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Original Research Article

An Analytical Case-Control Study to Assess the Maternal and Neonatal Risks Associated with COVID-19 in Pregnancy

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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to identify maternal and neonatal risks associated with COVID-19 in pregnancy.

Methods: This case–control study was conducted at the Department of Obstetrics and Gynecology BMIMS, PAWAPURI, Nalanda, Bihar, India. All COVID-19 positive women who delivered for the period of two years were included. During the study period, 2020, around 235 pregnant women were COVID-19 positive, of which 30 were discharged undelivered and 5 were spontaneous abortions, so were excluded, 200 were included in the study.

Results: According to disease severity, there were mild 192 cases, moderate 6 cases, and severe 2 cases. Cases were mostly from urban areas showing the trend of positivity in urban areas. Mean gestational age in the cases (37.13 ± 2.32weeks) was comparable to controls (38.42 ± 2.88 weeks). While in the moderate/severe category shortness of breath, fever, and cough were the commonest symptoms. Cases (30) had more co-morbidities than controls (16) which were statistically significant. Cases (55%) had more co-morbidities than controls (30%), which were statistically significant. More cases (54%) had caesarean delivery than controls (30%). This was also statistically significant. While maximum cases in the mild category had hospital stay ≤7 days which was comparable to controls. Among labor complications, 3 cases and 4 controls had an antepartum hemorrhage, 3 cases and 3 controls had a postpartum hemorrhage, 2 cases had retained placenta.

Conclusion: The results suggested that the majority of the COVID-19 infected women are asymptomatic, mild category and no adverse maternal–neonatal outcome due to disease at this phase of the pandemic. The adversity of maternal and neonatal outcomes depends on the severity and severity of the disease depends on advanced maternal age and the presence of co-morbidities.

Keywords: COVID-19 in pregnancy, Maternal and neonatal outcome, Medical morbidity, Pregnancy-related morbidity.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a global health crisis. COVID-19 disease was declared as a pandemic on 11th March 2020 by the World Health Organization (WHO), marking a turning point in human lives across the globe. [1] Many countries have witnessed a three-wave pattern in reported

cases of coronavirus disease during the ongoing pandemic, with the first wave before August 2020 followed by the second wave in late August and September 2020 [2] and the third wave in March 2021. [3] India reported its first case of COVID-19 in January 2020 [4] and registered a lower number of daily confirmed cases/million population in comparison to many other countries.

SARS-CoV-2 has human to human transmission and infection occurs due to close contact with infected person or from a contaminated surface or air borne route. [5,6] Vertical transmission (virus transmission from mother to child in antenatal and intrapartum period) is uncommon and in cases where it occurs, it is not associated with mode of delivery, rooming-in and method of feeding. [5] Experience from previous Coronavirus outbreaks in humans of SARS-CoV and MERS-CoV indicates poor outcomes in pregnant patients and their foetuses. Intensive care unit (ICU) admissions are common and mortality rate being as high as 35%. [7,8] Data from various studies on influenza have also shown higher maternal morbidity and mortality in comparison to non-pregnant women like Influenza pandemic (1918) had high maternal mortality rate of 37% when compared to 2.6% mortality rate of overall population. [9-11] During pregnancy physiological changes in the immune and respiratory system like changes in lung volumes, vasodilatation leading to respiratory mucosal oedema and increased respiratory secretions makes pregnant women vulnerable to develop severe disease. [9,12] Likewise, due to immature innate and adaptive immune systems, foetus and neonates are also vulnerable to infections. [13] Human Coronaviruses (HCoV) like 229E, NL63, OC43 and HKU1 primarily infect humans. Certain strains of Coronaviruses infecting animals have evolved and infect humans to cause serious illness. These are known as new HCoV like Middle East respiratory syndrome (MERS-CoV), severe acute respiratory syndrome (SARS-CoV) and SARS-CoV-2 which is causative organism of current COVID-19 pandemic. [14]

Pregnant women are likely to develop a severe illness due to physiological changes in immune and cardiopulmonary systems, after respiratory virus infection. In SARS-CoV and MERS-CoV infections, severe complications occur during the third trimester, like pneumonia, admission to ICU, need for mechanical ventilation with a high fatality rate.

The aim of the present study was to identify maternal and neonatal risks associated with COVID-19 in pregnancy.

