hypoxia	Day 16 postpartum

BMI = body mass index; cART = combined antiretroviral therapy; TB = tuberculosis; CS = caesarean section; NICU = neonatal intensive care unit; DM = diabetes mellitus; PLHIV = pregnant woman living with HIV.

Table 3. Demographics and outcome of live births to women with COVID-19

Neonatal outcomes	Live births (*N*=91)	Not exposed to HIV (*N*=66)	Exposed to HIV (*N*=25)	*p*-value
Gestation at delivery (weeks), median (IQR)	38 (36 - 39)	38 (36 - 39)	39 (38 - 39)	0.123
Delivered before 37 weeks, *n* (%)	27 (30)	21 (32)	6 (24)	0.466
Birth weight (g), median (IQR)	3 085 (2 350 - 3 520)	3 010 (2 380 - 3 475)	3 300 (2 350 - 3 545)	0.475
Low birthweight (<2 500 g), *n* (%)	25 (28)	18 (27)	7 (28)	0.945
Male, *n* (%)*	44/86 (51)	29/61 (48)	15/25 (60)	0.058
Neonatal ward admission, *n* (%)	15 (16)	11 (17)	4 (16)	0.606
Infant feeding, *n* (%)				
Exclusive breastfeeding	48 (53)	33 (50)	15 (60)	0.394
Exclusive formula feeding	8 (9)	4 (6)	4 (16)	n/a
Mixed feeding	4 (4)	4 (6)	0	n/a
Unknown	31 (34)	25 (38)	6 (24)	0.212
Neonatal death	1 (1)	1 (2)	0	n/a

IQR = interquartile range; n/a = not applicable.
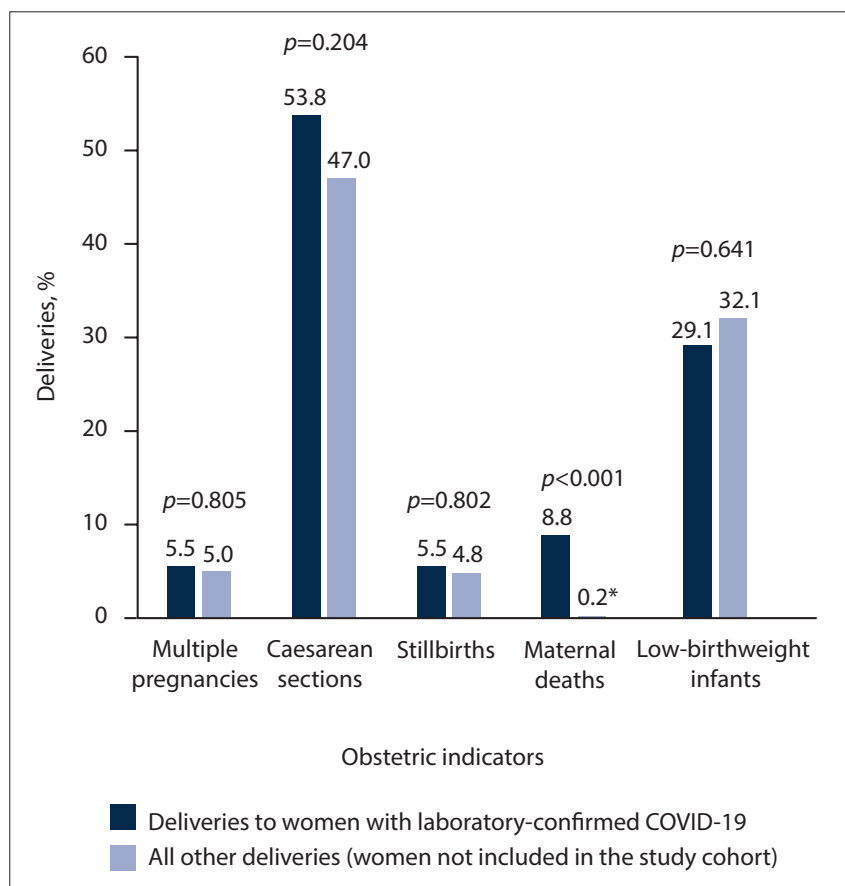*Sex unknown for 5 neonates.

Fig. 1. Key obstetric indicators for women with COVID-19 v. all other women pregnant delivering at Tygerberg Hospital but not included in the study cohort, 1 May - 31 October 2020. (*Two pregnant women who died of COVID-19 did not meet the inclusion criteria for this study: one was >7 days post partum, and the other, who was 8 weeks pregnant, was never managed by the obstetric team. These women were added to the numerator for calculation of maternal deaths of women not included in the study cohort.)

