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Original Research Article

Maternal and neonatal complications between post-COVID pregnant patient and normal patient: a tertiary care hospital-based comparative study

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ABSTRACT

Background: As the COVID-19 pandemic evolved the complications associated with acute infection have been well described. However, in the post-pandemic era, we must dwell on the obstetric sequelae of these infections. This study investigated the maternal and neonatal outcomes in post-COVID patients compared to normal pregnant women.
Methods: A prospective cohort study was designed where women who had a COVID-19 infection during pregnancy were compared with concomitant pregnant women without a COVID-19 diagnosis. Women were followed up from enrolment in the outpatient department until one-week post-partum, and data were collected.
Results: In this study, 201 women were included and divided into two groups. The women who had a COVID-19 infection during pregnancy had a significantly higher incidence of gestational diabetes mellitus (OR 3.6, 95% CI 1.0-12.6). There was also a significantly higher incidence of adverse perinatal complications (OR 1.5, 95% CI 1.1-2.0) particularly an increased rate of preterm delivery (OR 3.4, 95% CI 1.3-8.7) compared to the women who did not have a COVID-19 infection during pregnancy. Moreover, no significant differences existed in the measured outcomes when comparing women infected in the second trimester, to those infected in the third trimester.
Conclusions: The development of complications such as preterm delivery and gestational diabetes mellitus among women after a COVID-19 infection during pregnancy underscores the necessity for close monitoring of such patients and the promotion of strategies to prevent infection.

Keywords: Birth weight, GDM, Post-COVID 19, Preterm

INTRODUCTION

In March 2020, COVID-19 was officially declared a pandemic with widespread impact on health, particularly affecting vulnerable populations such as pregnant women. Contracting COVID-19 poses significant morbidity and mortality during pregnancy and even during the postpartum period, especially if the individuals are symptomatic or have underlying health conditions. Previous studies have focused on the effects of acute COVID-19 infection during pregnancy.[1-3] Factors such as physiological changes, anatomical changes, hormonal imbalance, alterations in immune systems, and increased expression of ACE2 may be associated with increased severity of COVID-19 during pregnancy.[4] A living systematic review that included nearly 22 studies from India revealed that pregnant women with COVID-19 have higher rates of maternal deaths, intensive care unit admissions, preterm births, caesarean sections, and neonatal unit admissions compared to pregnant women without the disease.[5] However, data on long-term effects and obstetric complications after complete recovery from the disease is limited. "Long COVID" is a term used to describe a wide range of subacute and chronic symptoms that occur after the acute phase of SARS-CoV-2 infection, regardless of the infection's severity.[6] The physiological

mechanisms behind this syndrome are still unclear. Hence, it's crucial to provide ongoing support and monitoring for these mothers and infants due to potential long-term health effects related to COVID-19.

This research work goal was to study the maternal and neonatal complications among post-COVID patients and compare their incidence with normal antenatal patients during the same period. Ultimately, this study aimed to contribute to existing knowledge about the maternal and neonatal outcomes of pregnant women after being infected with the SARS-CoV-2 virus. Identifying these potential complications is crucial for ensuring close monitoring, identifying high-risk pregnancies, and planning maternal care.

METHODS

We conducted a single-center prospective cohort study at the Malankara Orthodox Medical College Hospital, Kolenchery, Kerala to investigate the maternal and neonatal complications post-COVID-19 infection during pregnancy. The study was conducted from January 2021 up to January 2022. We assessed women who visited the antenatal outpatient department with a history of COVID-19 infection confirmed with a positive RT-PCR test during pregnancy and have completely recovered from the disease. When a woman who had a history of COVID-19 infection in the present pregnancy was enlisted in the study group, to avoid selection bias, one woman without a history of COVID-19 diagnosis of similar gestational age (±2 weeks) receiving standard antenatal care was enrolled that day. We continued this process until we enrolled a woman without a COVID-19 diagnosis for each woman with a COVID-19 diagnosis. If it wasn't possible to enroll a woman without a COVID-19 diagnosis or if they were lost to follow-up, we enrolled a woman without a COVID-19 diagnosis who delivered immediately after the woman with a COVID-19 diagnosis. The study included live and stillborn singleton pregnancies with a history of mild to moderate infection. We excluded patients with a history of chronic disease or any risk factors for preterm delivery. Additionally, among the women without a COVID-19 diagnosis, if anyone developed COVID-19 infection anytime during pregnancy they were excluded. The sample size was calculated based on the risk of preterm delivery in a previous study[7] and was determined to be 92 in each group. Since all women had to be followed up until delivery, we factored in an attrition risk of 15 percent and aimed to include 106 patients in each group.

