RESEARCH ARTICLE

Perinatal Outcomes of COVID-19 in Pregnancy in a Tertiary Care Center in South India

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Abstract

Aim: In light of the severe acute respiratory syndrome by a coronavirus-2 (SARS-CoV-2) pandemic, it was proposed that a variety of complications have occurred in women during pregnancy, which has further extended to the fetus, causing higher rates of morbidity and mortality. The objective of this study was to identify the complications that arose due to the coronavirus and asses how it impacted the pregnancy, the fetus, and the neonate.

Materials and methods: Our study was a descriptive and observational study, which investigated the various aspects, obstetric, fetal and neonatal outcomes, and the complications arising in mothers affected with by SARS-CoV-2 virus. All women who tested positive after 20 weeks of gestation were included in the study and their pregnancy was followed up till delivery, and neonatal outcomes were noted.

Results: About 220 women infected with SARS-CoV-2 were studied and outcomes were illustrated. The mean age of the study population was 26.87 years [±4.96 Standard Deviation (SD)]. About 90% of the study population had a mild illness. The main obstetric outcomes noted were preterm labor, preeclampsia, eclampsia, intrauterine growth restriction (IUGR), and intrauterine fetal demise (IUD). Only 4.1% required a cesarean section for worsening conditions. Neonatal intensive care unit (ICU) admissions were also noted to be higher, with a possibility of vertical transmission in six babies.

Conclusion: Severe acute respiratory syndrome by a coronavirus-2 can have serious implications and can pose a great risk in pregnancy if not caught and treated early. Therefore, it is vital to screen those at high risk for the virus to prevent severe complications from taking a toll on the mother and fetus.

Clinical significance: By identifying the main complications occurring in pregnancy, we can prevent the same by anticipating and monitoring carefully, thereby reducing mortality and morbidity rates.

Keywords: COVID-19 in pregnancy, Pandemic pregnancy, Preeclampsia, Preterm labor, Severe acute respiratory syndrome by a coronavirus 2, Vertical transmission COVID-19.

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Introduction

In December 2019, catastrophe struck, which ultimately led to the World Health Organization declaring a pandemic of the SARS-CoV-2 on March 11, 2020.[1]

With the entry of SARS-CoV-2, lives and lifestyles all over the world underwent a revolution, and it took a toll on the mental, physical, and emotional health of everyone affected by it.

In the light of coronavirus disease-2019 (COVID-19) pandemic, things were moving at an unwavering pace, while the SARS-CoV-2 virus continued to take over all of healthcare worldwide by causing its accelerated spread. With the growing variants of the illness, the infectivity only kept increasing, and it is well known that at least 2–3 persons are infected by one index case.[2]

The disease bears a wide spectrum of presenting features, ranging from being completely asymptomatic to having a very truculent course of illness leading to an enormous number of deaths. Till January 2022, there have been approximately 300 million reported cases, with over 5 million reported deaths globally, exhibiting the fast-paced spread of this virus, which has seen three waves of spread thus far.

The centers for disease control has asserted that those in the elderly age groups, those with comorbidities, an immunocompromised state, or disabilities are likely to be affected more severely than others, and should hence be more cautious and vigilant with their social activities.[3] They also emphasized that pregnant women also have a risk of developing a stormy course when infected with the virus, leading to an increased rate of hospitalizations, the need for mechanical ventilation, and even extracorporeal membrane oxygenation or even death, as compared to those who are not pregnant.[4]

This can be attributed to the variety of changes happening to one's body during pregnancy, physiologically, anatomically,[5] and mechanically, therefore encouraging a brisk progression to respiratory failure in them. The body is also immunocompromised during pregnancy, with the dominance of T-helper 2 (Th2) system and suppression of T-helper 1 (Th1), which protects the fetus and makes the woman more susceptible to infections.[2]

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This increased risk of COVID-19 in pregnancy extends further to the fetus, with the virus causing a higher risk of perinatal morbidity and mortality rates significantly.[3]

A rise in the number of obstetric complications has also been seen such as preeclampsia, placental insufficiency, preterm births, fetal distress, stillbirths, and increased rates of cesarean sections.[6,7] The objective was to identify the complications that arose due to the coronavirus and asses how it impacted the pregnancy, the fetus, and the neonate.

