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Impact of maternal SARS-CoV-2 infection on pregnancy outcomes and infant development: A comprehensive cohort study

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Abstract
Background: The impact of maternal SARS-CoV-2 infection on pregnancy outcomes and infant development has become a significant concern within the medical community. This study aims to contribute to the existing body of research by examining the intersection between maternal health, infectious diseases, and neonatal outcomes.
Methods: The study employed a comprehensive cohort design, incorporating both retrospective and prospective elements, and included a comparison group. Data was collected from pregnant women and their infants. Various tools were utilized for data collection, including questionnaires, developmental milestone inventories, and physical measurement instruments. Statistical analysis was conducted using SPSS, and logistic regression models were applied to adjust for potential confounders.
Results: The study found that there is limited data to demonstrate a significant influence of maternal COVID-19 infection on maternal, pregnancy, and neonatal outcomes, as well as early baby developmental milestones. The analysis of various developmental milestones, such as rolling over, head holding, sitting did not reveal substantial differences between infants born to COVID-positive and COVID-negative mothers while parameters like crawling, visual object tracking milestones and reaching object with one hand reached statistical significance.
Conclusion: The study concludes that further investigation with larger sample sizes and extended follow-up periods is necessary to validate the observed patterns and gain a deeper understanding of the potential impacts of maternal COVID-19 infection on pregnancy and neonatal outcomes, as well as on child development. Enhanced understanding in this field will contribute to the knowledge of the consequences of maternal COVID-19 infection on the health of both the mother and the newborn.

Keywords: COVID-19, pregnancy outcomes, neonatal health, maternal infection

Introduction

Infectious diseases, such as influenza, CMV, and Zika virus, are significant pregnancy risk factors that affect both the mother's and the unborn child's health. The COVID-19 pandemic began in December 2019 with the emergence of the new coronavirus, SARS-CoV-2, in Wuhan, China [1, 2]. Studies have shown inconsistent results on the relationship between maternal COVID-19 and pregnancy outcomes, and further research is needed to understand how maternal SARS-CoV-2 infection impacts pregnancy outcomes and newborn development [3, 4].

Significant studies have advanced our understanding of how maternal SARS-CoV-2 infection affects pregnancy outcomes and the growth of the unborn child. Studies have shown that pregnant women with COVID-19 have a higher chance of giving birth prematurely, and they have a greater prevalence of severe maternal morbidity compared to those without the infection [5, 6, 7]. Additionally, a study by Shimabukuro *et al*. (2021) examined the effectiveness and safety of immunisation against COVID-19 while pregnant, offering new information on treating COVID-19 infection in mothers [8].

Understanding how maternal SARS-CoV-2 infection affects pregnancy outcomes and the development of the unborn child is crucial for clinical care and public health initiatives to safeguard mother and child health during the ongoing pandemic. New research indicates that maternal COVID-19 may raise the likelihood of unfavourable pregnancy outcomes, including preterm birth, stillbirth, and problems in the newborn [9, 10, 11].

This cohort research aimed to investigate the effects of maternal SARS-CoV-2 infection on pregnancy outcomes and newborn health, focusing on gestational age at delivery, delivery type, obstetric problems, and neonatal outcomes. The study used an ambispective cohort design, which allowed for a large temporal cross-section of data and simplified comparisons before and after the pandemic started.

Materials and Methods

The study aimed to examine the impact of SARS-CoV-2 on pregnancy and new born development. It used an ambispective cohort study, incorporating aspects of both prospective and retrospective cases. The study was conducted at SCB Medical College in Cuttack, Odisha for a period of 30 months starting from July 2020 and commencing in December 2022. Ethical approval was obtained from the hospital ethical committee before commencing the study, and each subject gave written informed consent prior to enrolling in the study. There were 400 expectant women in the sample, divided equally for the retrospective and prospective cohorts into groups of 200 COVID-positive and negative individuals. Eligibility requirements included pregnant women who had antigen testing and an RT-PCR-verified positive SARS-CoV-2 test during their pregnancy. The study ran from the initial stages of recruitment until the exposure and comparison cohorts met predefined sample sizes. The follow-up to two years after delivery was extended to investigate any long-lasting effects of prenatal SARS-CoV-2 exposure on pregnancy and newborn development. Reference materials included a semi-structured, pre-validated questionnaire, a developmental milestone inventory, an infantometer, a digital scale, and a non-stretchable measuring tape.

Data were collected from the medical records of both prospective and retrospective cohorts, with details on COVID-19 exposure during pregnancy for the retrospective group through phone interviews and for the intended group through direct interviews. Hospital records were used to obtain information on gestational COVID-19 infection, antenatal period, delivery results, and growth measures of the infants. Important factors of baby growth and development were collected, including body weight, length, head and chest circumferences, and reaching developmental milestones.

