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Original Article

Obstetrics and Gynaecology Section

Evaluation of Neonatal Outcome (Major Congenital Malformation) in First Trimester Pregnant Women with SARS-CoV-2 Infection: A Prospective Cohort Study

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ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19) infection has been difficult to control despite advancements in medical science. Many short and long-term complications following COVID-19 infection are still being observed. The hypoxaemia episodes occurring in the first trimester of pregnant women and their potential role in causing congenital malformations in newborns remain unclear. Limited information is available regarding the effects of Severe Acute Respiratory Syndrome Coronavirus 2 (COVID-19) during the first trimester of pregnancy and its association with the risk of developing Major Congenital Malformations (MCMs).

Aim: To compare the development of congenital malformations in pregnant women who tested SARS-CoV-2 positive and those who tested negative during the first trimester of pregnancy.

Materials and Methods: A prospective cohort study was conducted in a small town in the Hooghly district of West Bengal between January 2021 and December 2021. Two nursing homes were selected for sample collection, with approximately 100 patients per centre. The study included 100 pregnant women in their first trimester who tested SARS-CoV-2 positive and another 100 pregnant women in their first trimester who tested negative. An unpaired t-test was performed to analyse the association between the development of MCMs in both groups.

Results: The mean maternal age was comparable between the COVID-19-exposed group (24.6 years) and the non-exposed group (25.2 years). The proportions of primigravida and multigravida women were also similar in both groups (62% vs. 64% primigravida, respectively). The odds ratio for MCMs in the COVID-19-exposed group was 0.49, indicating a lower likelihood compared to the non-exposed group. The average Appearance (skin color), Pulse (heart rate), Grimace (reflex irritability/response), Activity (muscle tone), and Respiration (breathing effort) (APGAR) scores at 1 and 5 minutes were slightly higher in the exposed group (7.01 and 7.45) than in the non-exposed group (6.8 and 7.28), though the differences were not statistically significant (p=0.28 and p=0.50, respectively).

Conclusion: The present study concludes that there is no evidence of increased risk of MCMs associated with first-trimester maternal SARS-CoV-2 infection. Overall, the findings do not support any major teratogenic effects resulting from maternal COVID-19 infection in early pregnancy.

Keywords: Cohort, First-trimester pregnancy, Malformations, Severe Acute Respiratory Syndrome Coronavirus 2 (COVID 19)

INTRODUCTION

Most pregnancies affected by COVID-19 were asymptomatic and went undetected. Limited access to healthcare and inadequate case registration have hindered researchers' ability to link maternal health records at the time of infection to newborn outcomes. Fever caused by COVID-19 in pregnant individuals may pose risks during pregnancy [1]. Typically, during pregnancy, the maternal immune system is suppressed, allowing the foetus-considered a foreign entity-to remain protected from immune attack [2].

Infections in early pregnancy may make the embryo vulnerable to malformations during neural tube formation, which occurs between days 20 and 28 of human development [3]. Currently, no reliable evidence supports transplacental transmission of COVID-19 during the first trimester of pregnancy [4].

A review suggested that COVID-19 can infect the infant during labour or breastfeeding, but transplacental infection has not yet been documented [5]. However, in-vitro studies have shown that COVID-19 can infect granulosa and cumulus cells in the ovaries [6]. Most high-quality studies do not support a clear link between maternal SARS-CoV-2 infection and an increased risk of MCMs. A small body of limited evidence suggests a possible risk in specific settings (e.g., very early infection), but these findings remain inconclusive and may be affected by confounding factors.

Continued surveillance-particularly focusing on early pregnancy exposures and comprehensive foetal assessment-will help clarify any subtle or rare associations [7]. Based on this background, the present study was conducted to evaluate neonatal outcomes, specifically MCMs and birth asphyxia, in infants born to mothers with SARS-CoV-2 infection during the first trimester compared to those born to SARS-CoV-2–negative mothers.