The lack of ample evidence[8] regarding appropriate management guidelines of COVID-19 in pregnancy, and the heightened risks associated with the same, mandated the need for further research on the subject and to predict, and thereby prevent the adverse complications that come with it.[9]

Materials and Methods

This was an observational cohort study carried out in St. John's Medical College hospital from August 2020 to August 2021, during the first and second waves of the pandemic. The Institutional Ethics Committee Clearance was obtained for the same. At the start of the pandemic, all pregnant women from "hotspot" zones who were symptomatic or near/in labor were tested. As the pandemic advanced, all pregnant women symptomatic or needing admission were tested.

All pregnant women from 20-week gestation who were tested positive for SARS-CoV-2 were included in the study during this time. Different types of tests were done such as reverse transcriptase polymerase chain reaction (RT-PCR), GeneXpert for COVID-19, point-of-care test for COVID-19 (POCT), and rapid antigen test (RAT). Positive results were considered as positive; however, a negative RAT required a confirmatory RT-PCR. Tests done in other centers that were equivalent to RT-PCR tests, within a span of one week, were also considered and were not repeated.

A total of 220 women were considered in our study, and informed consent was taken for each of them. Investigations pertaining to each individual case as well as a COVID-19 panel including complete blood counts, renal and liver function tests, inflammatory markers, and D-dimer were performed. Patients were observed for new symptoms and vitals were monitored. All positive patients were divided into "asymptomatic," "mild," "moderate," "severe," and "critical" COVID-19 as per National Institutes of Health guidelines[9] depending on vitals and symptoms, and each were managed as per institutional protocol, either symptomatically, with additional vitamin supplements (vitamin C, D, and zinc), with antibiotics, anticoagulation, and antivirals pertaining to each case. Those in labor were managed as per usual obstetric protocol in the labor ward, unless they needed noninvasive or invasive ventilation. Most cesarean sections were done for obstetric indication only unless patient's respiratory status was worsening and required immediate prone ventilation. Obstetric complications were all studied, along with mode of delivery and other maternal complications such as ICU admission and mortality. Neonatal outcomes such as poor Apgar scores, neonatal intensive care unit (NICU) admission, and evidence of vertical transmission were also reviewed.

Statistical Analysis

Kolmogorov–Smirnov test was used to test the normality. Summary statistics were obtained for all variables. Continuous variables that were normally distributed were summarized as mean (SD) and others summarized as median (interquartile range). Categorical variables were reported as frequency (%). Statistical Analysis was performed using the International Business Machines Corporation Statistical Package for the Social Sciences (Statistical Software), the IBM SPSS statistics 25.0.

Results

We studied 220 COVID-19-positive antenatal women and their outcomes in pregnancy. The RT-PCR test, which is considered to be the gold standard test for the detection of SARS-CoV-2,[10] was used to detect a positive status in 54.5% ($n = 120$) of them, while the GeneXpert test was used in 25%, POCT in 3.2%, and RAT in 17.3%.

The mean age of the study population was 26.87 years (±4.96 SD). Most of our study group consisted of primigravidae making up 59.1% ($n = 130$), and a large percentage (29.7%) were preterms.

The obstetric complications of importance noted in these cases of COVID-19 were gestational hypertension, preeclampsia, eclampsia, Hemolysis, Elevated Liver enzymes, Low Platelet (HELLP) syndrome, IUGR, oligoamnios, abruptio placentae, preterm labor, preterm/prelabor rupture of membranes, gestational diabetes mellitus (GDM), and IUD, among others as shown in Table 1. The total percentage of hypertensive disorders (HDP) in COVID-19 is 25%, while those of placental insufficiency was 47.27%, as compared to the annual statistical data of our hospital for non-COVID-19 patients, which account for 15.12% and 25%, respectively.