Statistical analysis was performed using SPSS software, using Fisher's exact test or the Chi-square test to compare categorical data, Mann-Whitney U or t-tests to analyze continuous variables, and logistic regression models to determine the odds ratios and 95% confidence intervals of the relationship between maternal COVID-19 status and newborn developmental outcomes.

Results

The mean age for the COVID-19 negative group was 25.69 years with a standard deviation of 4.38, whereas the mean age for moms testing positive for the virus was 26.45 years with a standard deviation of 4.06. The observed difference in mean mother age between the two groups was not statistically significant, this implies that within the group under study, pregnant women with and without COVID-19 do not differ in their maternal age (Table 1).

Preterm births were found to be higher in the COVID-19-positive group (37.5%), while term births occurred at or after 37 weeks of gestation in the COVID-19-positive group (62.5%). No significant variation was found in the frequencies of term and preterm births between the two groups. The delivery methods were also compared, with 43% of the COVID-19-negative group having vaginal deliveries (VD), 48% of the COVID-19-positive group having VD, and 52% of the COVID-19-positive group having lower segment caesarean section (LSCS). The study found no significant variation in delivery methods between COVID-19-infected and non-infected women. The findings suggest that COVID-19 status may not be a decisive factor for these outcomes in the population under study.

COVID-19 positive and negative groups had equal parity spread. In particular, the percentage of primiparous women was the same in both cohorts that is 47%. Likewise, 53% (n = 106) of each group were multiparous women. The p-value of 1.0 shows that there are no statistically significant variations in parity between pregnant women with and without COVID-19 which implied that the community was comparable (Table 1).

The mean diastolic and systolic blood pressures (SBP) of mothers were compared, finding no significant difference between the two groups. Preeclampsia incidence was found to be 7.5% in both groups, with no significant difference in the incidence rate. Postpartum haemorrhage (PPH) incidence was 0% in both groups. The oral glucose tolerance test (OGTT) results showed no significant difference in glucose tolerance between the two groups. The study concluded that COVID-19 status did not significantly affect SBP, DBP, preeclampsia rates, PPH incidence, or OGTT results in pregnant women. The mean values of the oral glucose tolerance test (OGTT) were 110.13 mg/dL in the positive group and 109.12 mg/dL in the negative group, indicating no significant difference in glucose tolerance between the two groups. The study concluded that COVID-19 status does not significantly affect these outcomes in pregnancy (Table 1).

The age distribution of the research sample showed that 56.5% of the COVID-19-positive cases were among women older than 25. By comparison, 45.5% of the patients in the same age group were negative for COVID-19. A comparable distribution for this age range between the two groups was shown by the 38.5% of mothers in the COVID-19-positive group and the 39% in the COVID-19-negative group. Significantly, moms under 20 years old had the lowest percentage of COVID-19-positive cases 5% compared to the 15.5% of COVID-19-negative cases. These results imply that, although women over 25 account for the bulk of COVID-19-positive cases, younger mothers (those under 20) are less likely to be positive than the older age groups (Table 2).

The study found no significant difference in Apgar scores between babies born to mothers who tested positive for COVID-19 and those who tested negative. The mean Apgar score at one minute was 8.53 for infants in the COVID-positive group, slightly lower than 8.64 in the COVID-negative cohort. At the 5-minute mark, mean scores were 9.06 for the COVID-positive group and 9.15 for the COVID-negative group. This suggests that the mother's COVID-19 status does not directly affect newborns' Apgar scores.

Birth weight and physical measurements showed that COVID-19 positive and negative cases were uniformly distributed and had no statistical significance. No significant variations were found between the groups in newborn length, head circumference, and chest circumference. These results suggest that variations in newborn measures or birth weight are unrelated to the mother's COVID-19 status.

The COVID-positive group had higher admission rates to the Specialised Neonatal Care Unit (SNCU) (12.5%) than the COVID-negative group (6.5%), but this difference did not reach statistical significance. The median (interquartile range) of the SNCU stay was similar in both groups, suggesting that although there is a tendency for higher SNCU admissions among newborns born to COVID-19-positive mothers, there is not

enough data to prove a clear relationship with the mother's COVID-19 status (Table 3).

