
OBSTETRICS

Comparison of Clinical Characteristics and Prognostic Markers in Pregnant Women during the First and Second Wave of COVID-19 in India

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ABSTRACT

Objectives: The world is experiencing unprecedented challenges from the coronavirus pandemic. There is a sparse data on Coronavirus disease-2019 (COVID-19) outcomes in pregnant women from India, especially during the second wave. We aimed to compare maternal clinical characteristics and prognostic markers during first and second waves of COVID-19 and to know the correlation of the laboratory markers with disease severity and to assess maternal and perinatal outcomes.

Materials and Methods: This prospective study of COVID-19 positive pregnant women was conducted at a tertiary care hospital in India from the 1st of August 2020 to the 30th of June 2021. Data on epidemiological history, clinical presentation, laboratory results, and maternal-fetal outcome in the first and second waves of the COVID-19 pandemic were collected and analyzed.

Results: One hundred eighteen patients participated in our study, with 64 belonging to the 1st wave and 54 in the 2nd wave. Fever and sore throat were common presenting symptoms, most women with bronchial asthma and cardiac disease progressed to severe/ critical illness. C-reactive protein, lactate dehydrogenase ($p < 0.05$ in both waves), ferritin ($p < 0.01$ in 2nd wave), and procalcitonin ($p < 0.05$ in 1st wave) positively correlated with the severity of the disease.

Conclusion: Our study showed that the clinical characteristics and severity of the disease did not differ significantly in both the waves. The adverse fetal outcome was significantly more in mothers with severe and critical disease. Laboratory markers correlated significantly with the severity of the maternal disease, hence can be used as prognostic indicators.

Keywords: COVID-19, pandemic, pregnancy, laboratory parameters, India.

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Introduction

COVID-19, a global public health emergency, is caused by enveloped, positive-sense single-stranded RNA viruses called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)⁽¹⁾. Though the number of COVID-19 positive cases in India was low, to begin with, the situation surprisingly changed in the second wave, when over 400,000 confirmed cases/day were reported. Lineage analysis in India showed the emergence of new SARS-CoV-2 variants, i.e., B.1.617.1 (kappa) and B.1.617.2 (delta), during April–May 2021⁽²⁾. Frequent hospital visits and alterations in cell-mediated immunity predispose pregnant women to respiratory and other infections⁽³⁾.

Though initial studies of COVID-19 did not demonstrate significant adverse effects on pregnant women, subsequent studies indicated greater severity of the infection and need for intensive care unit (ICU) admissions in them⁽⁴⁻⁶⁾.

Evidence on the correlation between the severity of COVID-19 and laboratory markers in the general population is established^(7,8). However, there is limited evidence on the correlation of these prognostic markers in the pregnant COVID-19 cohort. The prognostic indicators used in other populations cannot be extrapolated to pregnant mothers as pregnancy in itself modifies many of these parameters⁽³⁾.

With the above background, we aimed to study COVID-19 pregnancies in the Indian population. Our primary objective was to compare maternal clinical characteristics and prognostic markers during first and second waves of COVID-19. Secondary objectives were to know the correlation of the laboratory markers with disease severity and to assess maternal and perinatal outcomes of COVID-19 deliveries.

Materials and Methods

Study design and setting

A prospective study was conducted at Shri Dharmasthala Manjunatheshwara College of medical sciences and hospital Dharwad, Karnataka. A total of one hundred and eighteen COVID-19 positive pregnant women participated in the study. Patients enrolled from August 1, 2020, to January 31, 2021 (sixty-four patients)

and February 1 to June 30, 2021 (fifty-four patients) constituted the two successive waves, respectively.

COVID-19 was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) or rapid antigen test (RAT). After obtaining prior written informed consent, women with singleton/multiple gestations, all trimesters, and with/without comorbidities were included, while those who denied consent were excluded from the study. Nasal or pharyngeal swabs were used for the RT-PCR test. The Institutional ethics committee (IEC) approval was taken for the study with institutional review board number- SDMIEC: 79:2020.

Data collection

Data was collected on epidemiological history, clinical presentation, and laboratory test results. Epidemiological details included age, parity, and gestational age; clinical presentation included information on presenting symptoms, maternal comorbidities, vital parameters, and clinical severity (according to classification by National Institute of Health)⁽⁹⁾; laboratory parameters assessed were hemoglobin (Hb), total leukocyte count (TLC), lymphocytes and platelet count, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, procalcitonin, urea, and creatinine. Chest x-ray was evaluated for features of pneumonia. Additionally, maternal details like need of oxygen support, mode of delivery, complications, and newborn details like weight, 5 minutes Apgar score, outcomes [intrauterine death (IUD), stillbirths, miscarriages, neonatal death, and RT-PCR results] were noted.