Materials and Methods

This case–control study was conducted at the Department of Obstetrics and Gynecology BMIMS, PAWAPURI, Nalanda, Bihar, India. All COVID-19 positive women who delivered for the period of two years were included. During the study period, around 235 pregnant women were COVID-19 positive, of which 30 were discharged undelivered and 5 were spontaneous abortions, so were excluded, 200 were included in the study.

Women with symptoms (e.g., fever, cough, breathlessness), women in close contact with known COVID-19 case, who had a history of travel from high-risk areas, women coming from containment zone having their expected date of delivery within five days were tested by the Indian Council of Medical Research's (ICMR) guidelines. Their throat swab was collected and subjected to RT-PCR test at BMIMS, PAWAPURI, Nalanda, Bihar, India. All women who tested positive were admitted to the dedicated COVID Care Hospital (CCH) which is well equipped with a labor room, operation theatre, and intensive care unit (ICU). In the later part of the pandemic, ICMR approved private laboratories to do tests and Municipal Corporation made it compulsory to test all

pregnant women near their expected date of delivery, so all positive women at other facilities who were referred were also included.

All women were categorized as mild, moderate, and severe depending on their symptoms, comorbidities, and radiological findings as per ICMR guidelines and managed according to protocols given by the Ministry of Health and Family Welfare (MOHFW), Government of India.[15] Women coming in labor were delivered at CCH with all personal protective equipment. Asymptomatic women after investigations (complete blood count, renal function test, liver function test, electrocardiogram) were discharged for home quarantine or shifted to a quarantine center. Symptomatic women were advised to have X-ray chest and oxygen saturation monitoring.

Symptomatic women with comorbidities were advised erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, serum ferritin, D-dimer. Computerized tomography (CT) scan was advised in all symptomatic women who had X-ray changes and low oxygen saturation. Patients were accordingly treated with the anti-COVID-19 treatment protocol, consisting of oxygen therapy, hydroxychloroquine, azithromycin, vitamin C, and zinc tablet. Antiviral therapy (Faviparaivir), injection Remdesivir, steroids, and low-molecular-weight heparin (LMWH) were used when indicated. After delivery, babies were isolated from the mother, throat swab RT-PCR was done at 24 h. All women and their neonates were followed unto discharge and the outcome was noted. Women who delivered during the study period who were COVID-19 negative, after matching age, parity, and gestational age were selected as controls.

Data Collection

Demographic data, symptoms, history of contact, pre-existing medical disease, pregnancy-related disorder, laboratory investigations, classification of category, mode of delivery, and the fetal and maternal outcome noted and filled in pre-designed forms. Proper consent was taken from the women for inclusion in the study.

Patients were considered to be cases if they were RT-PCR positive and delivered at CCH during the study period. Untested patients were eligible to be cases if they were admitted in labor, and tested positive during delivery. Patients were excluded if they were persons under investigation who had negative COVID-19 testing or if they were positive but discharged before delivery. The maternal adverse outcome included length of hospital stay more than 10 days, ICU admission, need for mechanical ventilation, supplemental oxygen, and maternal death. The adverse neonatal outcome included low birth weight, stillbirth, low Apgar score, NICU admission, and neonatal death.

Statistical Analysis

Data was entered in MS Excel, coded, and analyzed in statistical software STATA, version 10.1, 2011. Descriptive statistics were used to summarize quantitative variables with mean and standard deviation, while frequency and percentages were used to summarize categorical (qualitative) variables. Inferential statistics included tests of significance and p-values. The significance of the mean difference in the two groups was tested by a two-independent sample t-test with equal variances. The significance of the difference in proportions in the two groups was assessed by Pearson's Chi-square test or Fisher's exact test (for small frequencies). Risk analysis was performed to quantify associations in terms of odds ratios (OR) along with 95% confidence intervals (CIs). Binary multiple logistic regression analysis was also performed to identify predictors of adverse fetal outcome adjusting odds ratios for maternal and fetal characteristics. A p-value <0.05 was considered statistically significant.

