e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(9); 899-906

Original Research Article

A Study on Neonatal Outcome Due to Placental Infection during Severe COVID-19

Alka Jaiswal[1], Ashvini Bhatnagar[2], Utsav Singh[3]

[1]Associate Professor, Department of Obstetrics and Gynecology, United Institute of Medical Sciences, Prayagraj, India

[2]Assistant Professor, Department of Obstetrics and Gynecology, United Institute of Medical Sciences, Prayagraj, India

[3]Senior Medical Officer, Nodal Officer, Covid-19 Centre, Prayagraj, India

Received: 11-06-2022 / Revised: 12-07-2022 / Accepted: 09-08-2022
Corresponding author: Alka Jaiswal
Conflict of interest: Nil

Abstract

Introduction: COVID-19 pandemic has severe consequences for the whole world. Each age group has been affected. Both the pediatric and geriatric populations have been worst affected by COVID-19. Even pregnant females were affected much and especially the neonates of pregnant women with COVID-19. The vulnerability increases in neonates of mothers with COVID-19. There is less literature and guidelines available which discussed the outcomes of neonates of mothers who had COVID-19 during gestation.

Aims and Objectives: To find out the effect on the fetus of mothers, who were infected with COVID-19 during gestation.

Method: This is a retrospective study which considered 120 pregnant women, comprising 60 pregnant females with COVID-19 (study group) and another 60 pregnant females without COVID-19 (control group). The baseline characteristics were obtained from the hospital in both groups and the outcomes were evaluated and analyzed.

Results: The study found that there are significant differences between the two groups in gestational age at the time of delivery, premature delivery occurred and neonatal death ($p<0.05$).

Conclusion: The study has concluded that the presence of COVID-19 in pregnant females caused placental infection affecting the fetus significantly, as evidenced by premature birth and neonatal deaths among the COVID-19 group.

Keywords: COVID-19, gestation, pregnancy, fetus, premature birth

Introduction

In late 2019 [1-3], the COVID-19 disease was discovered, with severe respiratory effects. It is now known as COVID-19 and was brought on by a fresh coronavirus mutation [1,4]. As of September 25, 2021, there were 230 million cases of the viral outbreak over the world [5]. One in 200 pregnant women has COVID-19 during their pregnancy, according to estimates [6]. The effects of potential vertical transmission are unknown through a placental infection, inflammation, and the

fetoplacental defense mechanisms in cases of maternal COVID-19 infection [7]. The viral genomes of this novel coronavirus and the SARS-CoV and MERS-CoV, which were responsible for the severe acute respiratory syndrome (SARS) and middle-east respiratory syndrome, respectively, share 80% and 50% similarities, respectively [8]. Pre-eclampsia, preterm birth, stillbirth, small-for-gestational-age, and low birth weight are just a few of the unfavourable obstetrical and neonatal outcomes that have been linked in the past to maternal infection and systemic inflammation [9]. This is because these outcomes are caused by interruptions in placental hemodynamics. Again, elevated estrogen during pregnancy causes physiological changes like the elevated diaphragm in response to the accommodation of the growing fetus, which lowers the pulmonary functional residual volume and causes mucosal oedema and friability in the respiratory tract. These pulmonary alterations and decreased cell immunity may put pregnant women at increased risk for serious viral pneumonia infections, which could have negative effects on the pregnancy [10]. By attaching its spike protein to angiotensin-2 converting enzyme (ACE2) receptors, COVID-19 enters host cells. The spike protein is primed by cell surface protease TMPRSS2. Transplacental transmission has been considered to be a feasible vertical transmission mechanism because ACE2 and TMPRSS2 have been demonstrated to be expressed on trophoblasts in the placenta, theoretically making the placenta susceptible to SARS-CoV-2 infection [11]. The co-expression of ACE2 and TMPRSS2 by placental cells has, however, been the subject of conflicting reports. While some groups claim that coexpression occurs in syncytiotrophoblasts during the first trimester of pregnancy and in extravillous trophoblasts during the second, others claim that coexpression of ACE2 and TMPRSS2 could be recognizable throughout the entire pregnancy [12]. Before a transplacental infection can occur, the virus must be present in the blood. Although viremia was observed in the majority of COVID-19 -infected patients, it is more common in COVID-19-infected patients who are extremely unwell, and it appears to be less common in pregnant COVID-19-infected patients [13]. The cervicovaginal route of vertical transmission, which exposes newborns to infected cells during delivery, was briefly considered as another mechanism because it is relevant to other viruses [11].

