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ORIGINAL ARTICLE | COVID-19 IN PREGNANCY

Clinical Features and Outcomes of COVID-19 Infection among Pregnant Women in South Africa

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ABSTRACT

Background and Objective: Studies among COVID positive pregnant women are limited. Previous studies reported high rate of symptoms, comorbidities, and poor fetal/neonatal outcome among women of different ethnicity. To date, no study was reported among pregnant African women. This study was conducted to determine the clinical features and outcomes of COVID-19 positive pregnant women in Ekurhuleni District in South Africa.

Methods: Retrospective record review of 103 COVID-19 infected pregnant women during the period of April to September 2020 was performed. Clinical features, symptoms, comorbidities, laboratory results, maternal, and neonatal outcomes were analyzed. Descriptive statistics (mean + standard deviation, number, and percentages) and inferential statistics (Chi-square test) were calculated. Ethical clearance was obtained from the Human Research Ethics Committee of the University of Witwatersrand, South Africa.

Results: Majority of patients (90%) were of African ethnicity and symptomatic (53%). The most common symptom, comorbidity, and laboratory abnormality was cough (62%), hypertension (23%), and high LDH (20%), respectively. Thrombocytopenia and lymphocytopenia occurred among 9% and 15% of the women, respectively. Although association was not significant, symptoms were more common among women who were HIV positive, had comorbidity, and had abnormal results. The most common complications were preterm labor (8%) and macerated stillbirths (6%). Six (6%) mothers died.

Conclusion and Global Health Implications: COVID-positive pregnant South African women were commonly symptomatic, but incidence of adverse fetal outcomes was low. High rate of preterm labor, macerated stillbirths, and maternal deaths was a concern. This study has several strengths. It included all COVID-positive women over a 6-month period at all healthcare facility levels, such as clinics, community health centers/midwifery units, district, and regional/tertiary hospitals conducted in an African country. Previous studies primarily included hospitals, which increased a high probability of mainly including severely-ill women. The study might benefit the health care workers in other African countries.

Keywords: • COVID-19 • Pregnancy • Ethnicity • Maternal and Fetal Outcome • South Africa

1. Introduction

South Africa has recorded the highest number of COVID-19 infections in Africa.[1] COVID-19 infected patients can be asymptomatic or symptomatic; the symptoms are of varying severity. The most common symptoms are dry cough, fever, sore throat, tiredness, and myalgia. Less common symptoms are conjunctivitis, diarrhea, nasal congestion, and headache.[2] Asymptomatic or mild disease is characterized by having oxygen saturation ≥ 95% on room air, respiratory rate < 25/minute, heart rate <120/minute, temperature 36-39°C, and normal mental status.[3]

In symptomatic patients, COVID-19 symptoms usually appear by 11.5 days in 97.5% patients, and the median incubation period is 5 days; hence, the recommended 14-day quarantine period is established.[4] Certain hematological changes were observed among symptomatic patients; among these, thrombocytopenia and lymphocytopenia were common.[5] High lactic dehydrogenase (LDH) level was found to be a predictor of disease severity.[6] Investigations should be done depending on the severity of the disease. Asymptomatic mild disease at least might require Human Immuno Deficiency Virus (HIV) testing. If the patient is HIV positive, a sputum test to exclude tuberculosis is recommended.[7]

About 80% of infected people do not require any hospital treatment. The World Health Organization and the South African National Institute for Communicable Diseases (NICD) recommended 14-day isolation for positive cases with mild or no symptoms. However, the duration has been reduced to 10 days with emergence of new information. Isolation can be done at patient's home or at a designated isolation facility if the patient is unable to self-isolate at home. Repeated testing was not recommended at the end of the 10 day-period.[2, 8] Globally, there are very few reports on COVID-19 infection among pregnant women limiting the knowledge of disease process among this group. Compared to the general population, limited evidence suggests that pregnant women are not at higher risk of infection and have worse maternal outcomes.[7] In a U.S. study that included 43 COVID-19 positive pregnant women, 37 (86%) exhibited mild disease, four (9.3%) had severe disease, and two (4.7%) had critical disease.[9] The most common symptoms among 15 pregnant Chinese women were fever (86.7%) and cough (60%), and the symptoms were mild. Lymphocytopenia was the most common (80%) abnormal laboratory finding.[10]