MATERIALS AND METHODS

The present prospective cohort study was conducted in two nursing homes-Sanjiban Nursing Home and Nilkantha DCC (P) Ltd., Tarakeswar-in the Hooghly district of West Bengal, India, from January 2021 to December 2021. A total of 50 cases and 50 controls were recruited from each nursing home, resulting in 100 cases and 100 controls in the study.

Inclusion criteria: Pregnant women who tested SARS-CoV-2 positive in their first trimester were included as cases, whereas those who tested SARS-CoV-2 negative in the first trimester were included as controls.

Exclusion criteria: Patients (both cases and controls) with conditions known to increase the risk of congenital abnormalities were excluded. This included mothers with diabetes mellitus and those taking medications such as antiepileptic drugs, warfarin (in

mothers with artificial cardiac valve replacement), and corticosteroids (in mothers with various forms of arthritis).

Study Procedure

Data analysis was performed using information collected from pregnant women after confirmation of their SARS-CoV-2 status. Nasal swabs were obtained for testing. Foetal monitoring was conducted using ultrasound and Doppler during the third trimester of pregnancy, and APGAR scores were assessed after delivery. One cleft palate was identified in the exposed group, while one case of imperforate anus and one case of hypospadias were identified in the non-exposed group. These newborns were referred to a tertiary care hospital for further evaluation and management. APGAR scores were recorded at the 1st and 5th minutes after birth.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS) software version 16 was used to analyse the data. An unpaired t-test was performed to assess the statistical association between the groups regarding the presence of MCMs. An unpaired t-test was also used to compare the APGAR scores.

RESULTS

The mean maternal age was comparable between the COVID-19-exposed group (24.6 years) and the non-exposed group (25.2 years). The proportions of primigravida and multigravida women were similar in both groups (62% vs. 64% primigravida, respectively) [Table/Fig-1] [8].

Variables	Mean age (years)	Gravida		Socioeconomic status (modified BG Prasad scale 2021) [8]					History of congenital anomalies in prior pregnancies
		Primi	Multi	I	II	III	IV	V	
Exposed (cases)	24.6	62	38	73	16	8	3	0	3
Non-exposed (controls)	25.2	64	36	76	14	7	3	0	2

[Table/Fig-1]: Socio-demographic characteristics of two groups - exposed (cases) and non-exposed (controls) [8].

The [Table/Fig-2] showed the odds ratio calculated using the formula:

Odds Ratio=(A×D)/(B×C)=(1×98)/(2×99)=98/198=0.49.

Since the odds ratio is less than 1, this indicates that the odds of MCM in the COVID-19-exposed group are lower than those in the non-exposed group. A p-value of 1.0 indicates that there is no statistically significant association between exposure and MCM in this dataset.

Variables	MCM	NO MCM	Total
Exposed (cases)	1 (A)	99 (B)	100
Non exposed (controls)	2 (C)	98 (D)	100
Total	3	197	200

[Table/Fig-2]: Comparison of MCMs between COVID-19-exposed and non-exposed pregnancies with corresponding odds ratio.

The [Table/Fig-3] shows that the average APGAR scores at one minute in the exposed and non-exposed groups were 7.01 and 6.8, respectively (calculated using the weighted average formula). These differences were not statistically significant (p=0.28).

Weighted Average formula = $(w_1x_1 + w_2x_2 + w_3x_3 + ... + w_nx_n) / (w_1 + w_2 + w_3 + ... + w_n)$

Where:

x_i = represents the individual values in the dataset.

w_i = represents the corresponding weights for each value.

n = is the total number of values [9].

APGAR score	Frequency
0-3	2 (2%)
4-6	30 (30%)
7-8	49 (49%)
9-10	19 (19%)

[Table/Fig-3]: Distribution of newborns by APGAR Scores at 1 minute postdelivery in the study population.

