ONLINE FIRST

ORIGINAL ARTICLE

Clinico Demographic profile and outcome of neonates born to mothers with COVID-19 infection at a Tertiary Care Hospital

Farhana Zafar[1], Shaista Ehsan[2], Lubna Khan[1], Bina Fawad[3]

1. Department of Pediatrics, Dr. Ziauddin Hospital, North Nazimabad, Karachi, Sindh-Pakistan.
2. Department of Pediatrics, Dr. Ziauddin Hospital, Clifton, Karachi, Sindh-Pakistan. 3. Department of Community Health Sciences, Ziauddin Medical College, Karachi, Sindh-Pakistan.

(Corresponding Author)

Dr. Shaista Ehsan
Associate Professor
Department of Pediatrics, Dr. Ziauddin University Hospital
4/B Shahrah-e-Ghalib Rd, Block 6 Clifton
Karachi 75600
Email: shaistaehsan@yahoo.com

ABSTRACT

OBJECTIVE: To determine the Clinico-demographic profile and outcome of neonates born to mothers with COVID-19 infection at a Tertiary Care Hospital.

METHODOLOGY: This cross-sectional study was conducted at Pediatrics Department, Ziauddin Hospital Karachi from March 2020 to August 2021. Sample size was 31, and a nonprobability purposive sampling technique was used. Neonates of COVID positive mothers who consented to Covid -19 testing were included. Neonates of Covid positive mothers who refused to participate were excluded. Diagnosis of coronavirus infection was based on Novel Corona Virus-2019 (nCoV-19) qualitative PCR test through the nasopharyngeal swab. Data regarding clinico-demographic profile and outcome of neonates recorded on a self-developed proforma. Standard protocols were followed per National Command and Operation Center guidelines. Data analyzed by SPSS version 20. Frequencies and percentages were calculated, chisquare test was applied as a significance test with a P-value of <0.05

RESULTS: First virology test was positive for 6 (19.4%) neonates, and second was positive for only 1 (3.2%) neonate; 17 (54.8%) neonates who were negative in the first virology test and stayed less than three days in the hospital refused to undergo a second test by their parents. After 14 days on follow-up 29 (93.5%) neonates became asymptomatic while 2 (6.5%) had symptoms of neonatal respiratory distress and required admission in the neonatal intensive care unit..

CONCLUSION: Vertical transmission of covid-19 can occur if the mother acquires infection in the last trimester. However, these infected neonates morbidity and mortality rate is negligible; therefore, breastfeeding and rooming should be encouraged.

KEYWORDS: COVID-19; neonates; Coronavirus; outcome; vertical transmission; respiratory distress; neonatal intensive care unit; Polymerase chain reaction; mortality

INTRODUCTION

The Corona Virus infection originated in Wuhan, China, and became a pandemic. The World Health Organization (WHO) officially named the novel coronavirus disease Corona Virus Disease 19 (COVID-19). Corona (SARS-Cov2) is an enveloped RNA virus that causes respiratory, gastrointestinal, hepatic, and neurological manifestations in varying degrees[1]. The time lapse between exposure and the appearance of symptoms of COVID-19 infection is two weeks but usually, patients present in the first week. Symptoms such as high body temperature, dry cough, headache and muscle aches are universally present. There is little understanding of the clinical spectrum of this disease in neonates and children. Initial research data from China showed that severe acute respiratory syndrome coronavirus (COVID-19) infection could harm pregnant women. However, newborns did not show clinical manifestations, and viral testing results were negative[2]. Though most studies suggest that vertical transmission of this infection is relatively weak, there are few case reports of neonates with early positive testing offering inutero transmission of the infection[3].

