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Original Article

Paediatrics Section

Mortality and Morbidity among Neonates Born to COVID-19 Positive Mothers in a Tertiary Care Hospital, Chennai: An Ambispective Cohort Study

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ABSTRACT

Introduction: The Coronavirus Disease-2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus, has had varied clinical impacts across different age groups. Understanding the morbidity and mortality rates among neonates born to COVID-19 positive mothers is crucial for ensuring preparedness within the healthcare system.

Aim: To compare the morbidity and mortality rates of newborns born to COVID-19 positive and negative mothers.

Materials and Methods: This ambispective cohort study was conducted at a tertiary care hospital in Chennai, Tamil Nadu, India between August 2021 and October 2022. Newborns born to mothers with COVID-19 at the time of delivery were classified as cases, while newborns born to the next two COVID-19 negative pregnant women who delivered immediately after the COVID-19 positive mother were considered as controls. The study included a sample of 214 COVID-19 positive mothers and 426 COVID-19 negative mothers. Clinical data were recorded, and all newborns were followed for one week to assess their morbidity and outcomes. Logistic regression analysis was performed to determine whether COVID-19 infection is a risk factor for adverse neonatal outcomes.

Results: Among the newborns, 357 (55.8%) were females, and 333 (52%) were delivered via caesarean section. Of the newborns, 39 (6.1%) were preterm and 95 (14.8%) had low birth weight. The overall mortality rate was 1.25%. Four (1.8%) neonates tested positive for COVID-19. Logistic regression analysis revealed that caesarean section, respiratory distress syndrome, and prematurity were statistically significant morbidities associated with maternal COVID-19 positive status. The odds ratios (with 95% confidence intervals) were 4.090 (2.840-5.882) for caesarean section, 2.291 (1.508-3.480) for respiratory distress syndrome, and 2.359 (1.181-4.712) for prematurity. The mortality and other morbidities were similar between the two groups.

Conclusion: Respiratory distress syndrome and prematurity were the common morbidities observed in newborns born to COVID-19 positive mothers.

Keywords: Caesarean section, Coronavirus infections, Pandemics, Preeclampsia, Premature birth, Respiratory distress syndrome

INTRODUCTION

The COVID-19 pandemic is an outbreak caused by the SARS-CoV-2 virus. There have been 643 million confirmed cases of COVID-19 reported to the World Health Organisation (WHO) [1]. Apart from the direct infection by the virus, the pandemic has influenced maternal health due to travel restrictions, limited access to prenatal care, and strained healthcare infrastructure [2]. Epidemiological evidence from previous influenza and Ebola pandemics has shown that pregnant women are at a higher risk of mortality and severe disease following viral infections. Additionally, viral infections may increase the likelihood of preterm delivery [3]. COVID-19 infection during the first or second trimester can lead to miscarriage, preterm birth, birth defects, and signs of congenital infection. Maternal infection later in gestation can result in active infection in the newborn and pose risks to healthcare workers [4]. The timing and mode of delivery depend on the gestational age of the foetus and the severity of COVID-19 infection in positive mothers [5,6]. Numerous studies from around the world have examined the patterns of maternal and neonatal morbidity and mortality due to COVID-19 infection in pregnant women [7-9]. These studies have demonstrated a significant impact of the COVID-19 pandemic on neonatal mortality and morbidity [10-12].

While neonates in developed countries have generally shown positive outcomes, data from low and middle-income countries indicate increased neonatal mortality (among both COVID-19 infected and non COVID-19 neonates), decreased admissions to neonatal units, increased stillbirth rates, and higher incidences of morbidities such as prematurity and perinatal asphyxia during the pandemic [8]. However, there is still a lack of data regarding mortality and morbidity among neonates in developing countries. Additionally, few studies have compared the patterns of morbidity among neonates in different waves of the pandemic [13,14].

Knowledge about the morbidity and mortality among neonates born to COVID-19 positive mothers is crucial for developing healthcare policies. Therefore, this present study was conducted to compare the morbidity and mortality of newborns born to COVID-19 positive and negative mothers.

MATERIALS AND METHODS

An ambispective cohort study was conducted in the Department of Obstetrics and Gynaecology and Department of Paediatrics at a tertiary care hospital in Chennai, Tamil Nadu, India, from August 2021 to October 2022. The study received approval

from the Institutional Ethics Committee (IEC) (protocol ID no. 592/2021, meeting held on 2/9/2021). Newborns born to COVID-19 positive mothers during the second wave of the COVID-19 pandemic were retrospectively studied from March 2021 to November 2021, while those born during the third wave were prospectively studied from January 2022 to March 2022. Written informed consent was obtained from pregnant mothers after a thorough explanation of the study objectives.