All women were followed from the time of enrolment until one-week post-partum. The study examined the development of any antenatal complications after the infection and any adverse perinatal complications including the risk of preterm delivery, presence of meconium-stained amniotic fluid, presence of intrapartum abnormal cardiotocography, the incidence of caesarean section and incidence of postpartum hemorrhage. For the neonates, the study analyzed gestational age at delivery, birth weight, unplanned NICU admissions, incidence of stillbirths, and neonatal deaths. Gestational age was determined from the patient's last menstrual period if she had regular cycles, or from the earliest available ultrasound if she had irregular cycles.

Data collection was done with informed consent, and confidentiality was strictly maintained. The study had received ethical clearance from the institutional review board before it commenced. The data was analyzed using SPSS (IBM; Armonk, NY, USA).

Statistical analysis

Descriptive statistics were used to determine the frequency distribution of the numerical variables. The normality assumption of the quantitative measures was verified by the Shapiro-Wilk test and the non-normally distributed numerical variables were analyzed using the Mann-Whitney U test. They are represented as a median and interquartile range. The Chi-square test was used to analyze the categorical variables. However, the categorical variables that did not fulfill the chi-square test requirement were analyzed using Fischer's exact test The odds ratio along with the 95% confidence interval was calculated for the outcome measures. Statistical significance was defined as $p<0.05$.

RESULTS

This study included 201 women, they were divided into two groups: Group A comprised women who had recovered from a Covid-19 infection during pregnancy and were asymptomatic, while Group B included women who had never been infected with Covid-19 during pregnancy. The median age of the patients in Group A was 27 years (IQR = 5), and 26 years (IQR = 6) in Group B. The age distribution (Figure 1) was similar between the two groups ($p = 0.92$).

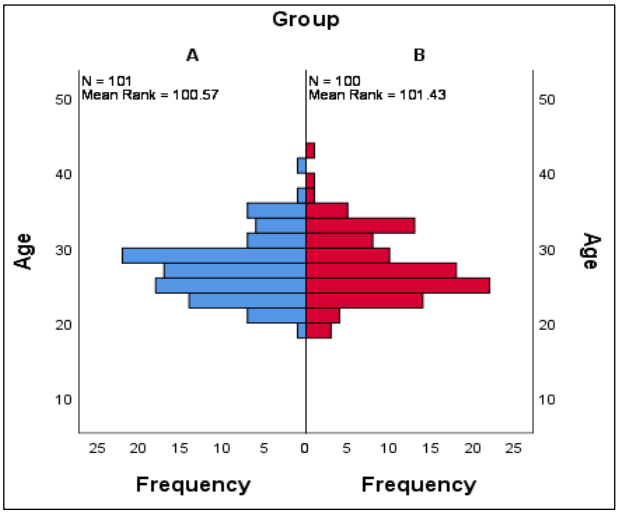

Figure 1: Distribution of age among the women in each group.

There was no significant difference in the number of nulliparous women between the two groups (55.4% vs 63%, p = 0.55).

We found that there were more antenatal complications during pregnancy among women who contracted COVID-19, although this association was not statistically significant. The various complications are depicted in Figure 2, with the most common being gestational diabetes mellitus (GDM), which had a three-fold increased likelihood of developing when infected with COVID-19 (OR 3.6, 95% CI 1.0-12.6). Incidence of other complications like anaemia (OR 0.33, 95% CI 0.04-3.11), hypertensive disorders of pregnancy (HDP) (OR 0.8, 95% CI 0.3-2.6), fetal growth restriction (OR 1.5, 95% CI 0.4-5.1) and oligohydramnios (OR 0.6, 95% CI 0.1-3.8) were not significantly different between the groups.

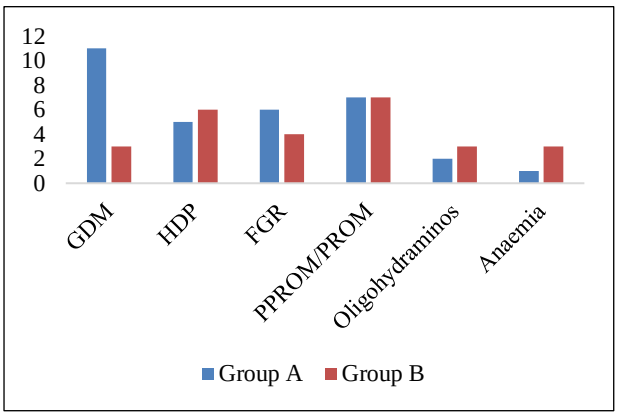

Figure 2: Distribution of antenatal complications developed by women in the two groups (GDM: Gestational Diabetes Mellitus; HDP: Hypertensive Disorders of Pregnancy; FGR: Fetal Growth Restriction, PPROM/PROM: Preterm Premature Rupture of Membranes/Premature rupture of membranes).