Despite a significant increase in both the incidence and prevalence of Coronavirus infection, there is limited data on the in-utero transfer of the virus from the mothers to infants during pregnancy, at the time of delivery or soon after. Feto-maternal transfer of the virus is possible as its genetic material has been detected in body fluids. Still, due to a high rate of false positive results, the mere detection of specific IgM antibodies on testing is insufficient evidence of infection[4]. Studies have also reported that lactation does not pose a risk of infection in babies of mothers with COVID-19 disease; therefore, breastfeeding is recommended. Research literature reports that infection in late pregnancy can lead to premature labor, neonatal respiratory difficulty, thrombocytopenia and low oxygen saturation in neonates and also increases the risk of unfavourable perinatal occurrences[5] These neonates may develop breathing problems, cyanosis, increased work of breathing, and rapid heartbeat, temperature instability, decreased oral intake, drowsiness and gut issues such as emesis, loose stools and increased abdominal girth. A few can also experience acute respiratory distress syndrome (ARDS)[6,7].

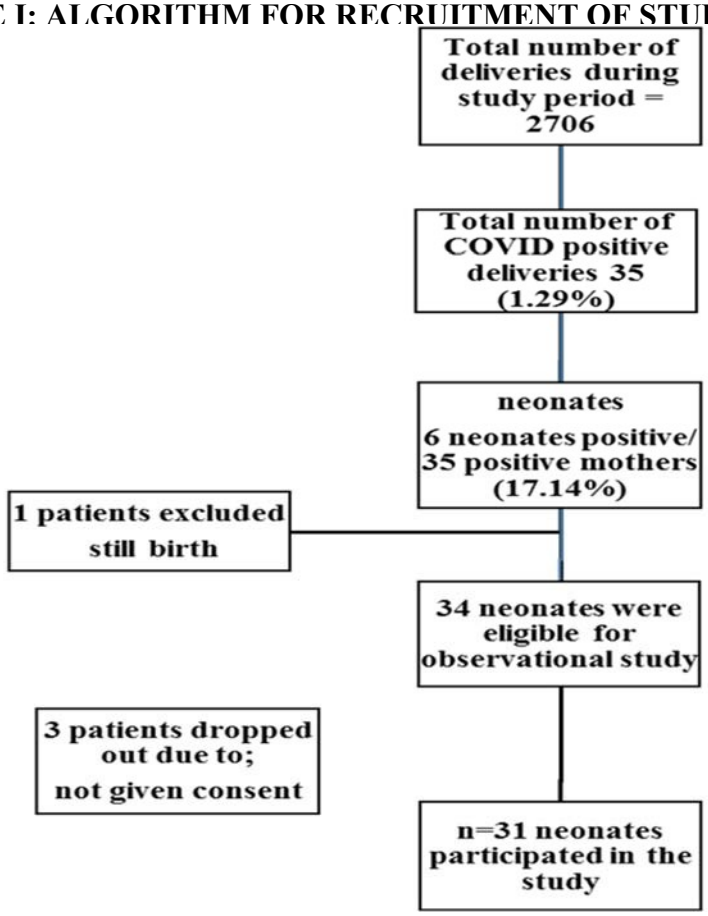
Babies born at appropriate gestational age to mothers who test positive primarily do not exhibit signs or symptoms[8]. Maternal vaccination in the antenatal period effectively reduces the risk of severe infection and pregnancy-related complications, especially in those with coexisting chronic diseases.[9]Nasopharyngeal swabs are the most common way of sampling, but its "positive detection rate" is less than 50%, so it needs to be repeated. Most studies have not suggested that infection can be transferred in utero from mothers to neonates. However, it is essential to analyze additional cases to determine if this remains true[10,11]. Therefore, this study is being conducted considering the existing shortage of research data, especially in the local context on the clinical presentation and outcome in babies with maternal infection. Moreover, testing neonates born to infected mothers helps better understand the disease pattern and aids in making informed decisions about instituting protective plans for better postnatal care.

METHODOLOGY

This prospective cross-sectional study was conducted at the Pediatric Unit of Ziauddin University Hospital Karachi from March 2020 to August 2021. The sample size was calculated following the results of **Anand et al.**[12]. By keeping a frequency of 2.3%; our total estimated sample size was n= 31 at a 95% confidence interval and 5% margin of error. For recruiting participants, a non-probability purposive sampling technique was used.

Newborns of COVID positive mothers of either gender and whose parents consented to conduct COVID-19 PCR tests in neonates were included. Newborns whose parents were unwilling to participate in the study were excluded.