Of the cohort of 100 pregnant women with COVID-19, most were overweight or obese and many had underlying risk factors for severe COVID-19, including hypertension and diabetes mellitus. Risk factors for severe and critical disease in pregnant women with COVID-19 are similar to those in non-pregnant populations.[22] Severe COVID-19 in pregnancy has been associated with high BMI (odds ratio 2.38; 95% CI 1.67 - 3.39; three studies, 877 women).[7] In our study, 90% of the 40 women who developed severe/critical COVID-19 were either obese or morbidly obese. The high proportion of our cohort that developed severe/critical COVID-19 exceeds previous reports,[23] but the finding is not surprising, because our institution serves as a referral centre for severely ill patients and manages high-risk pregnancies, and only symptomatic women were tested.

Accumulating evidence demonstrates that pregnant women with COVID-19 are more likely to need admission to an ICU and require invasive ventilation than non-pregnant women of reproductive age with COVID-19.[7,24] Fifteen women in our cohort required ICU admission, with 6 needing intubation and ventilation for impending hypoxaemic respiratory failure. The crude maternal mortality rate in pregnant women with confirmed COVID-19 was 44 times higher than that for pregnant women not suspected to have COVID-19 during the same period. Rates of multiple pregnancies, caesarean sections, stillbirths and LBW were unaffected by COVID-19. The high mortality rate in our cohort (9%) contrasts with outcomes of 462 pregnant women with COVID-19 in 10 New York hospitals, where the crude mortality rate was 0.4% (*n*=2/462).[25] Of women admitted to ICUs in this US cohort, 50% had no comorbidities. Before the emergence of COVID-19, maternal mortality rates in low- to middle-income countries substantially exceeded those in high-income countries, but the disparity in maternal outcomes by region has again been highlighted by the pandemic.[26]

Preterm birth rates of between 12.6% and 17% have been documented in women with COVID-19.[7,24] The overall preterm birth rate in our cohort was high (30%), but it is similar to that for our high-risk obstetric unit. No difference was observed between rates of LBW in women with COVID-19 v. women without. In contrast to many other studies, where a quarter of all neonates born to mothers with COVID-19 were admitted to a neonatal ward,[7] the majority of our neonates (84%) remained in the care of their mothers. Only 16% were admitted to the neonatal ward, mainly owing to complications of prematurity. No perinatal COVID-19 transmission was documented in the few neonates admitted to the neonatal ICU, in support of other literature showing that perinatal COVID-19 transmission is rare.[8]

Study strengths and limitations

To our knowledge, this is the first observational cohort from Africa to report on COVID-19 in high-risk pregnant women including PLHIV. It adds important information to aid in the management of PLHIV with COVID-19. SA has 7.7 million people living with HIV, with ~4.7 million on cART.[27] Further studies are needed to fully assess the impact of COVID-19 on PLHIV. The impact on PLHIV who are newly diagnosed and not virally suppressed also needs further investigation. SA has reported many COVID-19 cases, owing to a high burden of disease and good laboratory access for testing. Unfortunately, the spread of the disease elsewhere in Africa has been less well characterised, with only a few small observational studies documenting the effect of COVID-19 on African pregnant women.[28] Etti *et al.*[5] plan to address some of these knowledge gaps by screening >50 000 pregnant women from five sub-Saharan countries, which will provide more information on the burden of COVID-19 in pregnant women on the continent.

We acknowledge the following limitations of the study. TBH only manages high-risk pregnancies, and these results are not generalisable to all pregnant women. The high proportion of pregnant women with a BMI ≥40 kg/m^2 may have contributed to a higher proportion of severe COVID-19. The numbers are relatively small in some subanalyses, and results should be interpreted with caution. Information regarding the date of HIV diagnosis, staging of HIV disease, and type and duration of cART was not available. As the majority of our PLHIV cohort were virally suppressed, we could only assess the impact of COVID-19 on high-risk pregnancies with well-controlled HIV infection.

Conclusions

In this cohort of high-risk pregnant women with COVID-19, the impact of the disease in pregnancy was severe; however, no clinical differences in outcome attributable to virally suppressed HIV infection were noted. We observed a high maternal mortality rate with poor outcomes for mother and fetus in women who developed critical COVID-19, compared with our institution's baseline non-COVID-19-associated maternal mortality rate. Despite these pregnant women being very ill, all but one of the liveborn neonates survived to hospital discharge.

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