Another study in China did not find any differences in clinical features between nine pregnant women and the general population. In this study, fever was the most common (78%) symptom followed by cough (44%), sore throat (22%), and myalgia (33%). Lymphocytopenia was found in 55% of the patients.[11] Another study in China that compared 41 pregnant women with 14 non-pregnant adults reported that pregnant women were more likely to present with normal temperature and lymphocytopenia than non-pregnant adults.[12] On the contrary, a retrospective study on 116 pregnant women in China found that majority (76.7%) were symptomatic. The most common symptoms were fever (50.9%) followed by cough (28.4%). Eight (6.9%) had severe pneumonia but no maternal deaths.[13]

South Africa has nine provinces of which Gauteng is the smallest but has the largest population density (15.2 million, 26% of total population).[14] Each province has a well-developed district health system. Among the five districts under Gauteng province, Ekurhuleni Health District (EHD) is the second most densely populated (about 3.9 million).[15] Gauteng had 219,704 infected cases and 4, 244 deaths by September 30, 2020.[16] EHD had 48, 116 cases and 785 deaths by September 30, 2020, implicating the death rate of about 2%.[17]

EHD has six hospitals: one tertiary, one district and four regional hospitals, and eight community health centers that provide antenatal, labor, and postnatal care. Additionally, 95 primary health care clinics provide antenatal and postnatal care. All healthcare facilities followed the NICD guidelines for COVID-19 screening, testing, and management.[7,8] Furthermore, EHD established three COVID isolation centers where mostly asymptomatic and mildly symptomatic COVID-19 positive patients (who are unable to self-isolate and do not require admission at hospitals) are

admitted. Doctors and nursing sisters provide a 24-hour clinical services at these centers.

Although screening was universal, testing was done for the history of international travel, history of contact, suggestive symptoms, and at the discretion of attending health care workers. All regional hospitals implemented universal testing for all women that were admitted for cesarean sections. Women who were sent home for self-isolation were monitored telephonically by the nearest health care facilities. Women admitted in hospitals for COVID-19 related morbidity or obstetrics reasons were discharged when recovered and isolated at home or at COVID centers to complete the isolation period. There was a COVID-19 management team within the district where all health care facilities and COVID centers reported all COVID-positive patients on a daily basis. All health care facilities and COVID centers kept a register of COVID-19 positive patients where all information about the patients were recorded. Maternity case records (MCR), which contain antenatal, intrapartum, and postpartum information, are used for all pregnant women in SA. MCRs are kept in CHCs and hospitals after the women are discharged following delivery.

To date, there are no African studies performed on COVID-19 positive pregnant women. The aim of this study was to determine the clinical features and outcome of COVID-19 infection among COVID-19 positive pregnant women within the EHD, SA.

2. Method

COVID registers and MCRS of all COVID positive pregnant and postpartum women at the EHD, SA during the period of April to September 2020 were retrospectively reviewed. The study obtained ethical clearance from the Human Research Ethics Committee of the University of Witwatersrand, Ekurhuleni district research committee, Gauteng provincial research committee, and all participating health care facilities. All women were included and none were excluded due to pandemic status of the disease. Investigations related to COVID-19 were not done in mildly symptomatic and asymptomatic women. Results of investigation and detailed information were not available for some of the privately booked patients as private medical practitioners did not disclose their patients' information. Record keeping at the facilities were not complete at times. As a result, the sample size was not uniform for all variables. Comorbid conditions were diagnosed by the attending healthcare workers.