FIGURE I: ALGORITHM FOR RECRUITMENT OF STUDY PARTICIPANTS



Data was collected on a pre-designed proforma from parents/caregivers of neonates meeting the inclusion criteria and born to COVID-19-positive mothers admitted for delivery at Ziauddin hospital. Diagnosis of coronavirus infection in the mother and baby was based on Novel Corona Virus-2019 (nCoV-19) Qualitative polymerase chain reaction PCR (COVID-19) test through the nasopharyngeal swab. Antigen Detection Rapid Test (Ag-RDT) through nasopharyngeal swabs was considered for diagnosis for emergency surgeries. Informed and written consent was taken from the patient's parents/guardian. After taking detailed history and examination, a duty pediatric team member recorded the mother's and neonate's demographic and clinical features on the pre-designed proforma. Neonatal clinicians attended deliveries with all due precautions for Infection-control as per the hospital infection control policy. In babies with a potential requirement for resuscitation, measures were taken according to the hospital infection control policy.

Infants born at term to Covid-positive mothers were kept with mothers if the neonates were asymptomatic. A post-discharge telephone follow-up was performed by one of the pediatric residents. The newborns were bathed within 4 hours after Birth to remove the virus potentially present on skin surfaces. The clinical staff ensured the use of Droplet and Contact precautions until the newborn virology status was known to be negative by COVID-19 PCR testing. Hospitalization of neonates was done if they were symptomatic or their guardians wanted a hospitalized quarantine. Symptomatic and preterm neonates born to Covid -19 positive mothers were admitted to specific isolation areas physically separate from other newborns whose mothers were COVID Negative.

Maternal infection status was assessed according to WHO COVID severity staging. Information about the mode of delivery and if the pregnancy was booked or not was recorded on the proforma. If the newborn showed breathing problems and chest symptoms, these were recorded along with the duration of the hospital stay and outcome.

Neonate gestational age assessment was done by last menstrual period (LMP), first-trimester ultrasound, or Ballard examination (in case LMP and ultrasound were unavailable). Intrauterine growth status at Birth was assessed by birth weight and neonatal anthropometric charts. Mode of delivery, APGAR score, the need for ICU, signs and symptoms, duration of stay and outcome was recorded. The Workup of the healthy neonate was only a COVID PCR test after 24 hours of Birth. Subsequent testing was done as indicated (e.g. if the baby became unwell after a negative maternal result or as recommended by the clinician). For neonates who were positive at initial PCR testing, follow-up testing was done at 48-72 hours. For Sick neonates, laboratory tests, including a complete blood picture, acute phase reactant (CRP/ Procalcitonin), and blood culture to investigate for co-infection and X-ray/CT scan chest, were performed on admission. All blood reports, X-ray/CT, and chest scan findings were discussed and noted. Management was provided, including supportive management, oxygen therapy, Non-invasive ventilation, mechanical ventilation, nutritional support, and maintaining fluids and electrolyte balance. Specific management, including antibiotic, antiviral and immunomodulatory treatment, was given per WHO and National covid-19 guidelines. The outcome and prognosis of the neonates were assessed based on the duration of clinical and radiological improvement of disease, length of NICU stay and COVID-19 negative report. Data was recorded on predefined Proforma.

Data Analysis: It was done by the statistical software package SPSS version 20.0. The data was calculated in frequencies and percentages, and the chi-square test was applied with a P-value of <0.05, considered statistically significant.

RESULTS

A total of 31 neonates were included in the study. Among the newborns, 20 (64.5%) were males, and 11 (35.5%) were females. The mean gestational age of the neonates was 35.97±2.8 weeks. There was no significant difference among the demographic variables of covid-19 positive and negative neonates. **Table I** shows the demographic and laboratory data of neonates. There was no significant difference (p=0.237) in Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores of neonates who were covid-19 positive and those who tested negative. Most neonates, i.e. 45.2%, were born by Emergency caesarian surgery, whereas 16.1% were born through spontaneous vaginal delivery and 38.7% via elective caesarian section.