Numerous investigations have documented the occurrence of COVID-19 infection in neonates of COVID-19-positive mothers. The placenta is also abundantly found to contain the ACE-2 receptors, with which COVID-19 interacts in order to enter cells, indicating the biological plausibility of intrauterine Trans placental vertical transmission [14]. However, due to the absence of COVID-19 in samples of amniotic fluid, cord blood, and breast milk, some investigations questioned the viability of vertical transmission, whether it occurred through the placenta, after vaginal delivery, or during breastfeeding [15]. There are contradictory reports of viral positivity of placentas from COVID-19-positive pregnant patients, and not all infants delivered to these mothers will test positive for the virus. This implies that the presence or absence of specific receptors or signalling pathways may determine whether a protective mechanism or barrier within the placenta is successful. No report of congenital abnormality has been found [16]. Thus, by thoroughly evaluating the most recent information available, this study seeks to identify the probable neonatal consequences linked to a COVID-19-infected pregnancy.

Materials and Methods

Research Design

A retrospective study was conducted whose data comprised patients who visited our hospital from July 2021 to June 2022. This

study considered 120 pregnant females, who were admitted to gynecology and obstetrics either with COVID-19 or without it. A detailed medical history of the pregnant females was taken and examined. All the females included in the study were tested for COVID-19 through swab collection from the nasopharynx.

The patients with COVID-19 were confirmed by obtaining their RT-PCR results. The study considered 60 pregnant females with confirmed COVID-19 (Study group) and another 60 pregnant females without COVID-19 (Control group). A sample of formalin-fixed placental tissue with paraffin-embedded were collected from all the patients in the hospital. The study has obtained records of each parameter from the hospital. The baseline characteristics were obtained from the hospital in both groups and the outcomes were evaluated and analyzed.

Collection of Data

The study considered every data from the hospital related to their basic characteristics, placenta, the outcome of the pregnancy and the outcome of mother and fetus. Also, the comorbidities like hypothyroidism, scleroderma, and anaemia were collected. The symptoms like fever, cough, cold, fatigue and myalgia were examined in all the patients. The baseline characteristics were obtained by the hospital during the start of their treatment. The outcome data were obtained when the patients have finally had labour or cesarean section and the fetal status was recorded.

Inclusion and Exclusion Criteria

The pregnant females who came to the outpatient department of the gynaecology and obstetrics department of the hospital were included in the study. The included patients are those who visited the follow-up check and gave informed consent to our study. The study considered 120 such patients. Patients with COVID-19 or without COVID-19 were both included. The females who did not complete the protocol of the study or did not follow up on the study were excluded. The study also excluded the patients who did not provide informed consent and also who have other co-morbidities like chronic asthma or COPD.

Ethical Approval

The authors obtained consent from each patient for using their data in the study. Each patient has explained the study process and its intention. The study process has been approved by the Ethical Committee of the hospital and the concerned university.

Statistical Analysis

The study used SPSS 25 and excel software for effective statistical analysis. The continuous variables were expressed as mean±standard deviation. The outcome parameters were analyzed using ANOVA between two groups (study group and control group). The level of significance was considered to be $\alpha=0.05$.

Results

The females with COVID-19 (study group) show all the symptoms like fever, cough, cold, dyspnea, myalgia, ageusia, fatigue, and altered state of mind which are absent in the control group. The comorbidities like asthma, anaemia and hypothyroidism are seen in positive patients whereas scleroderma is resent in the control group. Pregnancy complications like fetal complications, gestational cholestasis, and AF anomalies are increasingly seen in study group patients.