Neonatal Health Outcomes by COVID-19 Status

The COVID-19-positive group reported eleven instances of intrauterine death (IUD), with mothers having severe preeclampsia in two and normal blood pressure in nine cases. Of the COVID-19 negative group, there were five IUD cases, mothers of two had severe pre-eclapmpsia, one had non-severe preeclampsia and two had normal blood pressure. There were 10 neonatal deaths in the COVID-19 positive group. Among then mothers of 5 had severe preeclampsia, 1 had non-severe preeclampsia and 4 had normal blood pressure. Of the 5 neonatal deaths in covid negative group, mother of one had preeclampsia without severe features and four had normal blood pressure. The pattern of newborn fatalities by age suggests that the COVID-19-positive group had more early neonatal deaths than the COVID-19-negative group did. More precisely, nine deaths happened by day seven, as opposed to one in the COVID-19 negative group. Days 15 through 21 saw one death in each group. The COVID-19 negative group reported two deaths, while the COVID-19 positive group reported none between days 22 and 28. Moreover, compared to COVID-19-negative mothers (9 vs. 4), a larger proportion of newborns born to COVID-19-positive mothers were preterm (<37 weeks), with one full-term delivery (>37 weeks) in each group. These results, which suggest that maternal COVID-19 infection may be associated with increased risks of catastrophic newborn outcomes, early neonatal deaths, and preterm births, call for more research and focused healthcare solutions for this population.

Motor Development milestone

The assessment of the motor development milestones for rolling over showed no appreciable difference between the children of COVID-19-positive and negative mothers; 92.7% and 88.4% of the children, respectively, showed normal development patterns ($p = 0.21$).

The majority of babies, 64.2% in the COVID-19 positive group and 60.5% in the negative group demonstrated normal head-holding skills; however, the difference did not reach statistical significance ($p = 0.52$). In COVID positive group, 93.3% and in COVID negative group 86.4% had had normal sitting with support milestone. With no statistically significant difference ($p = 0.24$), the capacity to sit without assistance yielded similar findings in both groups (Table 4).At the crawling milestone, on the other hand, there was a statistically significant difference ($p = 0.023$): a slightly greater percentage of the COVID-19 positive group (96.1%) achieved normal development than total normality (100%) in the COVID-19 negative group (Table 4).

Infants in both groups were very likely to be able to stand with assistance; in the COVID-19 positive group, this capacity was 98.9%, and in the COVID-19 negative group, it was 100%. This finding did not translate into a statistically significant difference (Table 4; $p = 0.023$).

Sensory Milestones

The analysis of sensory response to sound revealed a high percentage of normalcy in both groups, with 98.3% in the COVID-19-positive group and complete normalcy in the negative group; this difference was not significant ($p = 0.11$). In COVID positive group, 99.4% and in COVID negative group 100% had normal response to sound and repeating monosyllable words milestones. milestone.

However, a significant variance was noted in the ability to visually track objects, with 95.5% normal development in the COVID-19 positive group versus 100% in the negative group, marking a statistically significant difference ($p = 0.003$) (Table 4). For reaching objects with one hand milestone, 91.6% COVID positive and 82.1% with COVID negative had normal achievement. When passing objects from one hand to the other hand parameter was analysed, it was observed that 98.3% with COVID positive and 99.5% with COVID negative had normal milestone. Searching for things milestone had 99.4% from COVID positive and 100% of COVID negative infants who had normal achievement. None of these parameters had significant difference.

Social Engagement and Recognition Abilities

The evaluation of social smiling, recognition of familiar people and responding to own name showed a high level of normal development in both groups, with 98.3%, 98.9% and 98.9% in the COVID-19 positive group and 99.5%, 100%, 100% in the negative group, respectively. These differences did not reach statistical significance ($p = 0.36$ and $p = 0.48$, respectively) (Table 4).

The critical assessment of motor, sensory, and social development milestones suggests that infants born to COVID-19-positive mothers predominantly achieve developmental milestones in a manner consistent with those born to COVID-19-negative mothers. Notable exceptions were identified in the milestones of crawling, visual object tracking and reaching object with one hand where COVID-19-positive infants showed a slight delay. These findings imply that in-utero exposure to COVID-19 has limited effects on certain aspects of early motor and sensory development, with the broader developmental trajectory appearing largely on par with non-exposed peers.