Statistical analysis

The first and second wave data were entered in separate excel sheets with an exclusive code assigned to all non-available/not reported data. Statistical analysis was done using IBM SPSS version 25. Descriptive data for continuous and categorical data were represented as mean \pm standard deviation and proportions (%), respectively. The comparison of maternal and fetal outcomes and maternal severity between the two waves was made using chi-square test. Spearman's correlation was used for evaluating the relation between mothers'

clinical severity and their laboratory parameters. A p value of < 0.05 was considered significant for all analyses.

Results

One hundred eighteen patients participated in our study, with 64 belonging to the 1st wave and 54 in the 2nd wave.

Descriptive data

The mean age of the mothers was 28 years, with a more significant proportion of them at term gestation. The proportion of primigravida was significant in the second wave compared to the first wave. Fever and upper respiratory tract infections were the common presenting symptoms. Risks in pregnancy were comparable in both groups. Around 25% showed features of pneumonia in a chest x-ray. Pregnant women with mild to moderate disease were treated with antibiotics and supportive care. Patients with severe and critical diseases were managed with

steroids, remdesivir, low molecular weight heparin (LMWH), and antimicrobials. Of the total 118 patients, two patients were given oxygen support via face mask, while other 9 with non-re-breather mask (NRBM). Non-invasive ventilation (NIV) by continuous positive airway pressure (CPAP), was required in 03/118 (2.5%) patients and invasive ventilation was required in 4/118 (3.4%) patients. The low transverse cesarean section (LTCS) was the most common mode of delivery (83% of the first wave and 60% of the second wave). A total of 7 neonates required NICU admission because of a low Apgar score. Seventeen babies had a birth weight of less than 2,500 grams, though RT-PCR of the neonate was positive in a very negligible number (Table 1). Two maternal deaths were seen in the study period. One was a 28-year-old primigravida with bronchial asthma with early pregnancy, and the other was a 30-year primigravida with severe preeclampsia. Both presented with critical COVID-19 disease requiring mechanical ventilation and died due to non-resolving infection.

Table 1. Patient characteristics for the 1st and 2nd COVID-19 waves.

Variables	Values		p value
	1 st wave (n = 64)	2 nd wave (n= 54)	
Age	27.89 ± 4.66	27.70 ± 4.78	0.83
Gestational age			0.36
Pre-term	17 (26.6)	10 (18.5)	
Term	46 (71.9)	44 (81.5)	
Early pregnancy	1 (1.6)	0 (0)	
Parity-primi	16 (25)	23 (42.6)	0.04*
Chief complaints			
Fever	19 (29.7)	27 (50)	0.02*
URTI	28 (43.8)	24 (44.4)	0.94
Dyspnea	13 (20.3)	2 (3.7)	0.007**
Anosmia	7 (10.9)	6 (11.1)	0.97
GI problems	7 (10.9)	6 (11.1)	0.97
Headache and myalgia	15 (23.4)	11 (20.4)	0.68
Risk in pregnancy			
Preeclampsia	16 (25)	7 (13)	0.1
Oligohydramnios	6 (9.4)	1 (1.9)	0.08
GDM	6 (9.4)	3 (5.6)	0.43
PTL	5 (7.8)	2 (3.7)	0.34
PROM/PPROM	13 (20.3)	15 (27.8)	0.61
Bronchial asthma	1 (1.6)	1 (1.9)	0.90
Cardiac disease	4 (6.2)	1 (1.9)	0.38

Table 1. Patient characteristics for the 1st and 2nd COVID-19 waves. (Cont.)