Table 1: Emergency department and hospital characteristics of study cohorts

Parameters	Study Group (COVID-19 patients)	Control Group
No. of patients	60 (50%)	60 (50%)
Age, years	29.5±2.6	30.8±3.1
Gestational age during the time of admittance (weeks)	35.96±0.69	36.1±0.8
Smoker	2 (3.3%)	0 (0)
BMI (kg/m2)	26 (25-33)	24 (23-28)
Comorbidities		
Hypothyroidism	5 (8.3%)	0 (0)
Anaemia	4 (6.6%)	0 (0)
Adrenogenital syndrome	4 (6.6%)	0 (0)
Pregnancy complications		
Gestational diabetes	7 (11.6%)	13 (21.6%)
Gestational cholestasis	5 (8.3%)	0 (0)
Intrauterine growth retardation	0 (0)	3 (5%)
Amniotic fluid anomalies	7 (11.6%)	0 (0)
Premature rupture of membrane	7 (11.6%)	8 (13.3%)
Preterm - PROM	5 (8.3%)	5 (8.3%)
Fetal complications	7 (11.3%)	0 (0)
Indication for nasopharyngeal swab at ED presentation		
Screening	27 (45%)	57 (95%)
Signs and symptoms	36 (60%)	5 (8.3%)
Fever	21 (35%)	0 (0)
Cough	25 (41.6%)	4 (6.6%)
Dyspnea	12 (20%)	5 (8.3%)
Myalgia	7 (11.6%)	0 (0)
Anosmia	4 (6.6%)	0 (0)
Ageusia	5 (8.3%)	0 (0)
Indication for nasopharyngeal swab during hospitalization		
Intestitial pneumonia	21 (35%)	0 (0)
Pulmonary thromboembolism	7 (11.6%)	0(0)
Respiratory failure	8 (13.3%)	0(0)
Transfer to ICU	7 (11.6%)	5 (8.3%)
Respiratory support		
Oxygen therapy	12 (20%)	5 (8.3%)
Non-invasive ventilation	9 (15%)	0 (0)
Invasive ventilation	4 (6.6%)	5 (8.3%)
Pharmacological therapy		
Low-molecular-weight heparin	41 (68.3%)	23 (38.3%)
Before delivery	7 (11.3%)	0 (0)
After delivery	42 (70%)	23 (38.3%)

The study found that there is a significant difference between the two groups in gestational age at the time of delivery (p<0.05). The study also found that COVID-19 infection did not cause direct harm to the fetus as the placenta played a

role in providing barrier function but due to the placental infection, there were consequences caused to the fetus like premature delivery occurred significantly more in the study group as compared to control group (p<0.05). Neonatal death was also found to be significant in the study group as compared to the control group (p<0.05).

Table 2: Postpartum outcomes for mothers and newborns

Parameters	Study Group (COVID-19 patients)	Control Group	*p*-value
No. of patients	60 (50%)	60 (50%)	
Gestational age at delivery (gw+days)	35±0.8	39.9±0.7	p<0.05
Symptoms onset to delivery (days)	10 (5-12)	Not applied	
Confirmed diagnosis to delivery (days)	3 (2-7)	Not applied	
Premature delivery (<37 weeks)	18 (30%)	13 (21.6%))	p<0.05
Mode of delivery			
Vaginal delivery	42 (70%)	20 (33.3%)	p>0.05
Cesarean section	5 (8.3%)	38 (63.3%)	p>0.05
Spontaneous labour	21 (35%)	20 (33.3%)	p>0.05
Labour by induction	41 (68.3%)	4 (6.6%)	p>0.05
Maternal indication for labour induction			
SARS- CoV-2 infection	10 (16.3%)	Not applied	
Obstetrical indication for labour induction			
AF abnormalities	7 (11.6%)	0(0)	p>0.05
Fetal malformation	4 (6.6%)	0 (0)	p>0.05
Therapeutic miscarriage	4 (6.6%)	0 (0)	p>0.05
Suspected chorioamnionitis	0 (0)	0 (0)	p>0.05
Type of cesarian section			
Elective	27 (45%)	25 (41.3%)	p>0.05
Emergency	35 (58.2%)	37 (61.3%)	p>0.05
Indication for cesarean section			
Elective	27 (45%)	25 (41.3%)	p>0.05
Emergency	35 (58.2%)	37 (61.3%)	p>0.05
Indication for cesarean section			
Maternal request	7 (11.6%)	5 (8.3%)	p>0.05
Previous cesarean section	7 (11.6%)	5 (8.3%)	p>0.05
IUGR	0 (0)	5 (8.3%)	p>0.05
Uterine malformation	0 (0)	5 (8.3%)	p>0.05
Fetal distress	7 (11.3%)	16 (26.3%)	p>0.05
Symptomatic infection	4 (6.6%)	Not applied	
Symptomatic COVID-19 infection and previous CS	4 (6.6%)	Not applied	
Neonatal outcome			
Apgar score, in 1st minute	9.7±0.24	10.1±0.21 (7-9)	p>0.05
Apgar score, 5th minute	11.98±1.25	12.75±0.4	p>0.05
Newborn birth weight (g)	3030 (2550-3370)	3040	p>0.05
Placental weight (g)	510.62±12.74	540.36±9.54	p>0.05
Neonatal arterial pH	7.5±0.1	7.4±0.3	p>0.05
Neonatal death	8 (13.3%)	0	p<0.05