Data was collected using a data collection tool created by the researcher. Data included demographic information, such as age, ethnicity, and place of isolation/admission. Obstetrics factors such as parity, pregnancy status (antenatal or postnatal), antenatal complications, and gestational age (GA) at delivery were also included. COVID-19 related factors such as GA at COVID-19 diagnosis, reason for testing, travel history, history of contact, symptoms, comorbidity and blood results (platelets, lymphocytes and LDH), and maternal and neonatal outcomes, were also included. The HIV result was included as recommended.[7] Statistical analysis was done by Pass software (NCSS, Kayesville, UT, USA). Descriptive statistics included mean with standard deviation (SD), actual number, and percentages. Inferential statistics included the Chi-square test, which was used to determine if there was any association between symptoms and other variables, such as comorbidity, HIV status, and abnormal laboratory results. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Demography, Age and Parity

The study included 103 COVID-19 positive pregnant and postpartum women. EHD had 48, 116 COVID positive cases among general population.[17] Therefore, pregnant women contributed 0.21% (103/48,116) of the total infections. Ninety-three (90%), 2 (2%), and 8 (8%) were African, Caucasian, and mixed ethnicity women, respectively. Age and parity are described (Table 1). Employment status was available for 96 women. Forty-six (48%) and 50 (52%) of the women were employed and unemployed respectively.

3.2. Antenatal Care

A total of 99 (96%) women were booked. Four (4%) women never initiated antenatal care. Mean (± SD) gestational age (GA) at booking was 16.8 (SD ±

Table 1: Demographic characteristics and comorbidities of COVID-19 positive pregnant and postpartum women, Ekurhuleni Health District, Gauteng province, South Africa

Age and parity distribution (N =103)					
Age		**Parity**		**Booking trimester***	**N (%)**
Mean (SD)	30 (+ 5.67) years	Mean (SD)	1.48. (+ 1.06)		N (%)
Minimum	16 years	Minimum	0	First trimester (up to 12 weeks)	25 (25)
Maximum	46 years	Maximum	6	Second trimester (12 – 24 weeks)	63 (64)
16 to 19 years	3 (3%)	Primigravidae	17 (18%)	Third trimester (24 - 40 weeks)	11 (11)
20 to 35 years	84 (81%)	P 1 to P 4	85 (82%)		
36 to 40 years	12 (12%)	P > 5	1 (1%)		
> 40 years	4 (4%)				
Reasons for testing/place of isolation (N = 103) and comorbidity (N = 30)					
Reasons for testing	**N (%)**	**Place of admission**	**N (%)**	**Comorbidity****	**N (%)**
Symptomatic	55 (53)	Hospital & home	27 (26)	Hypertension	24 (23)
Contact positive	15 (15)	COVID hospitals	26 (25)	Diabetes	5 (4)
Routine test for cesarean section	29 (28)	Home	17 (17)	Morbid obesity	1 (1)
Obstetrics morbidity	3 (3)	Hospital	33 (32)	Cancer	1 (1)
Travel history	1 (1)				

*N = 99 (booked women)
**One woman had combined PIH & obesity and one had combined PIH and Diabetes

6.10) weeks with a range of 6–33 weeks. Majority of the patients booked in the 2nd trimester (Table 1).

3.3. Indications for Testing and Time of Diagnosis

Majority (33,32%) of the patients were admitted in the hospital for various reasons (symptomatic, planned cesarean section, and obstetrics complications) to complete isolation period (Table 1). Ninety (87%), 12 (12%) and one (1%) was antenatal, postpartum and post-miscarriage at the time of COVID-19 diagnosis respectively. The mean GA at the time of diagnosis was 32 (+ 9.02) weeks.

3.4. Symptoms

Twenty-four (44%) women had single symptoms, and 31 (56%) presented with multiple symptoms. Symptoms were categorized as mild (having normal vital signs and receiving only symptomatic treatment or no treatment), moderate (requiring hospital admission), and severe (high care or intensive care unit admission; Table 2).

3.5. Comorbidities

Seventy-three (71%) women had no comorbidities, and two had multiple comorbidities (Table 1). Among 30 (29%) women who had comorbidities, 16 (53%) were symptomatic, and 14 (47%) had no symptoms. A Chi-square test showed no significant (P = 0.67) association between comorbidity and symptoms. Among 30 of the women who had comorbidities, hypertension was the most common (80%), followed by diabetes mellitus (13%), morbid obesity (3%), and cancer (3%).