Table 1: Obstetric complications noted in COVID-19 positive patients

Obstetric complications seen in COVID-19 positive patients	*N (%)*
Bad obstetric history	18 (8.2%)
Reduced movements	16 (7.3%)
Rh negative	13 (5.9%)
Gestational hypertension	8 (3.7%)
Preeclampsia	28 (12.7%)
Eclampsia	5 (2.3%)
HELLP	7 (3.2%)
Doppler changes	9 (4.1%)
IUGR	28 (12.7%)
Oligoamnios	12 (5.9%)
Polyhydramnios	5 (2.3%)
Malpresentation	12 (5.5%)
Previous LSCS	32 (14.5%)
Abruptio placentae	7 (3.2%)
Placenta previa	2 (0.9%)
Preterm labor	30 (13.6%)
PROM/PPROM	27 (12.3%)
Multiple gestation	9 (4%)
GDM	28 (12.7%)
IUD	16 (7.3%)
Acute fatty liver of pregnancy	1 (0.5%)
Pruritic urticarial papules and plaques of pregnancy	1 (0.5%)
Macrosomia	4 (1.8%)
Cholestasis of pregnancy	1 (0.5%)
Chorangioma placenta	1 (0.5%)
Fetal anomalies	4 (1.8%)

LSCS, lower segment cesarean section; PROM/PPROM, prelabour rupture of membranes/preterm PROM

Table 2: Medical complications noted in COVID-19 positive patients

Medical complications	*N (%)*
Chronic hypertension	7 (3.2%)
Anemia	35 (15.9%)
Hypothyroidism	39 (17.7%)
Liver disease	1 (0.5%)
Prior respiratory disease	4 (1.8%)
Hematological disorders	3 (1.4%)
Connective tissue disorder	5 (2.3%)
Neurological disorder	3 (1.4%)
Heart disease	4 (1.8%)
Sepsis	1 (0.5%)
Klippel-Feil	1 (0.5%)
Acute kidney injury	2 (0.9%)
Tuberculosis	1 (0.5%)

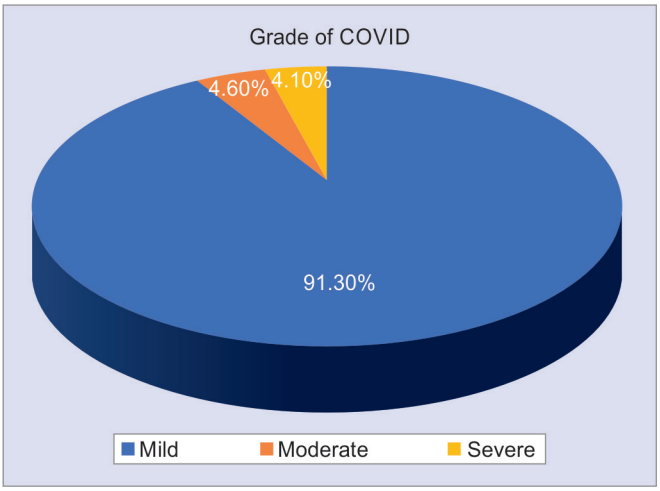

Fig. 1: Grades of COVID-19 seen in our study population

Among the already existing medical conditions, the two most common ones seen in those who have caught the illness were hypothyroidism and anemia, followed by Type II diabetes mellitus and chronic hypertension as shown in Table 2.

About 77.7% of all our patients were asymptomatic who presented in/near labor, while 13.6% had mild symptoms, 4.6% moderate disease, 4.1% severe disease, and 0.9% critical disease. as seen in Figure 1.

The most common symptoms were cough, fever, headache, and malaise. About 7.8% had atypical symptoms too, such as gastrointestinal symptoms, anosmia, headache etc. Most of these women had a normal oxygen saturation (spO_2) level at admission, and only 8.7% (n = 19) required immediate attention for the provision of oxygen. About 6.9% of those who had a normal spO_2 at admission desaturated during their stay and need external oxygen supply. About 76.8% (n = 169) received prophylactic anticoagulation for a minimum of 3 days, while 7.7% required steroids in view of the inability to maintain spO_2 on room air (Table 3). Only two women were treated with remdesivir (an antiviral), while 8 (3.6%) required intensive care in the ICU.