The [Table/Fig-4] shows that the average APGAR score at five minutes in the exposed and non-exposed groups was 7.45 and 7.28, respectively (calculated using the weighted average formula). These observations regarding the 5-minute APGAR score were also not statistically significant (p=0.5).

APGAR score	Frequency
0-3	2 (2%)
4-6	18 (18%)
7-8	54 (54%)
9-10	26 (26%)

[Table/Fig-4]: Distribution of newborns by APGAR Scores at 5 minute postdelivery in the study population.

DISCUSSION

Scientific evidence indicates that the causative agent of COVID-19, SARS-CoV-2, appears capable of crossing both the placental barrier (as suggested by viral Immunoglobulin M (IgM) detected in infants hours after birth) [10] and the blood-brain barrier (virus detected in cerebrospinal fluid) [11]. The German COVID-19 Related Obstetric and Neonatal Outcome Study (CRONOS) study reported a 1.96% prevalence of congenital malformations among 8,032 pregnancies, but did not associate these anomalies with maternal COVID-19 infection [12]. Similarly, a study in Scotland found no increased risk of congenital malformations following COVID-19 infection (1,574 infected vs. 4,722 non-infected; odds ratio 0.94, 95% CI 0.57-1.54) [13].

A study conducted in Norway, Sweden, and Denmark demonstrated that the rate of congenital anomalies in 10,000 infants born to mothers infected with SARS-CoV-2 during the first trimester was comparable to those born to uninfected mothers [14]. A large Canadian study examining 420,222 births across both pandemic and pre-pandemic periods found no increase in congenital anomalies following first-trimester COVID-19 infection. However, an increase in microcephaly was noted in late-pandemic births, possibly due to improved detection rates [15].

A recent study reported that newborns of mothers diagnosed with COVID-19 had a 25.4 fold higher risk of receiving an APGAR score below seven compared to newborns of uninfected mothers, indicating a potential impact of maternal infection on neonatal health [16].

Studies from Saudi Arabia [17] and China have highlighted an increase in specific congenital conditions, including Neural Tube Defects (NTDs) and situs inversus [18,19]. These findings contrast with reports from Scandinavian countries (Sweden, Denmark, and Norway), where no increase in foetal situs inversus was observed during the pandemic [14]. Maternal health and nutritional status must also be considered, as confounding factors-particularly folic acid deficiency-may influence congenital outcomes. This was noted in both the Saudi Arabian study and an Indian study reporting a significant increase in NTDs during the pandemic [20].

The risk of an APGAR score of 7 or lower was 25.4% greater in the exposed group compared to the control group, possibly due to increased foetal distress, preterm labour, and prematurity among COVID-19 positive mothers [16]. Population-based data also suggest that women with viral pneumonia have an increased risk of delivering newborns with APGAR scores ≤7 [21]. The UK Obstetric

Surveillance System (UKOSS) study similarly found higher rates of Neonatal Intensive Care Unit (NICU) admission among infants born to COVID-19 positive mothers compared to controls [22].

The present prospective cohort study recommends the initiation of long-term follow-up for infants born to infected mothers to evaluate delayed neurodevelopmental and cognitive outcomes beyond the neonatal period. It also recommends stratifying outcomes based on the trimester of maternal infection to identify potential critical periods of foetal vulnerability. Additionally, studies from low and middle-income countries are needed to better capture global patterns and regional disparities. Although no definitive link between maternal COVID-19 infection and congenital anomalies has been established, subtle impacts on neonatal health warrant continued clinical vigilance and ongoing data monitoring.

Limitation(s)

A limitation of the study is that vaginal discharge, amniotic fluid, and placental samples were not collected for COVID-19 testing. The study was conducted on a small sample of exposed and non-exposed individuals within a limited geographical area and time frame. Therefore, the results may not be generalisable to larger populations.

CONCLUSION(S)

Based on the present small cohort study, first-trimester maternal SARS-CoV-2 infection does not appear to increase the risk of major congenital malformations in newborns. However, larger, multicentre studies are required to confirm these findings.

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