Table 1: Comparison of Maternal Characteristics and Pregnancy Outcomes between COVID-19 Positive and Negative Cases

General characteristic	Covid positive cases (n=200)	Covid negative cases (n=200)	P Value
Mothers Age (years)	**26.45±4.06**	**25.69±4.38**	**0.07**
Gestational Age			
<37 weeks	75(37.5)	90(45)	0.15
>37 weeks	125(62.5)	110(55)	
Type of delivery			
VD	96(48)	86(43)	0.275
LSCS	104(52)	114(57)	
Obstetrics index			**1.0**
Primi	94(47)	94(47)	
Multi	106(53)	106(53)	
Pregnancy Outcome			
SBP	118.91±13.98	118.16±13.31	0.58
DBP	83.0±7.96	82.20±8.98	0.29
Preeclmpsia	15(7.5)	15(7.5)	
PPH	0	0	
OGTT	110.13±6.36	109.12±7.6	0.15

Table 2: Maternal Age Distribution in COVID-19 Positive and Negative Cases

Mothers Age (years)	Covid positive cases (%)	Covid negative cases (%)
<20	10(5)	31(15.5)
20-25	77(38.5)	78(39)
>25	113(56.5)	91(45.5)

Table 3: Comparative Analysis of Neonatal Outcomes and Specialized Care Requirements between Infants Born to COVID-19 Positive and Negative Mothers

Fetal outcome	Covid positive cases	Covid negative cases	P Value
Apgar score at 1 mint	8.53±0.75	8.64±0.65	0.10
Apgar score at 5 mint	9.06±0.70	9.15±0.67	0.19
Birth weight			
<1000	2(1)	2(1)	0.24
1000-1499	5(2.5)	10(5)	
1500-2499	40(40)	52(26)	
≥2500	135(76.5)	136(68)	
Length of baby	48.5±1.88	48.23±1.88	0.16
Head circumference	33.64±0.49	33.57±0.49	0.21
Chest circumference	31.43±0.78	31.34±0.82	0.26
SNCU Admission	25(12.5)	13(6.5)	0.06
Duration of admission	4(3-4)	4(3-5.5)	

Table 4: Impact of Maternal COVID-19 Status on Infant Developmental Milestones

Milestones		Covid positive cases(n=179)	Covid negative cases(n=190)	P Value
Rolling Over(n)	Normal	166(92.7)	168(88.4)	0.21
	Abnormal	13(7.3)	22(11.6)	
Head holding	Normal	115(64.2)	115(60.5)	0.52
	Abnormal	64(35.8)	75(39.5)	
Sitting with support	Normal	167(93.3)	166(87.4)	0.07
	Abnormal	12(6.7)	24(12.6)	
Sitting without support	Normal	177(98.9)	190(100)	0.24
	Abnormal	2(1.1)	0(0)	
Crawling	Normal	172(96.1)	190(100)	0.023
	Abnormal	7(3.9)	0(0)	
Standing with support	Normal	177(98.9)	190(100)	0.23
	Abnormal	2(1.1)	0(0)	
Turning towards sound	Normal	176(98.3)	190(100)	0.11
	Abnormal	3(1.7)	0(0)	
Responding to sound	Normal	178(99.4)	100(100)	0.48
	Abnormal	1(0.6)	0(0)	
Repeating monosyllable words	Normal	178(99.4)	190(100)	0.48
	Abnormal	1(0.6)	0(0)	
Watching objects as they move	Normal	171 (95.5)	190(100)	0.003
	Abnormal	8(4.5)	0(0)	
Reaching the object with one hand	Normal	164(91.6)	156(82.1)	0.009
	Abnormal	15(8.4)	34(17.9)	
Passing objects from one hand to the others	Normal	176(98.3)	189(99.5)	0.36
	Abnormal	3(1.7)	1(0.5)	
Searching for things	Normal	178(99.4)	190(100)	0.48
	Abnormal	1(0.6)	0(0)	
Social smiling	Normal	176(98.3)	189(99.5)	0.36
	Abnormal	3(1.7)	1(0.5)	
Recognizing familiar people	Normal	178(99.4)	190(100)	0.48
	Abnormal	1(0.6)	0(0)	
Responding to own name	Normal	177(98.9)	190(100)	0.23
	Abnormal	2(1.1)	0	

Discussion

The goal of this study was to assess in detail how maternal COVID-19 infection affected many aspects of maternal health, pregnancy, neonatal outcomes, and the early developmental milestones of the child. To determine any correlations between maternal COVID-19 infection and poor pregnancy outcomes, health issues in newborns, and anomalies in early infant developmental patterns, we looked at factors including maternal age, gestational age, type of delivery, obstetric characteristics, pregnancy outcomes, neonatal health, and infant developmental milestones. The results of this investigation greatly advance our knowledge of how maternal COVID-19 infection affects the health of both mothers and newborns. They provide insightful information that can help medical practitioners better understand the potential consequences of maternal COVID-19 infection on pregnancy, newborn health, and early childhood development.