Inclusion criteria: All pregnant women were screened for COVID-19 infection using nasopharyngeal and oropharyngeal swabs tested by Real-Time Polymerase Chain Reaction (RT-PCR). Newborns born to women diagnosed with COVID-19 at the time of delivery were considered as cases, while newborns born to the next two pregnant women without a COVID-19 diagnosis who delivered immediately after the women with a COVID-19 diagnosis were considered as controls.

Exclusion criteria: Newborns born to mothers who did not give consent were excluded from the study.

Sample size: The sample size was calculated based on a previous study [12] that reported a prevalence of prematurity of 22.5% in COVID-19 positive mothers compared to 13.6% in COVID-19 negative mothers, with an α error of 5% and β error of 20%, and a ratio of cases to controls as 1:2, using the following formula:

$$n=\frac{\{Z_{1-\alpha/2}\sqrt{(r+1)p(1-p)}+Z_{1-\beta}\sqrt{rp^1(1-p^1)+p^2(1-p^2)}\}_2}{r(p^2-p^1)^2}$$

P^1+rp^2

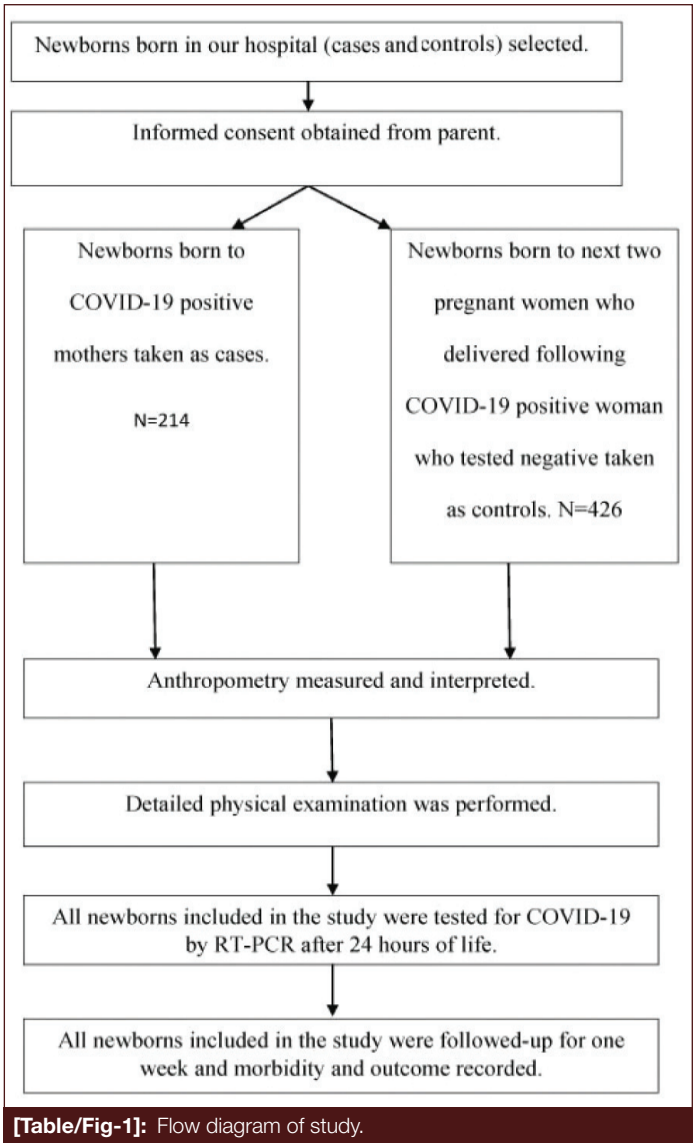
Where, p= 1+r

The sample size was calculated to be 214 cases and 426 controls.