Discussion

A study shows that 17 out of 164 women tested positive for COVID-19 (10.3%) in the first trimester, according to a study by Cosma et al. One woman who gave birth at another hospital and tested positive for COVID-19 was excluded. Composite adverse obstetric outcomes were seen in 6.2% (1/16) COVID-19-positive and 10.5% (11/105) COVID-19-negative women, as well as 12.5% (2/16) and 7.6% (8/105), respectively, in composite adverse neonatal outcomes [17]. The same antibodies were found in arterial cord blood of neonates of women who had developed IgG antibodies, while the nasopharyngeal swab test for COVID-19 was negative. There were no reports of maternal pneumonia or hospitalization related to coronavirus disease-19. As would be predicted in women who were infected early during pregnancy, rectal swabs taken at delivery were negative, and COVID-19 faecal contamination of the neonatal or/nasopharynx during vaginal birth was excluded. When COVID-19-positive women were compared to a group of COVID-19-negative women who were matched for gestational age, the rates of composite adverse obstetric and neonatal outcomes were not statistically different [18].

Additionally, we discovered that between 76% and 85% of babies born to COVID-19-positive mothers had birthweights greater than 2500 g [19]. The average weight at birth ranged from 2590 to 3436 grams. Compared to babies born to COVID-19 asymptomatic mothers, neonates from symptomatic COVID-19 mothers had lower birth weights [19,20]. The median and mean birth weights were 3120g and 3144.71g, respectively, which was similar to the results of prior systematic reviews. Even though the findings were encouraging, it was indicated that women who contracted COVID-19 early in pregnancy or who had chronic hypoxia needed more frequent monitoring of the foetal growth to check for intrauterine growth restriction or retardation [18,21]. However, Tadas et al. found that neonates of COVID-19-positive mothers had a statistically significant greater mean birthweight than the controls. The variation in socioeconomic level and baseline nutrition was blamed for the disparity, as the majority of patients were from metropolitan regions with acceptable nutrition [13]. According to studies, newborns with low 5-minute Apgar scores had a 20–100-fold higher relative chance of developing cerebral palsy than those with high scores of 7–10 [22]. In line with recent systematic reviews [22], the majority of neonates born to COVID-19-positive mothers have an excellent Apgar score of greater than 7 at 1-minute and 5-minute. According to Verma et al., both asymptomatic and symptomatic COVID-19-positive pregnant women had similar APGAR ratings [23]. If the neonates were born prematurely, it was believed that a low Apgar score in newborns of COVID-19-positive mothers was secondary to pulmonary immaturity. The majority of the infants in our review were delivered by caesarean section. The increasing rate of cesarean births was justified by the need to lessen both the strain on women during labour and the danger of infection from COVID-19-positive women. However, according to recent recommendations, COVID-19 infection should not be the only factor considered, when deciding whether to have a caesarean section or have a premature baby [24]. The rates of neonatal COVID-19 infection in a Spanish investigation with a 6.9% (5/72) infection rate for vaginal births and caesarean sections were not different [25]. Maternal disease severity and comorbidities, maternal and fetal condition, and gestational age should all be considered when deciding whether to have a caesarean section [25]. The safety of vaginal delivery has been substantiated by studies since no samples of vaginal secretions from pregnant women who tested positive for