Results

Table 1: Demographic characteristics

Maternal characteristics	Case	Control	p-value
Age in years	27.40 ± 5.130	26.50 ± 4.105	0.930
Parity			
Nulliparous	80 (40)	88 (44)	0.220
Multiparous	120 (60)	112 (56)	
Disease severity			
Mild	192 (96)	190 (95)	0.123
Moderate	6 (3)	8 (4)	
Severe	2 (1)	2 (1)	
Area			
Rural	34 (17)	128 (64)	0.000
Urban	168 (83)	72 (36)	
Gestational age	37.13 ± 2.32	38.42 ± 2.88	0.102

According to disease severity, there were mild 192 cases, moderate 6 cases, and severe 2 cases. Cases were mostly from urban areas showing the trend of positivity in urban areas. Mean gestational age in the cases (37.13 ± 2.32weeks) was comparable to controls (38.42 ± 2.88 weeks).

Table 2: Severity classification, symptoms, and treatment

COVID-19 cases	Mild (n = 192)	Moderate and severe (n = 8)
Severity		
Mild	192 (96%)	–
Moderate	–	6 (3%)
Severe	–	2 (1%)
Symptoms		
Asymptomatic	120 (60%)	1 (0.50%)
Fever	14 (7%)	1 (0.50%)
Cough	16 (8%)	4 (2%)
Sore throat	8 (4%)	6 (3%)
Shortness of breath	1 (0.50%)	
Myalgia	1 (0.50%)	
Diarrhea	2 (1%)	
Labor pains	56 (28%)	
Treatment		
Hydroxychloroquine	3	
Azithromycin	8	
Favipiravir	20	5
LMWH	14	5
Steroids		5
Remdesevir		8
Oxygenation		2
Ventilation		

In mild cases, 60% were asymptomatic and in symptomatic commonest symptoms were fever, cough followed by sore throat, myalgia, and diarrhea and 56 (28%) came with labor pains. While in the moderate/severe category shortness of breath, fever, and cough were the commonest symptoms.

Table 3: Maternal outcome (morbidity and mortality)

Characteristics	Cases (n = 200)	Controls (n = 200)	p-value
Medical morbidity	30 (15%)	16 (8%)	0.03
Pregnancy morbidity	110 (55%)	60 (30)	0.000
Mode of delivery			
Vaginal	90 (45%)	138 (69%)	0.000
Cesarean	108 (54%)	60 (30%)	
Instrumental	2 (1%)	2 (1%)	
Duration of hospital stay			
≤7days	140 (70%)	192 (96%)	0.001
8–14 days	50 (25%)	8 (4%)	
>14 days	10 (5%)	0	
Labor complication			
APH	3	4	0.3
PPH	3	3	
Retained placenta	2	0	
ICU admission	1	3	
Mortality	1	3	

Cases (30) had more co-morbidities than controls (16) which were statistically significant. Patients in both groups had pregnancy-related conditions like hypertensive disorders, gestational diabetes, previous cesarean, preterm labor, fetal growth restriction, liquor abnormalities, malpresentation, and multiple pregnancies. Few of them had more than one disorder. Cases (55%) had more co-morbidities than controls (30%), which were statistically significant. More cases (54%) had caesarian delivery than controls (30%). This was also statistically significant. Length of hospital stay was more in cases than controls; this is because of added morbidity due to disease. This was also statistically significant. All cases in the moderate category had hospital stay more than 14 days, while severe the case died on the 14th day. While maximum cases in the mild category had hospital stay ≤7 days which was comparable to controls. Among labor complications, 3 cases and 4 controls had an antepartum hemorrhage, 3 cases and 3 controls had a postpartum hemorrhage, 2 cases had retained placenta.

Table 4: Neonatal outcome

Neonatal outcome	Case (n = 200)	Control	p-value
Birth weight (kg)	2.4 ± 0.55	2.6 ± 0.60	0.03
Stillbirth	6	6	1
NICU admission	10	12	0.5
Neonatal death	1	4	1

Mean birth weight was 2.4 ± 0.55 kg in cases and 2.6 ± 0.60 kg in controls which was statistically significant (p-value = 0.003). There were six stillbirths in each group. The underlying cause of stillbirth was being pre-eclampsia and intrauterine growth restriction. A total of 10 in cases and 12 in controls were transferred to NICU due to low birth weight, prematurity, respiratory distress syndrome, meconium aspiration syndrome, hypoxic-ischemic encephalopathy, or hyperbilirubinemia. There was one neonatal death in cases on the 4th day due

to severe birth asphyxia and 4 deaths in the control group. In cases, there was one stillbirth in the moderate/severe group, while three babies no morbidity. Four babies were COVID-19 positive after birth in cases; these babies were of mothers whose COVID-19 report came after delivery and were not separated from mother, all were healthy at discharge from hospital. Those babies who were separated from their mother at birth, none were positive.