Most of these patients who presented to us delivered within a week of the infection, totaling 194 individuals. There were two

Table 3: Clinical course of illness of COVID-19 positive patients during admission

Clinical course	*N (%)*
Symptomatic	48 (21.8%)
Fever	20 (13.7%)
Cough	26 (11.9%)
Malaise	16 (7.3%)
Dyspnea	10 (4.6%)
Myalgia	9 (4.1%)
Sore throat	9 (4.1%)
Diarrhea	4 (1.8%)
Other (anosmia and gastrointestinal disturbances)	17 (7.8%)
Saturation at admission	
≤94%	200 (91.3%)
>94%	19 (8.7%)
Tachycardia	40 (18.3%)
Blood pressure	
Low (<100/60 mm Hg)	6 (2.7%)
Normal (100/60–139/89 mm Hg)	173 (79%)
High (≥140/90 mm Hg)	40 (18.3%)
Tachypnoea	17 (7.8%)
Grade	
Mild	200 (91.3%)
Moderate	10 (4.6%)
Severe	9 (4.1%)
Treatment given	
Anticoagulation	169 (76.8%)
Steroids	17 (7.7%)
Remdesivir	2 (0.9%)
ICU admission	8 (3.6%)

Table 4: Time span between COVID-19 infection and delivery

Time span between infection and delivery in weeks	*N (%)*
0	194 (90.7%)
1	4 (1.9%)
2	5 (2.3%)
3	3 (1.4%)
4	4 (1.9%)
5	2 (0.9%)
7	1 (0.5%)
9	1 (0.5%)

patients whose pregnancy was prolonged by more than five weeks post infection without complications (Table 4).

We did not see a large variation in laboratory investigations such as renal and liver function tests from the normal; however, it was interesting to note that 78.7% (n = 122) had an elevated neutrophil–lymphocyte ratio (NLR) of >3, which was significant; [11] 41.7% (n = 65) had leukocytosis and 54.1% (n = 72) had an elevated C-reactive protein (CRP).[8] Of the 8 who had a severe illness, 87.5% had an elevated NLR and 75% had an elevated CRP. We found that D-dimer levels were raised beyond 600 ng/mL in a majority of the

Table 5: Grades of COVID-19 and their clinical parameters, obstetric, and neonatal outcomes