Data collection: Maternal risk factors such as gestational hypertension, gestational diabetes, anaemia complicating pregnancy, multiple gestation, polyhydramnios/oligohydramnios, premature rupture of membranes, meconium-stained liquor, and obstructed or prolonged labour were recorded. The mode of delivery was noted, and the maturity of the neonates was assessed using the New-Ballard score [15]. The baby's weight was measured using an infant weighing scale, while length and head circumference were measured using a non stretchable measuring tape. The Intergrowth 21 chart [16] was used to interpret the growth of preterm neonates, and the WHO chart was used for term neonates [17]. The mothers' socio-economic status was assessed using the modified Kuppusami's socio-economic status scales [18]. All newborns included in the study were tested for COVID-19 after 24 hours of life using RT-PCR according to the institution's protocol. All newborns were followed-up until discharge for any morbidity. The outcome of babies at the end of one week of life was noted and considered for analysis. The patient flow in the study is depicted in [Table/Fig-1].

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 23.0. The proportion of babies with various morbidities and mortality was expressed as a percentage with a 95% confidence interval. Logistic regression analysis was conducted to determine whether COVID-19 infection is a risk factor for adverse neonatal outcomes.



[Table/Fig-1]: Flow diagram of study.

RESULTS

The study included a total of 640 mothers, of which 214 (33.4%) were COVID-19 positive and 426 (66.6%) were COVID-19 negative mothers, with a case-control ratio of 1:2. In this study, the majority of the enrolled neonates were female, 357 (55.8%). Females were more prevalent in the COVID-19 negative group; however, the gender-wise difference between the groups was not statistically significant. The socio-economic status of the mothers revealed that the majority belonged to the lower-middle class (509, 79.5%), while 7 (1.1%) mothers were classified as upper-middle class, and 124 (19.4%) were classified as upper lower class. Although a similar trend was observed in both groups, this difference in social class was not statistically significant.

Significantly, more mothers in the COVID-19 positive group had a caesarean section compared to the COVID-19 negative group. Although not statistically significant, there were more term neonates than preterm neonates in both groups. Out of the total neonates, 548 (85.6%) were appropriate for gestational age, 90 (14.1%) were small for gestational age, and 2 (0.3%) were large for gestational age [Table/Fig-2]. Among the neonates of COVID-19 positive mothers, 4 (1.8%) neonates were COVID-19 positive, while none of the neonates born to COVID-19 negative mothers tested positive for COVID-19.

The maternal risk factors of gestational diabetes (22, 10.3% vs. 30, 7%), gestational hypertension (32, 15% vs. 43, 10%), anaemia

Category	COVID-19 positive mother (n=214) N (%)	COVID-19 negative mother (n=426) N (%)	p-value
Gender of neonate			
Male	106 (49.53)	177 (41.55)	0.055
Female	108 (50.47)	249 (58.45)	
Maturity			
Term	194 (90.65%)	407 (95.54%)	0.014
Preterm	20 (9.35%)	19 (4.46%)	
Category by birth weight			
AGA	172 (80.37)	376 (88.26)	0.027
SGA	41 (19.16)	49 (11.50)	
LGA	1 (0.47)	1 (0.23)	
Anthropometry			
Microcephaly	2 (0.93)	4 (0.94)	0.995
Socio-economic status			
Upper middle	3 (1.40)	4 (0.94)	0.159
Lower middle	161 (75.23%)	348 (81.69)	
Upper lower	50 (23.37)	74 (17.37)	
Mode of delivery			
Vaginal delivery	53 (24.77)	243 (57.04)	<0.001
Assisted vaginal delivery	3 (1.40)	8 (1.88)	<0.00001
Caesarean section	158 (73.83)	175 (41.08)	<0.001

[Table/Fig-2]: Demographic details and COVID-19 status.

S no	Variable		COVID-19 status		p-value
			Positive n (%)	Negative n (%)	
1.	Gestational diabetes	Yes	22 (10.3)	30 (7)	0.169
		No	192 (89.7)	396 (93)	
2.	Gestational hypertension	Yes	32 (15)	43 (10)	0.090
		No	182 (85)	383 (90)	
3.	Anaemia complicating pregnancy	Yes	29 (13.6)	37 (8.7)	0.073
		No	185 (86.4)	389 (91.3)	
4.	Multiple gestation	Yes	6 (2.8)	2 (0.5)	0.019
		No	208 (97.2)	424 (99.5)	
5.	Obstructed labour and Prolonged labour	Yes	3 (1.4)	4 (0.9)	0.692
		No	211 (98.6)	422 (99.1)	
6.	Polyhydramnios and Oligohydramnios	Yes	15 (7)	40 (9.4)	0.371
		No	199 (93)	386 (90.6)	
7.	Meconium stained liquor	Yes	9 (4.2)	19 (4.5)	1.00
		No	205 (95.8)	407 (95.5)	
8.	Premature rupture of membrane	Yes	18 (8.4)	52 (12.2)	0.179
		No	196 (91.6)	374 (87.8)	