3.6. Laboratory Results

Ninety-nine (96%) women underwent HIV testing, of which 61 (62%), and 38 (38%) tested HIV negative and positive, respectively. Twenty-one (55%) of the HIV-positive women were symptomatic. Thirty-two (52%) of the HIV negative women were symptomatic. Association between HIV positivity and symptoms was not significant (P = 0.83).

Table 2: Types and severity of COVID symptoms among COVID-19 positive pregnant and postpartum women in Ekurhuleni Health District, Gauteng province, South Africa

COVID-19 Symptoms (N = 103)			
	N (%)		**N (%)**
Symptoms present *	55 (53)	Symptoms absent	48 (47)
Dry cough	28 (51)	Contact positive	15 (15)
Productive cough	6 (11)	Routine testing for planned Cesarean section (obstetrics reasons)	29 (28)
Fever	14 (25)	Obstetrics complications	3 (3)
SOB	11 (20)	History of travel	1 (1)
Nasal congestion	7 (13)		
Sore throat	6 (11)		
Running nose	6 (11)		
Loss of smell	4 (7)		
Headache	3 (5)		
Not feeling well	2 (4)		
Sneezing	2 (4)		
Itchy throat	2 (4)		
Loss of appetite	2 (4)		
Hoarse voice	1 (2)		
Severity of COVID-19 symptoms (N = 55)			
Symptom	**N (%)**		
Mild	34 (62)		
Moderate	10 (18)		
Severe	11 (20)		

*Twenty-four (44%) women had single symptoms and 31 (56%) women had multiple symptoms

Among the patients, COVID-19 could be attributed to thrombocytopenia of seven (9%), high LDH counts of four (20%), and lymphocytopenia of three (15%) who had no comorbidities (Table 3). Comorbidities might affect the platelets, lymphocytes, and LDH count. Therefore, only patients who had abnormal results but no comorbidities were included for interpreting the abnormal results. Among nine women who had thrombocytopenia, six (67%) were symptomatic and the association was not significant (Chi-square test, p = 0.30). Among four women who had lymphocytopenia, all (100%) were symptomatic and it was not significant (Chi-square test, p = 0.26). Among eight women who had high LDH count, six (75%) were symptomatic, and it was not significant (Chi-square test, p = 1).

3.7. Antenatal Complications

Fifteen (15%) mothers and four (4%) fetuses had antenatal complications. Among 15 women who had complications, preterm labor (PTL) was the most common (53%) complication followed by anemia (20%), abruption placenta (13%), preterm rupture of membrane (7%), and miscarriage (7%). Among four fetuses who had complications, two (50%) had intrauterine growth retardation (IUGR), and remaining two (50%) had intra-uterine fetal deaths (Table 3). A Chi-square test between comorbidities (hypertension and diabetes mellitus) and outcome (PTL, anemia, abruption placenta, and PPROM) showed outcomes.

3.8. Gestational Age at Delivery

Sixty-eight women delivered 69 babies (one twin). Mean (+ SD) GA at delivery was 38.42 (+ 2.30) weeks.

3.9. Mode of Delivery

Twenty-four (35%) women delivered vaginally. Forty-four (65%) had cesarean section (CS), of which 32 (78%) had planned CS, and 12 (22%) had emergency CS.

3.10. Neonatal Outcome

The mean (+ SD) weight of the neonates was 3,060 (+ 566.59) grams. Among six (9%) neonates who had poor outcomes, two (33%) babies had poor Apgar scores at 5 minutes, and four (66%) babies were macerated still born. A Chi-square test between comorbidity (hypertension and diabetes) and neonatal outcomes was not significant.

3.11. Maternal Mortality

Six (6%) mothers died, and 97 (94%) women were discharged in a healthy condition.

4. Discussion

This study on COVID-19 positive pregnant women in SA has similarities and differences to other studies.