Sixty -two percent of the women who belonged to Group A had an adverse perinatal outcome (OR 1.5, 95% CI 1.1-2.0) compared to 41% in Group B (Table 1). This difference was statistically significant (p=0.002). In particular, the rate of preterm delivery among patients who had the infection during pregnancy (OR 3.4, 95% CI 1.3-8.7) was statistically higher when compared to the control group. On sub-group analysis, women who did not have any complications other than COVID-19 infection, eleven women had preterm delivery compared to none in the other group. Among the women in Group A, 40.6% had spontaneous onset of labour pains compared to 19% in Group B. The majority (66%) of the women delivered vaginally in both groups, and of the women who underwent caesarean section, the numbers were comparable among the groups (32% vs. 35%). The most common indication for caesarean section in women who had been infected was a previous caesarean presenting in labour (31.3%) which was not seen in Group B. The most common indication in this group was failed induction (37%). There was no significant difference in the number of abnormal CTG and meconium staining of amniotic fluid among the groups. However, the incidence of postpartum hemorrhage was higher in Group A, but this difference was not significant (OR 1.98, 95% CI 0.7-5.5). In Group A, the median gestation period at delivery was around 38 completed weeks, while in Group B it was around 39 completed weeks. The former group also had a significantly lower median birth weight compared to the latter. This notable difference was also evident in the higher number of unplanned admissions to the Neonatal Intensive Care Unit (NICU) when the mother had a history of COVID-19 infection during pregnancy. The main indications for admission were respiratory distress (23.8%) and neonatal hypoglycemia (23.8%), both of which were absent among women without a COVID-19 infection. Additionally, there was one stillborn and one neonatal death in Group A.

Table 1: Outcome parameters measured in the whole sample.

	Group A (n=101), N (%)	Group B (n=100), N (%)	P value
Antenatal complications	29	24	0.45
Preterm delivery	17	5	0.007
Gestational age at delivery (days)	267 (12)	274 (11)	<0.05
Meconium-stained amniotic fluid	4	4	1.00
Pathological CTG	5	8	0.18
Cesarean section	32	35	0.61
Post-partum haemorrhage	10	5	0.18
Birth weight (kg)	2.93 (0.78)	3.06 (0.6)	0.032
Unplanned NICU admission	21	10	0.03

Quantitative data are presented by median with interquartile range. For qualitative factors, absolute frequencies are given. Mann-Whitney U test was used for continuous data Chi-square test was used for non-continuous data. p<0.05 was considered significant

Among the infected women, 49% were infected in the 2nd trimester, 43% in the 3rd trimester, and 9% in the first trimester. We compared women who had the infection in the second trimester to those who were infected in the third trimester. The median gestational age of infection in the 2nd trimester infection was 22 completed weeks (157 days; IQR = 48) and in the third trimester was 34 completed weeks (238 days, IQR = 38). Women who had a COVID-

19 infection in the 2nd trimester had a higher incidence of GDM of 14.3% compared to 2.3% in the third trimester but this was not significantly different (p = 0.06). Even though the gestational age at delivery and the median birth weight were similar between the two groups, the rate of preterm delivery was higher when infected in the third trimester, and the incidence of antenatal complications was higher when infected in the second trimester. However, none of these differences showed any statistically significant association.

Table 2: Outcome parameters measured depending on the time of COVID-19 infection.

	2nd trimester (n=49), N (%)	3rd trimester (n=43), N (%)	P value
Antenatal complications	17 (34.7)	8 (18.6)	0.08
Preterm delivery	6 (12.2)	11 (25.6)	0.1
Gestational age at delivery (days)	267 (11)	268(16)	0.99
Meconium-stained amniotic fluid	1 (2)	2 (4.7)	0.59
Pathological CTG	3 (6.1)	2 (4.7)	0.38
Cesarean section	16 (32.7)	14 (32.6)	0.99
Post-partum haemorrhage	6 (12.2)	4 (9.3)	0.74
Birth weight (kg)	2.93 (0.58)	2.93 (0.97)	0.82
Unplanned NICU admission	10 (20.4)	8 (18.6)	0.38

Quantitative data are presented by median with interquartile range. For qualitative factors, absolute and relative frequencies are given. Mann-Whitney U test was used for continuous data. Chi-square test was used for non-continuous data. p<0.05 was considered significant.