[Table/Fig-3]: Maternal risk factors and COVID-19 status.

complicating pregnancy (29, 13.6% vs. 37, 8.7%), multiple gestation (6, 2.8% vs. 2, 0.5%), and obstructed labour/prolonged labour (3, 1.4% vs. 4, 0.9%) were more commonly encountered in COVID-19 positive mothers [Table/Fig-3]. However, none of these differences were statistically significant in bivariate analysis. It was observed that delivery by caesarean section was more common in COVID-19 positive mothers, and this difference was statistically significant. Among neonatal morbidities, prematurity, low birth weight, and respiratory distress syndrome were commonly encountered in neonates born to COVID-19 positive mothers in bivariate analysis [Table/Fig-4].

No	Condition	COVID-19 positive N=214 N (%)	COVID-19 negative N=426 N (%)	p-value
1	LSCS	158 (73.8)	175 (41)	<0.001
2	Prematurity	20 (9.3)	19 (4.46)	0.022
3	Low birth weight	47 (22)	48 (11.3)	0.001
4	Respiratory distress syndrome	85 (39.7)	87 (20.4)	<0.001
5	Intrauterine growth restriction	6 (2.8)	9 (2.1)	0.672
6	Neonatal jaundice	83 (38.8)	134 (31.5)	0.077
7	Neonatal sepsis	27 (12.6)	49 (11.5)	0.699
8	Neonatal seizures	3 (1.4)	16 (3.8)	0.137
9	Hypoxic ischemic encephalopathy	2 (0.9)	8 (1.9)	0.509
10	Shock	5 (2.3)	26 (6.1)	0.049
11	Neonatal mortality	3 (1.4)	5 (1.17)	1.000

[Table/Fig-4]: Bivariate analysis of neonatal mortality and morbidities.

Three neonates of COVID-19 positive mothers expired, while five neonates of COVID-19 negative mothers died, resulting in a comparable mortality rate. Logistic regression analysis showed that caesarean section, respiratory distress syndrome, and prematurity were statistically significant independent morbidities associated with COVID-19 positive status in the mother [Table/Fig-5].

S. no	Variable	p-value	Adjusted odds ratio	95% confidence interval
1	Preterm	0.015	2.359	1.181 to 4.712
2	LSCS	<0.001	4.090	2.840 to 5.882
3	Low birth weight	0.289	1.323	0.789 to 2.217
4	Respiratory distress syndrome	<0.001	2.291	1.508 to 3.480

[Table/Fig-5]: Multiple logistic regression analysis of the morbidities.

The odds ratio (95% confidence interval) for caesarean section was 4.090 (2.840-5.882), for respiratory distress syndrome was 2.291 (1.508 to 3.480), and for prematurity was 2.359 (1.181-4.712). The mortality and other morbidities were similar in both groups.

DISCUSSION

The study evaluated the effect of COVID-19 on maternal and neonatal morbidity and mortality. The results revealed that caesarean section, respiratory distress syndrome, and prematurity were independently associated with COVID-19 positive status in the mother. Although certain neonatal morbidities like low birth weight, jaundice, sepsis, and intrauterine growth restriction were observed to be common in neonates born to COVID-19 positive mothers, they were not found to be independently associated with COVID-19 positivity in the mother. The mortality of neonates born to COVID-19 positive mothers was comparable to that of neonates born to COVID-19 negative mothers. Although none of the maternal morbidities were significantly associated with COVID-19 positive mothers in present study, a few studies have reported an increased occurrence of preeclampsia and gestational diabetes in COVID-19 positive mothers [7,12,19].

In this study, it was observed that gestational hypertension/ preeclampsia was more common among COVID-19 positive mothers compared to COVID-19 negative mothers (15% vs. 10%, p-value=0.090). A similar observation was made in France, where

a higher frequency of preeclampsia/eclampsia (4.8% vs. 2.2%, p-value < 0.001) was observed in mothers with COVID-19 infection [7]. Villar J et al., observed that pregnant women with COVID-19 infection had a higher risk of preeclampsia/eclampsia {RR 1.76 (95% CI 1.27-2.43)} [12]. Similar to the observations made in mothers with preeclampsia, the frequency of gestational hypertension was higher in mothers with COVID-19 infection compared to the non-COVID-19 group (2.3% versus 1.3%, p-value <0.03) [7]. Several studies have observed an increased incidence of preeclampsia among mothers with COVID-19 infection. A preeclampsia-like syndrome has been described in severe COVID-19 infection among pregnant women, and tests like soluble fms-like tyrosine kinase (sFlt-1), Lactate Dehydrogenase (LDH), and Uterine Artery Pulsatility Index (UtAPI) are considered necessary to distinguish between the two conditions [21].