Table 3: Laboratory results and antenatal complications among COVID-19 positive pregnant and postpartum women, Ekurhuleni Health District, Gauteng province, South Africa

Laboratory Investigations			
	Platelets (N = 75)[a]	**Lymphocyte (N = 20)[b]**	**LDH (N = 20)[c]**
Mean (SD)	226.82. (+ 77.79) x 109 / liter	1.55. (+ 0.48) x 109/liter	413.7. (+198.20)
Minimum	44 x 10^9/liter	0.66. x 109/liter	188 x U/liter
Maximum	534 x 10^9/liter	2.34. x 109/liter	831 x U/liter
Normal count N (%)	65 (87)	16 (80)	10 (50)
Low count N (%)	9 (12)	4 (20)	2 (10)
High count N (%)	1 (1)	0	8 (40)
Antenatal complications (maternal) (N = 103)		**Antenatal complications (fetal) (N = 103)**	
	N (%)		**N (%)**
Abruptio placenta	2 (2%)	IUGR	2 (2%)
PTL	8 (8%)	IUD	2 (2%)
PROM	1 (1%)	Miscarriage	1 (1%)
Anemia N (%)	11 (11%)		

[a]Thrombocytopenia, less than 150 x 10^9 / liter is defined as thrombocytopenia; [b]LDH count of more than 400 U/liter is defined as high LDH count;
[c]Lymphocyte count less than 1 x 10^9/liter is defined as lymphocytopenia; IUGR, Intrauterine Growth Restriction

4.1. Demography

This is the first study where patient majority (90%) were of African ethnicity. Most of the published studies had a different ethnic population. This study had three (3%) teenagers, which was not found in other studies.[12, 13, 14, 15] This might have reflected the challenge of teenage pregnancies in African countries. Majority (83%) were multigravida which was different from the 55% of primigravidae reported in another study.[16] Other studies did not report parity; hence, it was difficult to compare if parity had any association with COVID-19 infection in pregnancy.

4.2. Indications for Testing and Time of Diagnosis

To understand testing coverage in different health care facility levels, the reasons for COVID testing were analyzed. The majority of patients (53%) were tested for symptoms followed by testing for elective cesarean section (28%). Majority (87%) were diagnosed during the antenatal period which was different from other studies where majority of infections were reported during the postpartum period.[12,13,16] This difference might de due to the indications for testing.

4.3. Symptoms

The study observed a higher rate (47%) of asymptomatic women than that (13% to 33%) of other studies.[12, 13, 18] Although majority (62%) were mildly symptomatic in this study, other studies had much higher rates of mild disease (86% - 93%).[9, 13, 18] In this study, the majority of patients presented with cough (62%), while fever was found to be the most common symptom in other studies.[18, 19]

4.4. Comorbidities

Thirty (29%) women had comorbidities. Studies reported varying rates (22% to 34%) of comorbidities including antepartum hemorrhage, polycystic ovary, and hypothyroidism, which might not have had relevance for COVID-19.[18,19] Incidence of hypertension (23%) was similar to other studies (25%/23%) [18,19] and also higher (7%) than other studies.[12] The incidence of diabetes mellitus was lower (4%) than reported (20%) in other studies.[19,20] Higher proportions (53%) of comorbid women were symptomatic, although association between symptoms and comorbidity was insignificant. Association analysis was not perform in other studies.[18,19,20]

4.5. Laboratory Results

Laboratory investigations were for few women which was one of the limitations for this study. This is the only study where HIV status was discussed. Although statistically insignificant, HIV-positive women were more likely to present with symptoms compared to those who were HIV negative (55% vs 52%). Rate of lymphocytopenia was lower (20%) than that (55%/64%/80%) reported in other studies.[13,14,15] Only symptomatic women had lymphocytopenia; however, this observation was statistically significant. The incidence of thrombocytopenia was lower (9%) when compared to another study (38%).[18] Thrombocytopenia was more (67%) common among symptomatic women, although statistically not significant. High LDH (20%) was the most common abnormality observed. This test was not reported in other studies. Unlike other studies which included laboratory results for all female patients, irrespective of comorbidities, we excluded patients with comorbid conditions, as these could affect the interpretation of results, such as platelet, lymphocyte, and LDH counts, leading to an erroneous conclusion that a higher number of COVID-19 infected pregnant women had abnormal laboratory results.