Variables	Values		p value
	1 st wave (n = 64)	2 nd wave (n= 54)	
Clinical features			
Tachycardia	9 (14.1)	10 (18.5)	0.51
Febrile	10 (15.6)	16 (29.6)	0.06
Hypertension	15 (23.4)	3 (5.6)	0.007**
Tachypnoea	13 (20.3)	12 (22.2)	0.80
Hypoxia	10 (15.6)	8 (15)	0.68
Diagnosis			0.03*
RAT	6 (9.4)	13 (24.1)	
RT PCR	58 (90.6)	41 (75.9)	
Admission			0.63
LR	48 (75)	41 (75.9)	
HDU	9 (14.1)	5 (9.3)	
ICU	7 (10.9)	8 (14.8)	
Lab parameters			
Hb gm/dl	11.26 ± 1.34	11.18 ± 1.89	0.79
TLC x109 cells/litre	13.53 ± 7.69	15.84 ± 2.46	0.47
Platelets x 109 cells/litre	229.51 ± 75.14	210.71 ± 73.85	0.17
CRP mg/dl	43.81 ± 59.68	34.87 ± 50.52	0.38
LDH IU/L	337.59 ± 215.33	430.33 ± 361.13	0.08
Ferritin ng/ml	104.83 ± 234.13	64.81 ± 57.72	0.22
Procalcitonin ng/ml	0.81 ± 6.01	64.81 ± 57.72	0.60
Urea mg/dl	23.31 ± 11.33	18.96 ± 8.88	0.02*
Creatinine mg/dl	0.66 ± 0.27	0.60 ± 0.14	0.19
Chest X-ray-pneumonia	17 (26.6)	15 (27.8)	0.88
Treatment			
Steroids	13 (20.3)	18 (33.3)	0.10
Remdesivir	3 (4.7)	8 (14.8)	0.05
LMWH	27 (42.2)	15 (27.8)	0.10
Anti-microbials	64 (100)	54 (100)	-
Oxygen support			0.14
Face mask	0 (0)	2 (3.7)	
NRBM	6 (9.4)	3 (5.6)	
NIV (CPAP)	3 (4.7)	0 (0)	0.14
Mechanical ventilation	1 (1.6)	3 (5.6)	
Mode of delivery			0.004**
PTVD	6 (9.4)	6 (11.1)	
FTVD	3 (4.7)	16 (29.6)	
LTCS	53 (82.8)	32 (59.3)	
Expulsion	1 (1.6)	0 (0)	
Baby weight in kilograms	2.74 ± 0.97	2.66 ± 0.59	0.61
5 minutes APGAR score < 7	5 (7.8)	2 (3.7)	0.25
Neonatal RTPCR positive	3 (4.7)	1 (1.9)	0.17
Prolonged hospital stay	11 (17.2)	10 (18.5)	0.64

* significant at p<0.05, ** significant at p<0.01

Primi: primigravida, URTI: upper respiratory tract infection, GI: gastrointestinal, GDM: gestational diabetes mellitus, PTL: preterm labor, PROM: premature rupture of membranes, PPROM: preterm- premature rupture of membranes, RT PCR: real-time reverse transcription-polymerase chain reaction, RAT: rapid antigen test, LR: labour room, HDU: high dependency unit, ICU: intensive care unit, Hb: hemoglobin, TLC: total leucocyte count, CRP: C reactive protein, LDH: lactate dehydrogenase, LMWH: low molecular weight heparin, NRBM: non re-breathing mask, NIV: non invasive ventilation, CPAP: continuous positive airway pressure, PTVD: pre term vaginal delivery, FTVD: full term vaginal delivery, LTCS: low transverse caesarean section.

Clinical severity vs laboratory parameters

Comparing maternal clinical severity with laboratory parameters yielded a significantly positive correlation for

CRP and LDH in patients of both waves. In contrast, procalcitonin and ferritin were correlated considerably only in the first and second waves, respectively (Table 2).

Table 2. Correlation between clinical severity of mothers and their lab parameters.

Variable	Lab parameter	1 st wave		2 nd wave	
		Spearman's rho	p value	Spearman's rho	p value
Clinical severity	TLC	- 0.051	0.686	0.008	0.955
	Lymphocyte count	- 0.052	0.684	- 0.173	0.211
	c reactive protein	0.493**	0.000	0.512**	0.000
	LDH	0.322**	0.009	0.583**	0.000
	ferritin	- 0.085	0.503	0.438**	0.001
	Procalcitonin	0.262*	0.037	0.244	0.075

TLC: total leucocyte count, LDH: lactate dehydrogenase

Comparison of the maternal and fetal outcomes and severity of maternal disease between the two waves

Maternal complications and adverse fetal

outcomes did not vary significantly during the first and the 2nd wave (Table 3). Maternal severity did not vary much across the two waves. (Table 4).

Table 3. Comparison of maternal and fetal outcome between the patients of two waves.

Outcome	n (%) in 1 st wave	n (%) in 2 nd wave	Chi-square	p value
Miscarriages	2 (3.1)	0 (0)	1.717	0.19
APH	1 (1.6)	4 (7.4)	6.404	0.17
Poor obstetric outcome			11.404	0.12
IUD	0 (0)	3 (5.6)		
Still birth	0 (0)	2 (3.7)		
PND	2 (3.1)	0 (0)		
Expulsion/Abortion	1 (1.6)	0 (0)		

APH: ante partum hemorrhage, IUD: intrauterine death, PND: post natal death.