COVID-19 also tested negative for COVID-19 [26,27]. Additionally, it was discovered that exposure to maternal vaginal secretions was linked to the emergence of an immunogenic response in newborns [27,28].

Conclusion

The study has concluded that there is not much evidence of vertical transmission of the fetus, although, the presence of COVID-19 in pregnant females caused the placental infection, which in turn, caused significant harm to the fetus, mainly evidenced by premature birth. Finally, there was a significant number of neonatal deaths among the COVID-19 group while there was not a single death in the control group. There is a need to carry out more studies with varied populations for better conclusions. This current study has highlighted important findings regarding fetal status in COVID-19 and recommends adopting higher prevention techniques for COVID-19 among the pregnant population.

Reference

1. Wang C.L., Liu Y.Y., Wu C.H., Wang C.Y., Wang C.H. and Long, C.Y. Impact of COVID-19 on Pregnancy. International Journal of Medical Sciences, 2021;18: 763-767.
2. Ahn D.G., Shin H.J., Kim M.H., Lee S., Kim H.S., Myoung J., et al. Current Status of Epidemio -logy, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). Journal of Microbiology and Biotechnology, 2020;30: 313-324.
3. Mohamadian M., Chiti H., Shoghli A., Biglari S., Parsamanesh N. and Esmaeilzadeh, A. COVID-19: Virology, Biology and Novel Laboratory Diagnosis. The Journal of Gene Medicine, 2021;23: Article No. e3303.
4. World Health Organization (WHO) WHO Coronavirus (COVID-19) Dashboard. World Health Organization, Genava. 2020.
5. Abedzadeh-Kalahroudi M., Sehat M., Vahedpour Z. and Talebian P. Maternal and Neonatal Outcomes of Pregnant Patients with COVID-19: A Prospective Cohort Study. International Journal of Gynecology & Obstetrics, 2021;153: 449-456.
6. Figueiro-Filho E.A., Yudin M. and Farine D. COVID-19 during Pregnancy: An Overview of Maternal Characteristics, Clinical Symptoms, Maternal and Neonatal Outcomes of 10,996 Cases Described in 15 Countries. Journal of Perinatal Medicine, 2020;48: 900-911.
7. Lu R., Zhao X., Li J., Niu P., Yang B., Wu H., et al. Genomic Characterisation and Epidemiology of 2019 Novel Coronavirus: Implications for Virus Origins and Receptor Binding. Lancet, 2020;395: 565-574.
8. Yao W.L., Qiu J.C., Xiao Z.R. and Ouyang S. Pregnancy and COVID-19: Management and Challenges. Revista do Instituto de Medicina Tropical de São Paulo, 2020;62: Article No. e62.
9. Goldenberg R.L., Culhane J.F., Iams J.D. and Romero R. Epidemiology and Causes of Preterm Birth. Lancet, 2008;371: 75-84.
10. Chawanpaiboon S., Vogel J.P., Moller A.B., Lumbiganon P., Petzold M., Hogan D., et al. Global, regIonal, and National Estimates of Levels of Preterm Birth in 2014: A Systematic Review and Modelling Analysis. The Lancet Global Health, 2019;7: e37-e46.
11. Akhtar H., Patel C., Abuelgasim E. and Harky A. COVID-19 (COVID-19) Infection in Pregnancy: A Systematic Review. Gynecologic and Obstetric Investigation, 2020;85: 295-306.
12. Kyle MH, Hussain M, Saltz V, Mollicone I, Bence M, Dumitriu D. Vertical Transmission and Neonatal Outcomes Following Maternal COVID-19 Infection During Pregnancy. Clinical Obstetrics and Gynecology. 2022 Mar;65(1):195.
13. Phoswa W.N. and Khaliq O.P. Is