Clinical parameters		*Grade of COVID-19*	
Total count			
Increased	59 (43.1%)	1 (10%)	4 (50%)
Normal range	77 (56.2%)	9 (90%)	4 (50%)
Reduced	1 (0.7%)	0 (0%)	0 (0%)
Platelet count (per cu mm)			
<50000	2 (1.1%)	0 (0%)	0 (0%)
51000–100000	4 (2.3%)	0 (0%)	1 (11.1%)
100001–150000	18 (10.3%)	3 (30%)	2 (22.2%)
>150000	151 (86.3%)	7 (70%)	6 (66.7%)
TSH (microIU/L)			
<0.1	2 (1.1%)	0 (0%)	0 (0%)
0.2–4	168 (91.3%)	8 (100%)	8 (88.9%)
>4	14 (7.6%)	0 (0%)	1 (11.1%)
NLR			
0–2.9	30 (22.1%)	2 (20%)	1 (12.5%)
>3	106 (77.9%)	8 (80%)	7 (87.5%)
D-dimer (ng/mL)			
0–599	71 (47%)	3 (37.5%)	2 (25%)
>600	80 (53%)	5 (62.5%)	6 (75%)
CRP (mg/L)			
0–0.99	58 (50%)	1 (12.5%)	2 (25%)
>1	58 (50%)	7 (87.5%)	6 (75%)
Creatinine (mg/dL)			
0–7.99	106 (99.1%)	9 (100%)	9 (100%)
>8	1 (0.9%)	0 (0%)	0 (0%)
Liver function test abnormalities	9 (8.5%)	3 (42.9%)	2 (25%)
Derangement in sugars	157 (83.5%)	8 (88.9%)	5 (62.5%)
Mode of delivery			
Attempted induction of labor	63 (33.3%)	1 (12.5%)	2 (25%)
Spontaneous onset of labor	44 (23.3%)	1 (12.5%)	0 (0%)
Vaginal	81 (42.9%)	2 (25%)	2 (25%)
LSCS	108 (57.1%)	6 (75%)	6 (75%)
Post-partum hemorrhage	16 (8%)	2 (20%)	1 (11.1%)
Neonatal outcomes:			
Apgar score at 5 min	Mild	Moderate	Severe
0–6.99	17 (9.2%)	0 (0%)	4 (50%)
≥7	168 (90.8%)	8 (100%)	4 (50%)
Birth weight (gm)			
0–2499	58 (30.9%)	6 (75%)	5 (62.5%)
≥2500	130 (69.1%)	2 (25%)	3 (37.5%)
Meconium-stained liquor	18 (9%)	1 (10%)	0 (0%)
NICU requirement	69 (36.9%)	5 (62.5%)	7 (87.5%)
COVID-19 positive status of baby	6 (3%)	1 (10%)	0 (0%)
Maternal mortality	0 (0%)	1 (12.5%)	2 (25%)
Neonatal mortality	0 (0%)	0 (0%)	0 (0%)
Stillbirth	1 (0.5%)	0 (0%)	0 (0%)

patients; however, 8.3% of the people had values above the third trimester cutoff in pregnancy, being 1700 ng/mL.[12]

Labor management in our center was purely as per obstetric indication. A total of 41.3% delivered vaginally, and 58.7% ($n = 21$) had a cesarean section (Table 5). Only 4.1% ($n = 5$) of these cesarean sections were in view of worsening maternal condition. The incidence of meconium-stained liquor was 8.6% and fetal distress was 12.3%. Complications such as postpartum hemorrhage

occurred in 8.6%. About 40.2% of the babies delivered required NICU admission for a variety of reasons, majority being for respiratory distress. Five-minute Apgar scores of <7 were seen in 9.2% of the mild cases, and 50% of the severe cases of COVID-19. About 32.5% of the babies were of low birth weights (<2500 gm). A total of seven babies tested positive for COVID-19, with six of them suggestive of vertical transmission, while one was horizontal transmission. Most patients who presented for delivery were detected to have the virus at the time of admission; however, 9.3% presented in a range of 1–9 weeks after infection. Out of the patients that presented later than 1 week of infection, 25% presented in preterm labor, 25% had IUGR, 30% had HDP in pregnancy, and 5% had IUD. Ten (4.8%) patients had postpartum complications such as desaturation, cardiac arrest, mucormycosis, and sepsis. There were three maternal mortalities and one neonatal mortality. Eight patients opted to get discharged against medical advice.

Discussion

Our study mainly summarizes the perinatal outcomes of 220 pregnant women who had the COVID-19 infection during pregnancy.

- Clinical features, laboratory investigations, and existing conditions:
  In our study, the majority were asymptomatic and incidentally detected to be COVID-19 positive. This could be due to pregnancy being a condition of modulated immune system, which makes them more susceptible to infections. Consistent with Liu et al.[13] and Chen et al.,[14] we found that most of these patients had an elevated NLR and CRP.

  Our study also showed a majority of the women belonging to an O blood group. Zhao et al.[15] reported a link between the ABO blood group and susceptibility to COVID-19. Contradictory to our study, they found that those with blood group A have a higher risk, whereas people with blood group O have a lower risk of infection.