Table 4. Comparison of maternal severity between the patients of two waves.

Severity	n (%) in 1 st wave	n (%) in 2 nd wave	Chi-square	p value
Asymptomatic	13 (20.3)	20 (37)		
Mild	34 (53.1)	19 (35.2)		
Moderate	7 (10.9)	7 (13)	5.81	0.21
Severe	8 (12.5)	5 (9.3)		
Critical	2 (3.1)	3 (5.6)		

APH: ante partum hemorrhage, IUD: intrauterine death, PND: post natal death.

In addition, it was observed that fetal complications like IUD and stillbirth were significantly greater in mothers with one or more symptoms than asymptomatic

mothers. (maternal severity vs. fetal outcome; 1st wave chi-square: 49.32, $p < 0.001$; 2nd wave chi-square: 31.69, $p = 0.002$). (Table 5 and 6)

Table 5. Comparison of maternal severity between the patients of two waves.

Maternal clinical severity	Fetal outcome; n (%)								Chi square (p value)
	Live birth	LBW	IUGR	IUD	SB	PND	Miscarriage	Expulsion	
Asymptomatic	11 (84.6)	1 (7.7)	1 (7.7)	0	0	0	0	0	49.322 (0.001)
Mild	28 (82.4)	5 (14.7)	0	0	0	0	1 (2.9)	0	
Moderate	4 (57.1)	1 (14.3)	1 (14.3)	0	0	1 (14.3)	0	0	
Severe	7 (87.5)	0	0	0	0	1 (12.5)	0	0	
Critical	0	1 (50)	0	0	0	0	0	1	

LBW: low birth weight, IUGR: intrauterine growth restriction, IUD: intrauterine death, SB: still birth, PND: post natal death.

Table 6. Association between clinical severity of mother and fetal outcome for 2nd wave.

Maternal clinical severity	Fetal outcome; n (%)								Chi square (p value)
	Live birth	LBW	IUGR	IUD	SB	PND	Miscarriage	Expulsion	
Asymptomatic	20 (100)	0	0	0	0	0	0	0	31.691 (0.002)
Mild	15 (78.9)	2 (10.5)	0	1 (5.3)	1 (5.3)	0	0	0	
Moderate	3 (42.9)	2 (28.6)	0	1 (14.3)	1 (14.3)	0	0	0	
Severe	2 (40)	2 (40)	0	1 (20)	0	0	0	0	
Critical	0	3 (100)	0	0	0	0	0	0	

LBW: low birth weight, IUGR: intrauterine growth restriction, IUD: intrauterine death, SB: still birth, PND: post natal death.

Correlation between maternal severity and associated risk in pregnancy

Thirteen patients progressed to severe disease during both waves of which 4/13 (31%) were having preeclampsia, 3/13 (23%) had cardiac disease. Five of the patients had critical COVID-19 illness during both waves. Among them 2/5 (40%) of them had bronchial asthma and 1/5 (20%) had underlying cardiac illness.

Discussion

Current data on the effects of COVID-19 in pregnancy comparing the two waves are sparse. We were interested in finding differences in the clinical characteristics and maternal and fetal outcomes across the two waves and identifying laboratory markers to indicate the severity of the disease in low-resource settings.

According to an Indian study, a prevalence of 12.3% (mean 9.4, 95% confidence interval (CI) 6.6 - 12.1) was seen in pregnant women⁽¹⁰⁾. The mean maternal age of 28 years in our study was similar to other Indian studies by Sumitra Bachani et al (26 years)

and Tadas et al (27 years)^(11, 12).

Many studies have demonstrated that the clinical characteristics of COVID-19 in pregnant women were no different from non-pregnant adults in the general population⁽¹³⁾.

Upper respiratory tract infection (URTI) was the most common presenting complaint during the first wave, whereas it was fever during the second wave, which agrees with other studies^(11,12,14). Patients with bronchial asthma, cardiac disease, and preeclampsia progressed to severe and critical illnesses that required ICU care and prolonged hospital stay. The same trend was even seen in studies by Nayak et al and Gajbhiye et al^(16,17). Li et al, attributed severe clinical manifestations in hypertensive patients to dysregulation of placental angiotensin-converting enzyme 2 (ACE2) at the maternal-fetal interface by SARS-CoV-2, leading to high rates of preeclampsia in them⁽¹⁸⁾. Further studies are necessary to conclude whether preeclampsia is a significant contributor to the development of severe COVID-19 infection. The fraction of women with hypertension was significant during the first wave when

compared to the second.