4.6. Antenatal Complications

About 15% women had complications which was lower (21% - 56%) than that of other studies.[13,18,19] PTL (8%) and miscarriage (2%) in this study were comparable to other studies which reported lower rate (2%, 6%) of PTL.[13,17] However, few studies reported much higher rates (41% to 47%) of PTL.[20,21,22] Miscarriage was found in one (2%) woman which was similar (1%) to another study.[16] Much higher (65%) rate of miscarriage was observed in another study.[20] A Chi-square test between comorbidities and maternal outcomes was not significant.

4.7. Mode of Delivery

A majority of the patients (65%) had CS delivery, of which planned CS was performed for 78% of the them. CS was done for obstetrics indications. It was similar to the only other study performed in the U.S., where the CS rate (44%) was much lower, and it was performed only for obstetrics indications.[9] Most studies from China reported higher (86% - 100%) rates of CS where COVID-19 was a routine indication for CS.[10,11,13,18,19] Reasons for performing CS for all COVID positive women were not discussed in these studies.

4.8. Neonatal Complications

About 9% of neonates had complications which was higher than other studies (1%).[18] Observed fetal/neonatal outcomes in this study were 4 (6%) macerated newborns and two (3%) newborns who had poor Apgar scores at 5 minutes. Other studies reported lower rates (3%) of stillborn and lower rate (1%) of neonatal asphyxia.[19,16] A Chi-square test between comorbidities and neonatal outcomes was not significant.

4.9. Maternal Mortality

This study observed higher rate (6%) of maternal deaths than that (1%) of other study.[18] There were two case studies that reported two maternal deaths.[23,24] Maternal deaths were much higher (78%) in another report.[25]

In summary, important findings in the study were that pregnant women of African ethnicity might have a low incidence of COVID-19 and have complications in comparison to other studies but may suffer from moderate to severe symptoms, preterm labor, IUGR, IUD, MSB, maternal deaths, and high LDH count. Additionally, most parous and hypertensive women in their 3rd trimester of pregnancy contracted the disease, presenting primarily with cough. Although statitically insignificant, it is clinically important to note that most symptomatic and comorbid patients had laboratory abnormalities, including higher numbers of HIV-positive patients who were also symptomatic.

4.10. Limitations

Sample size was not uniform for all variables. Laboratory testing were not performed for all patients. COVID testing was performed only in symptomatic patients, and some patients underwent CS, which might have led to incidence under-estimation.

5. Conclusion and Global Health Implications

This study provided a valuable insight into the COVID-19 infection among African pregnant women and its outcome. We included women from all levels of health care facilities over a specified period in an African country, which has its merit of applicability to other parts of SA and African countries. Incidence was low. Abnormal laboratory results warrant mandatory laboratory testing for pregnant women. Infection in pregnancy among African women, regardless of the HIV status, was associated with adverse pregnancy outcomes and high maternal mortality. Large proportion (47%) of asymptomatic women raise a question if testing should be universal for all pregnant women which might be answered in further research in Africa.

Compliance with Ethical Standards

Conflicts of Interest: *None.* ***Financial Disclosure:*** *None to disclose.* ***Funding/Support:*** *None.* ***Ethics Approval:*** *Ethical clearance was obtained from the University of Witwatersrand.* ***Acknowledgments:*** *Authors would like to acknowledge all healthcare workers at all health care facilities and COVID centers at the Ekurhuleni Health District for their moral support and record keeping.* ***Disclaimer:*** *None.*

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Key Messages

- As one of the first studies of clinical features and outcome of COVID positive pregnant women in Africa, we found that the incidence of COVID-19 infection was low among pregnant women compared to general population.
- Laboratory tests were infrequently done and high lactic dehydrogenase was common. Preterm labor and maternal mortality was high.
- Universal testing for pregnant women might be warranted.
- A significant proportion (47%) of asymptomatic women raised the question of whether testing should be universal for all pregnant women, which might be answered in further research in Africa.

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