In this study, it was observed that the frequency of gestational diabetes was higher in mothers with COVID-19 infection (10.3% vs. 7%, p-value=0.169), but the difference was not statistically significant. A study by Epelboin S et al., also reported that the rates of gestational diabetes were not significantly different between COVID-19 positive and negative mothers [7].

The increase in the incidence of diabetes among pregnant women with COVID-19 infection is said to be due to damage to the pancreatic beta cells caused by the virus infection. Additionally, the entry of the virus is facilitated by an increase in Angiotensin Converting Enzyme 2 (ACE2) receptor expression in diabetes. Diabetes is also associated with complement defects, immunodeficiency, and increased inflammatory activity [22]. [Table/Fig-6] shows comparison of present study with other studies [11,12,22-24].

In this study, the rate of caesarean section among COVID-19 positive mothers was 73.8%, compared to 41.1% in COVID-19 negative mothers (p-value <0.001). Similar observations were made in France, where mothers in the COVID-19 group had a higher frequency of caesarean section compared to the non COVID-19 group (33.0% vs. 20.2%, p-value <0.001) [7]. Multivariate analysis showed that the risk of caesarean section was significantly increased in the COVID-19 group, regardless of the indication (16.7% vs. 7.1%, aOR = 1.8, 95% CI 1.6 to 2.1, p-value <0.001) [7]. Several earlier studies have also observed a significant association between caesarean section and COVID-19 positive status [11,23-25]. A systematic review and meta-analysis reported a pooled prevalence of 85% (95% CI 72-94) for caesarean deliveries. It was also observed that the caesarean delivery rate was higher in the second wave compared to the first [13].

It was observed that regardless of the mode of delivery, the incidence of preterm birth was significantly higher in COVID-19 positive mothers, which was in agreement with previous studies [7,12]. Similar observations were made by Epelboin S et al., who found that the risk of preterm birth was significantly increased in

Authors name [ref no]	Place and year of the study	Sample size	Findings
Zhu H et al., [22]	January 20 to February 5, 2020, Hubei province, China	10	80% were male, 60% were preterm. A 20% were Small-for-Gestational-Age (SGA) infants and 10% were large-for-gestational-age (LGA). The most common clinical symptom observed in neonates was respiratory distress.
Zhang L et al., [23]	January 30 to February 17, 2020. Wuhan University, China	A retrospective comparison of the pregnancy outcomes was done between 16 women with COVID-19 and 45 women without COVID-19.	The delivery was by caesarean section in both the groups. There were no significant differences in the birth weight of the newborn between the two groups (p-value >0.05). There were no significant differences in foetal distress, meconium-stained amniotic fluid, preterm birth, and neonatal asphyxia between the two groups.
Zaigham M and Andersson O [24]	Systematic review. 18 articles reporting data during the period December 2019 and April 2020	108 pregnancies	91% of the women were delivered by caesarean section. One neonatal death and one intrauterine death were also reported.
Smith V et al., [11]	Systematic review searched from November 1, 2019 to March 28, 2020.	Of 73 identified articles, nine were eligible for inclusion	63.8% (30/47) had preterm births, 61.1% (11/18) foetal distress and 80% (40/50) Caesarean section. 76.92% (11/13) of neonates required NICU admission and 42.8% (40/50) had a low birth weight.
Villar J et al., [12]	43 institutions in 18 countries. March to October 2020,	A total of 706 pregnant women with COVID-19 diagnosis and 1424 pregnant women without COVID-19 diagnosis were enrolled	Women with COVID-19 diagnosis were at higher risk for preeclampsia/eclampsia {Relative Risk (RR), 1.76; 95% CI, 1.27-2.43}, severe infections (RR, 3.38; 95% CI, 1.63-7.01), preterm birth (RR, 1.59; 95% CI, 1.30-1.94), medically indicated preterm birth (RR, 1.97; 95% CI, 1.56-2.51), severe neonatal morbidity index (RR, 2.66; 95% CI, 1.69-4.18), and severe perinatal morbidity and mortality index (RR, 2.14; 95% CI, 1.66-2.75).
Present study	August 2021 to October 2022	Study included a total of 640 mothers of which 214 (33.4%) were COVID-19 positive mothers and 426 (66.6%) COVID-19 negative mothers	Gestational hypertension was observed in 15% among COVID-19 positive mothers as compared to 10% among mothers who were COVID-19 negative. Among neonates of COVID-19 positive mothers, 49.5% were male, 80% were AGA, 19% were SGA and 0.5% were LGA. Delivery was by caesarean section in73.8% mothers who were COVID-19 positive and 41.1% mothers who were COVID-19 negative. Neonatal morbidities like prematurity (9.3%), low birth weight (22%), Intrauterine growth restriction (2.8%), respiratory distress syndrome (39.7%), neonatal jaundice (38.8%), sepsis (12.6%) were commonly encountered in the neonates born to COVID-19 positive mothers. Three neonates (1.4%) of COVID-19 positive mothers expired while five neonates (2.3%) of COVID-19 negative mothers died.