Almost all of them in the 1st wave (83%) and more than half of second wave patients (60%) underwent LTCS. The proportion of LTCS was slightly lesser (43%, 50%) in other studies^(12, 16). These discrepancies could have been due to urgent deliveries because of severe respiratory compromise or the fear of transmission to neonates in vaginal deliveries due to longer exposure time.

Around 3 % of neonates in our study tested positive at 48 hours which is in concordance with the findings of Facchetti and Hosier et al^(19, 20). Amniotic fluid, cord blood, neonatal throat swab, and breast milk samples have been found to be negative for SARS-CoV-2 by few studies⁽¹³⁾. Past studies have reported that SARS-CoV-2 has a similar receptor binding domain structure to that of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). This suggested that COVID-19 might have a similar pathogenesis to SARS-CoV-1 infection. Thus, the risk of vertical transmission might be as low as that of SARS-CoV-1⁽¹³⁾. Neonatal infection could be probably due to close contact with infected mothers during breastfeeding. 10% of the patients delivered preterm, which corresponds with the background risk of preterm labour in India⁽⁹⁾.

Although diagnosis of infection by RT-PCR is considered to be gold standard and was the only method available in the initial phase of pandemic⁽¹³⁾, later on COVID-19 RAT were made widely available. They are low cost, easy to use, and results are readily available in 15 minutes, hence are an excellent diagnostic tool at point of care as well as in resource limited settings. One study tested diagnostic accuracy of COVID-19 RAT tests from various manufacturers. The overall sensitivity of all fourteen RATs tested was 74.3% and the specificity was 100%. The more sensitive RAT tests are even considered to have the ability to identify contagious individuals⁽²¹⁾.

Elevated levels of CRP, LDH, ferritin and procalcitonin significantly correlated with greater severity. Ferritin, however, did not correlate with the severity in 1st wave. The effect could be confounded by low Hb in severely ill patients and relatively smaller

sample size. Procalcitonin was not significantly elevated in the 2nd wave, as it is raised only during the critical phase of COVID-19 infection. The timing of sample collection could have confounded the interpretation. Hence serial monitoring of laboratory markers may be needed.

The fetal complications could have been due to D614G mutation in the spike protein of newer variants that promotes interaction with host cell ACE2 receptors and associated escalated damage⁽²²⁾. Similar rates of IUDs were also found in previous studies⁽¹⁶⁾. The adverse fetal outcome was significantly more in mothers with severe to critical disease for both waves (Table 5, Table 6).

Recent studies have shown that the severity of the disease significantly reduces with the administration of the COVID-19 vaccine. During the initial phase of the COVID-19 vaccination, the safety of these vaccines in pregnant women was not known. Hence, none of our patients had been vaccinated against COVID-19. The Federation of obstetrics and gynecology society India (FOGSI) has recently recommended it to be safe in this cohort⁽²³⁾. Although various approved vaccines are in use and many are being developed, studies reporting efficacy of these vaccines in pregnant population are awaited. Until the pandemic is officially declared to have subsided, it is imperative that the 'new normal' life with COVID-19 appropriate behaviour is practiced diligently⁽²⁴⁾.

The immediate effects of COVID-19 on health care and particularly, obstetrics and gynaecology are readily evident. However, its long-term effects are predicted to unfold over months to years down the lane. COVID-19 infection itself is proposed to decrease birth rate by decrease conception, delaying further conception, and increase fetal loss. The socioeconomic impact of COVID-19 is catastrophic. Derailed cancer screening programmes during the pandemic is speculated to increase the number of gynaecological cancer patients presenting in advanced stage in the forthcoming years⁽²⁴⁾.

Observational single-center study design, lack of serial monitoring of laboratory parameters, and

COVID-19 testing in the neonate after 24-48 hours, confounding the vertical transmission, can all be the limitations of our study. However, the study has its distinctive features. Unlike previously published studies, our study has reported outcomes on the first and second waves. It was a prospective study and showed the correlation of the prognostic markers with the severity of maternal illness from the Indian population. The conclusions of this study would aid health care providers in better managing COVID-19 pregnancies in resource-poor settings by triaging the patients.

Conclusion

Our study showed that the clinical characteristics and severity of the disease did not differ significantly in both waves. The adverse fetal outcome was significantly more in mothers with severe to critical disease. Laboratory markers correlated significantly with the severity of the maternal disease; hence can be used as prognostic indicators.

Potential conflicts of interest

The authors declare no conflict of interest.

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