Discussion

7Pregnant women are likely to develop a severe illness due to physiological changes in immune and cardiopulmonary systems, after respiratory virus infection. In SARS-CoV and MERS-CoV infections, severe complications occur during the third trimester, like pneumonia, admission to ICU, need for mechanical ventilation with a high fatality rate. [15] Currently, there is no evidence that pregnant women are more susceptible to COVID-19 infection or are more prone to developing severe pneumonia. [16]

According to disease severity, there were mild 192 cases, moderate 6 cases, and severe 2 cases. Cases were mostly from urban areas showing the trend of positivity in urban areas. Mean gestational age in the cases (37.13 ± 2.32weeks) was comparable to controls (38.42 ± 2.88 weeks). Pre-pregnancy chronic diseases like diabetes and chronic hypertension are considered as risk factors for getting infected and hospitalization according to RCOG. [17] In mild cases, 60% were asymptomatic and in symptomatic commonest symptoms were fever, cough followed by sore throat, myalgia, and diarrhea and 56 (28%) came with labor pains. While in the moderate/severe category shortness of breath, fever, and cough were the commonest symptoms which was similar to the PregCOV-19 Living Systematic Review with 74% pregnant women with SARCoV-2 infection being asymptomatic. [18] The main findings in our study were that majority of women who come with COVID-19 infection are in the mild category and asymptomatic. This may be because as universal testing became mandatory more asymptomatic cases were diagnosed. Due to this, as compared to the number of asymptomatic cases the severe cases of Covid bronchopneumonia are less in this part if India. This may be because as universal testing became mandatory more asymptomatic cases were diagnosed. Fever, cough, and sore throat were common symptoms. This was similar to other studies carried out in China. [19,20]

Length of hospital stay was more in cases than controls; this is because of added morbidity due to disease. This was also statistically significant. All cases in the moderate category had hospital stay more than 14 days, while severe the case died on the 14th day. While maximum cases in the mild category had hospital stay ≤7 days which was comparable to controls. Among labor complications, 3 cases and 4 controls had an antepartum hemorrhage, 3 cases and 3 controls had a postpartum hemorrhage, 2 cases had retained placenta. One study had hospital stays ranging from 3 to 26 days median being 6.5 days. [19] Adverse maternal outcomes, in terms of increased hospital stay, operative delivery, preterm labor, admission to ICU, ventilation, are mere common in moderate/severe cases than mild cases. The adverse maternal outcome increases with age, presence of medical morbidity, and the severity of the disease. Adverse neonatal outcomes in terms of low birth weight, stillbirth, NICU admission, and neonatal death were not more due to the disease. Maternal and neonatal outcome in the severe category was adverse in terms of mortality while in moderate category fetal outcome was good and there was maternal morbidity in terms of increased hospital stay. A study carried out in India showed that there is no effect of COVID-19 infection on maternal and perinatal outcome. [21] Overall there was no

increased maternal and neonatal adverse outcome, and it is determined by the severity of the disease. Other studies also had similar findings. [19, 22] Wong et al studied maternal and perinatal outcome of 12 women with SARS in 2003 in Hong Kong and concluded high incidence of preterm birth (4/5 patients after 24weeks), 57% incidence of spontaneous abortion in first trimester (4/7), 2 cases of foetal growth restriction in second and third trimester and high case fatality rate of 25% (3/12) and no newborn had perinatal SARS infection. [23] Alfaraj et al reported mortality of 27%, foetal demise in 27% and 54% patients requiring ICU admission in 11 pregnant patients with MERS. [24,25]

Conclusion

The results suggested that the majority of the COVID-19 infected women are asymptomatic, mild category and no adverse maternal–neonatal outcome due to disease at this phase of the pandemic. The adversity of maternal and neonatal outcomes depends on the severity and severity of the disease depends on advanced maternal age and the presence of co-morbidities. Regular screening of women to detect coronavirus infection early will avoid complications and reduce the severity and improve maternal and fetal outcomes.

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