We found no statistically significant difference between the cohorts of those who tested positive for COVID-19 and those who tested negative in our study of mother age. This suggests that the distribution of maternal age between pregnant women with COVID-19 and those without is not appreciably different. These results support earlier studies that, in turn, revealed no statistically significant relationship with COVID-19 infection during pregnancy and maternal age [4]. Furthermore, we found no appreciable differences between the groups that tested positive and negative for COVID-19 in terms period of gestation or the type of delivery. In particular, there were no differences in the frequencies of full-term and preterm deliveries or in the mode of delivery. These results suggest that the existence of COVID-19 may not significantly impact the outcomes in the investigated group. This aligns with systematic reviews that have analyzed delivery types and gestational age across large cohorts [12, 13]. The percentage of primiparous and multiparous women demonstrates that the distribution of parity status was the same between the COVID-19 positive and negative groups. These results support earlier studies indicating no significant relationship between parity status and maternal COVID-19 infection [11, 14].

Our in-depth analysis of pregnancy outcomes gave us a clear picture of the potential consequences of a COVID-19 infection in the mother. Unlike our first expectations, we did not see any appreciable differences in the systolic and diastolic blood pressure measurements of the mothers who tested positive or negative for COVID-19. This agrees with recent research that emphasizes the complex link between COVID-19 infection and cardiovascular health in pregnant women [15]. Moreover, the incidence of preeclampsia, a serious pregnancy complication, did not differ much across the two groups. This supports other studies showing that the etiology of preeclampsia is complex rather than being only viral [16]. Furthermore, the fact that neither group experienced any postpartum hemorrhage emphasizes the necessity of more investigat [21, 22] ion into the potential effects of COVID-19 on the blood coagulation systems of mothers [17, 18]. The findings of the oral glucose tolerance test also showed no appreciable differences. This suggests that COVID-19 status of mother may not significantly impact her glucose metabolism during pregnancy. According to new research by Zambrano *et al*. (2020), viral infections during pregnancy may affect glucose metabolism [7]. These results underline the significance of adopting several approaches to guarantee the health of the mother and fetus, as well as the necessity of closely monitoring pregnancy outcomes during the COVID-19 pandemic.

We carefully evaluated several aspects of newborn outcomes, including birth weight, Apgar ratings, physical measurements, and the necessity for specialized neonatal care. We found no appreciable differences between babies delivered to mothers who tested positive for COVID-19 and those who tested negative. Specifically, we observed no statistically significant differences in the rates of admission to specialized newborn care units, birth weight categories, physical measures such as length, head circumference, and chest circumference, or Apgar scores at one and five minutes after delivery. Other studies suggest that maternal COVID-19 infection may not significantly impact these important neonatal outcomes, as supported by these results. Studies by Buonsenso *et al*. (2020) and Flaherman *et al*. (2021) have shown encouraging results for newborn health when a mother has COVID-19 [19, 20].

In order to ascertain if COVID-19 status of mother had any long-lasting effects on the development of babies, we measured their early developmental milestones. After a thorough evaluation of motor, sensory, and social developmental milestones, we discovered that children born to mothers who tested positive for COVID-19 often achieved developmental milestones comparable to those born to mothers who tested negative. Notable exceptions were little delay in crawling, visual object tracking milestone and reaching object with one hand. These differences were nevertheless insufficiently significant to imply that a mother's COVID-19 status had any negative impact on the general development of her children. Recent studies by Gabriel *et al*. (2020) and Vivanti *et al*. (2020) suggest that while children delivered to mothers who tested positive for COVID-19 may slightly miss some developmental milestones, this has no effect on their overall development [21, 22].

Through the use of a thorough cohort design, we included a comparison group and both retrospective and prospective components in a thorough cohort design. This strategy allowed for a rigorous examination of historical and current case data, which improved our knowledge of the effects of SARS-CoV-2 on pregnancy and the development of the resulting baby. Careful data collection techniques, including demanding questionnaires, developmental milestone inventories, and actual measuring devices, guaranteed the precision and dependability of our results. Our findings suggest that maternal COVID-19 infection may not significantly impact early developmental milestones of the newborn, maternal, pregnancy, and neonatal outcomes. As a result, compared to individuals without COVID-19, pregnant women with it may not require any additional treatments or specialist care. To confirm these results and provide better knowledge of the possible effects of maternal COVID-19 infection on pregnancy and newborn outcomes, another study with larger sample sizes and longer follow-up periods is required.

Despite its advantages, our study has a number of drawbacks, which we have recognised. The somewhat small sample size is one drawback that could make our results less applicable in general. Moreover, the fact that we carried out our study at a single medical school could restrict the generalizability of our findings. Furthermore, the short two-year postpartum follow-up time could not fully reflect the long-term consequences of prenatal SARS-CoV-2 exposure on pregnancy outcomes and newborn growth.

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