  There were a number of positive patients among those who had anemia and hypothyroidism in our study population, possible due to anemia being a state of easy susceptibility for infections.
- Obstetric outcomes:
  We report an increase in the number of HDP in pregnancy, preterm deliveries, and IUD as compared to our annual statistical data. Mendoza et al.[16] introduced a concept claiming that COVID-19 induced a state called the "preeclampsia-like syndrome" that was hard to distinguish from preeclampsia but posed the same features; however, the difference being that it normalized soon after recovery from the viral illness. The prospective cohort study of the effects of COVID-19 in pregnancy and the neonatal period (INTERCOVID) done by Papageorghiou et al.[7] also similarly stated that preeclampsia is strongly associated with COVID-19. This could be due to vascular pathology induced by COVID-19, very similar to endothelial dysfunction, and inflammation as in preeclampsia, in addition to the formation of microthrombi, therefore causing features of HDP in pregnancy and placental insufficiency.

  Dang et al.[17] researched the potential effects of the illness on the fetus and suggested that the virus utilizes angiotensin-converting enzyme 2 as its receptor, thereby causing an insufficiency of the same in pregnant women, leading to hypoxemia, and subsequently placental insufficiency, IUGR, Doppler changes, and possibly even IUDs, explaining our results. Blitz et al.,[18] in concurrence with the INTERCOVID study, suggested that preterm births are twice as more in those with COVID-19, similar to an increase seen in our study, either spontaneously or iatrogenically.

  Most of our patients who had these complications showed a lengthened duration between illness and delivery, suggesting a possible prolonged pathogenesis.
- Delivery:
  Five of our patients required cesarean sections for worsening maternal conditions and two even needing prone ventilation.

  Higher rates of fetal distress and meconium staining of amniotic fluid were noted, which could be explained by the theory of hypoxemia in the placental vasculature caused by the virus as explained by Schoenmakers et al. who stated that fibrin deposition caused by the virus in the placenta led to a decreased placental interface for the exchange of gases.[19]
- Neonatal outcomes:
  There were higher NICU admissions in our study, possibly due to some degree of placental insufficiency, chronic hypoxia, and hence distress during labor. Half the babies born to those with severe illness had a low 5-minute Apgar score. Most of these babies recovered quicker than expected, posing that this may be a transient respiratory distress. We had seven babies who tested positive, out of which one was horizontal transmission. There are still insufficient data to prove vertical transmission; however, the previous studies have shown the presence of IgM antibodies to SARS-CoV-2 in the baby's blood 2 hours after birth, suggesting the strong potential of vertical transmission, by possible exposure to infection during the pregnancy.[20] There is also a possibility of developing multisystem inflammatory syndrome in the neonate, which is a hyperinflammatory syndrome in neonates, possibly due to transplacental transfer of IgG antibodies. However, we did not test the babies at our hospital for the same.[21] However Garg et al. did not find vertical transmission in their study at Agra.[22–24]

Coronavirus has been found to be affecting women in other ways too like associated psychological stress that can lead to transient menstrual irregularities too.

Strengths and Limitations

Our research involved collecting data from those beyond 20 weeks of gestation; therefore, any compromise that could have occurred early in pregnancy leading to an adverse outcome in the later trimesters could have possibly gone unnoticed.

Another limitation is that this is purely a descriptive and observational study; hence, the strength of associations cannot be accurately made.

A strength to our study was the vast sample size taken, thereby making the results more statistically significant. We also followed up most of our positive patients until delivery therefore, attempting to study long-term implications of the disease on the perinatal outcomes.

Conclusion

Most maternal characteristics vary from the general population, as symptoms may be less frequently observed in those who are pregnant. Severe acute respiratory syndrome by a coronavirus-2

can have serious implications as noted in our study and can pose a great risk in pregnancy if not caught and treated early. Therefore, it is vital to screen those at high risk for the virus to prevent severe complications from taking a toll on the mother and fetus. It is also essential to strictly monitor the woman in pregnancy and in labor even if asymptomatic in order to prevent fetal compromise and ensure timely delivery.

Neonates are at risk for developing the infection either vertically, horizontally or by inflammatory response; however, further studies are required to study this association.

Clinical Significance

By identifying the main complications occurring in pregnancy, we can prevent the same by anticipating and monitoring carefully, thereby reducing mortality and morbidity rates.

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