[Table/Fig-6]: Discussion on the results of the present study compared to the previous studies [11,12,22-24].

the COVID-19 group (16.7% vs. 7.1%, aOR= 2.52, 95% CI 2.1 to 3.1, p-value <0.001) [7]. These findings were also supported by a multinational cohort study, which reported a higher risk of preterm birth (RR, 1.59; 95% CI, 1.30-1.94) and medically indicated preterm birth (RR, 1.97; 95% CI, 1.56-2.51) [12]. A systematic review and meta-analysis reported a pooled prevalence of premature birth of 17.80% (95% CI: 12.47-23.13) [26]. The rise in prematurity in COVID-19 maternal infection may be due to maternal stress, increased inflammatory processes, or early induction of delivery or caesarean section for severe maternal illness [10,13].

In this study, it was observed that neonatal morbidities such as prematurity (9.3% vs. 4.5%), low birth weight (22 % vs. 11.3%), intrauterine growth restriction (2.8% vs. 2.1%), respiratory distress syndrome (39.7% vs. 20.4%), neonatal jaundice (38.8% vs. 31.5%), and sepsis (12.6% vs. 11.5%) were more common in neonates born to COVID-19 positive mothers. In a study conducted by the GENESCO-COVID-19 working group, it was found that there was no difference in neonatal symptoms and the need for admission due to maternal COVID-19 infection [27]. A study done in India revealed that 23% of neonates needed intensive care and the morbidity pattern was similar to that of non infected women [10]. Preterm births and low birth weight were common morbidities observed in a systematic review [11]. Villar J et al., observed that the risk of neonatal morbidities was higher among neonates of COVID-19 positive mothers (RR, 2.66; 95% CI, 1.69-4.18) [12].

In this study, it was observed that respiratory distress syndrome was more commonly observed among neonates of COVID-19 positive mothers (85 (39.7%) vs 87 (20.4%)). It was observed in a previous study that newborns born to COVID-19 positive mothers were three times more likely to present with respiratory distress in the first few days of life (OR= 3.016, 95% CI: 1.128 to 8.0633). [27]. The most common cause of respiratory distress was transient tachypnoea of the newborn, followed by pneumonia and respiratory distress syndrome [28]. Respiratory symptoms in newborns born to COVID-19 positive mothers were most likely due to prematurity, transient tachypnoea, and respiratory distress rather than COVID-19 pneumonia [29].

In this study, it was observed that four neonates tested positive for COVID-19 infection. Other studies have identified a higher rate of COVID-19 positivity ranging from 4.3-9.4% [10,30,31]. The neonatal swab positivity rate for COVID-19 infection was found to be 1.8% in the AAP-SONPM registry and 2.0% in the PAN-COVID-19 registry, which was more in line with present study [31]. Present study did not report excess mortality in neonates born to COVID-19 positive mothers, but a systematic review reported a higher mortality [26].

Limitation(s)

The limitations of the study were that it was limited to a single center and the morbidity pattern of the two waves studied was not compared.

CONCLUSION(S)

Caesarean section, respiratory distress syndrome, and prematurity were significant morbidities observed in COVID-19 positive mothers. The mortality and other morbidities were similar in the two groups. There is a need to plan future studies to evaluate the pattern of maternal and neonatal morbidity and neonatal mortality after the introduction of the COVID-19 vaccine. It has been observed that the incidence and severity of COVID-19 infection have been modified by the COVID-19 vaccination in several countries around the world. The impact of the changing clinical profile of maternal infection on neonatal outcomes needs to be studied.

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