DISCUSSION

Pregnant women who get infected by the SARS-CoV-2 virus are at increased risk of experiencing adverse outcomes. To analyze the effects after a woman recovers from acute COVID-19 infection, we conducted a single-center, prospective cohort study to assess the proportions of maternal and neonatal complications associated with a history of COVID-19 infection during pregnancy. We found a higher incidence of antenatal complications and adverse perinatal outcomes in women who had been diagnosed with COVID-19 compared to those without the diagnosis. The PRIORITY (Pregnancy CoRonavIrus Outcomes RegIsTrY) study found that pregnancy-related COVID-19 is linked to worse perinatal outcomes and maternal morbidity, including higher rates of preterm birth, hypertensive disorders of pregnancy, and thromboembolic events.[8] In our study, there was a significantly increased incidence of preterm birth but no increase in hypertensive disorders of pregnancy or reports of thromboembolic events. However, gestational diabetes mellitus (GDM) was significantly higher among women who had a COVID-19 infection. Similar results were obtained in a retrospective case-control study which reported a significantly higher incidence of GDM in pregnant women infected with SARS-CoV-2 compared to historical controls.[9] A more recent cohort study attributed the increase in GDM incidence a result of the indirect effects of the pandemic-related restrictions. They studied GDM pre-COVID-19 and during the first and second years of the pandemic which demonstrated a progressive increase in the rate of GDM with pandemic exposure. The pandemic was associated with changes in maternal baseline characteristics, including increases in most of the traditional risk factors for GDM, and greater gestational weight gain.[10]

We found that more women who had been infected with COVID-19 went into spontaneous labour, but there were no differences in the mode of delivery between the groups. Metz et al. found that patients with SARS-CoV-2 infection were not at significantly increased risk of cesarean birth (34.7% vs 32.4%; aRR, 1.05 [95% CI, 0.99-1.11] compared to those without the infection.[11] However, in the INTERCOVID Multinational Cohort study women with a COVID-19 diagnosis had a lower rate of spontaneous initiation of labor but a higher cesarean delivery rate.[12] This study also reported that women with COVID-19 diagnosis delivered earlier than those without COVID-19 diagnosis after approximately 30 weeks' gestation, with the greatest difference less than 37 weeks' gestation.[12] Similarly in this study the gestational age at delivery was lower among women who had a COVID-19 diagnosis. Analysis of data from the GRAVID study revealed that 28.9% of those who tested positive for SARS-CoV-2 and 28.6% of those who tested negative had a previous cesarean birth as the indication for their current cesarean birth[11]. In the group of women with a COVID-19 diagnosis that we studied, 31% who underwent a cesarean section had a previous cesarean presenting in labor as the indication. Our study suggested a three-fold increased risk for preterm delivery (OR 3.4, 95% CI 1.3-8.7) among women who had been infected with COVID-19 (16.8% vs. 5%). This was reflected in slightly higher rates of NICU admissions, although the difference was not statistically significant. A prior study also found that SARS-CoV-2 exposure was significantly associated with preterm birth at less than 37 weeks' gestation (17.7% vs 14.1%; difference, 3.7% [95% CI, 2.1%-5.4%]; aRR, 1.15 [95% CI, 1.02-1.30]) and NICU admission (aRR, 1.15, 95% CI, 1.04-1.27).[11] Furthermore, a Canadian surveillance study reported an elevated rate of preterm birth, even in cases of mild COVID-19 not requiring hospitalization (9.3%).[3]

The study had some limitations, such as a small sample size and inadequate assessment of early pregnancy complications because most patients were approached in the second trimester. Additionally, the study was conducted before the COVID-19 vaccination was available to pregnant women in India. Since the COVID testing was symptom-based, there is a possibility that the group of women without a COVID-19 diagnosis may have included some asymptomatic infected individuals, which could affect the accuracy of the results. Furthermore, it's important to note that after the study was conducted, a large number of COVID variants have emerged worldwide, and these variants may have different effects.

CONCLUSION

It may be necessary to continue screening and closely monitor women who have had a COVID-19 infection during pregnancy, even if they don't have other risk factors, to identify high-risk pregnancies. Women with a history of COVID-19 can expect adverse prenatal outcomes, particularly an increased likelihood of preterm birth compared to women who have not been infected.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of MOSC Medical College Hospital Kolenchery, Kerala, India

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