Pregnancy a Risk Factor of COVID-19? European Journal of Obstetrics & Gynecology and Reproductive Biology, 2020;252: 605-609.
14. Salem D., Katranji F. and Bakdash T. COVID-19 Infection in Pregnant Women: Review of Maternal and Fetal Outcomes. International Journal of Gynecology & Obstetrics, 2021;152: 291-298.
15. Robbins JR, Bakardjiev AI. Pathogens and the Placental Fortress. Curr Opin Microbiol. 2012;15(1):36–43.
16. Cosma S, Carosso AR, Cusato J, Borella F, Bertero L, Bovetti M, Bevilacqua F, Mengozzi G, Mazzone R, Ghisetti V, Di Perri G. Obstetric and neonatal outcomes after SARS-CoV-2 infection in the first trimester of pregnancy: A prospective comparative study. Journal of Obstetrics and Gynaecology Research. 2022 Feb; 48(2):393-401.
17. Saccone G., Sen C., Di Mascio D., Galindo A., Grunebaum A., Yoshimatsu, J., et al. Maternal and Perinatal Outcomes of Pregnant Women with COVID-19 Infection. Ultrasound in Obstetrics & Gynecology, 2021;57: 232-241.
18. Khong J, Teoh J, Hashim SS, Jahan NK. Neonatal Outcomes of COVID-19 Positive Pregnant Women: A Systematic Review. Open Access Library Journal. 2021 Sep 29;8(10):1-24.
19. Tadas M.P., Prashanthi S. and Waikar M. Maternal and Neonatal Outcomes of Pregnant Women with Covid-19: A Case-Control Study at a Tertiary Care Center in India. Journal of South Asian Federation of Obstetrics and Gynaecology, 2021;13: 44-49.
20. Ehrenstein V. Association of Apgar Scores with Death and Neurologic Disability. Clinical Epidemiology, 2009; 1: 45-53.
21. Moster D., Lie R.T., Irgens L.M., Bjerkedal T. and Markestad, T. The Association of Apgar Score with Subsequent Death and Cerebral Palsy: A Population- Based Study in Term Infants. The Journal of Pediatrics, 2001;138: 798-803.
22. Lie K.K., Grøholt E.K. and Eskild A. Association of Cerebral Palsy with Apgar Score in Low and Normal Birthweight Infants: Population Based Cohort Study. BMJ, 2010;341: Article No. c4990.
23. Dubey P., Reddy S.Y., Manuel S. and Dwivedi A.K. Maternal and Neonatal Characteristics and Outcomes among COVID-19 Infected Women: An Updated Systematic Review and Meta-Analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2020;252: 490-501.
24. Verma S., Bradshaw C., Auyeung N.S.F., Lumba R., Farkas J.S., Sweeney, N.B., et al. Outcomes of Maternal-Newborn Dyads after Maternal COVID-19. Pediatrics 2020;146: Article ID: e2020005637.
25. Dube R. and Kar S.S. COVID-19 in Pregnancy: The Foetal Perspective—A Systematic Review. BMJ Paediatrics Open, 2020;4: Article ID: e 000859.
26. Qi H., Luo X., Zheng Y., Zhang H., Li J., Zou L., et al. Safe Delivery for Pregnancies Affected by COVID-19. BJOG: An International Journal of Obstetrics & Gynaecology, 2020;127: 927-929.
27. Penfield C.A., Brubaker S.G., Limaye M.A., Lighter J., Ratner A.J., Thomas K.M., et al. Detection of Severe Acute Respiratory Syndrome Coronavirus 2 in Placental and Fetal Membrane Samples. American Journal of Obstetrics & Gynecology MFM, 2020;2: Article ID: 100133.
28. Mahgoob N., & Saber Ali D. M. Acute Appendicitis Due to Missed Intrauterine Contraceptive Device/A Case Report and Literature Reviews. Journal of Medical Research and Health Sciences, 2022;5(8): 2177–2181.