TABLE I: DEMOGRAPHIC AND LABORATORY PARAMETERS OF NEONATES BORN TO COVID-19 POSITIVE MOTHERS

	Mean	SD
Gestational age (weeks)	35.97	±2.81
Birth weight (kg)	2.71	± .69
APGAR score at 1 minute	7.53	±1.46
APGAR score at 5 minutes	8.83	± .95
Hb (g/dl)	14.64	±3.33
TLC (/mm^3)	16.96	±6.40
Platelet count (/ mcL)	242.64	±128.39
CRP (mg/dl)	5.95	±13.18

CRP = C-reactive protein; Hb = Hemoglobin; TLC= Total Leukocyte count
APGAR= Appearance, Pulse, Grimace, Activity, Respiration

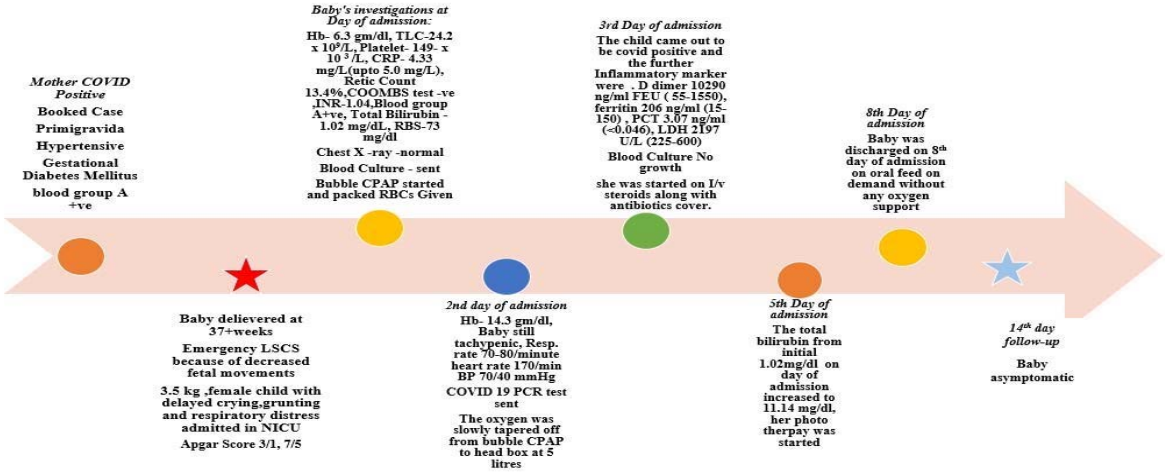
After delivery, out of 31 neonates born to COVID-19-positive mothers, 22 (71%) neonates required admission to NICU for various reasons. **Table II** shows the causes of NICU admission, symptoms of newborns at delivery and outcome in the study population. Out of 22 (71%) neonates who were admitted to NICU, 8 (36.3%) were admitted for less than three days, 7 (31.8%) were present in NICU for 4-7 days, and 7 (31.8%) required observation in NICU for more than seven days. The first PCR test was positive for 6 (19.4%) neonates, and the second virology test was positive for only 1 (3.2%) neonate. Furthermore,17(54.8%) neonates who were PCR negative in the first virology test and had a hospital stay of fewer than three days, their caregivers refused to send the neonates' second PCR test. At 14 days of follow-up, 29 (93.5%) neonates were asymptomatic. However, 2 (6.5%) had symptoms of respiratory distress. Three neonates born at 28^{th},29^{th} and 33 weeks of gestation, respectively, expired. They all were COVID PCR negative, done after 24 and 48 hours of delivery per the methodology's protocol. The mortality rate was, therefore =9.7%. Two newborns remained admitted for > 14 days, and one expired within 48 hours of delivery due to severe hyaline membrane disease. After delivery, 13 (41.9%) neonates were exclusively breastfed, 3 (9.67%) were kept on mixed feeding practices (Mother feed and formula milk), and 15 (48.3%) neonates received formula milk. Furthermore, it is also worth mentioning that one of the term neonates born during the study period had shown severe anemia at the time of Birth; subsequent investigations revealed hemolytic anemia secondary to COVID infection. **Figure II** shows the case timeline of the neonates.

TABLE II: SYMPTOMS OF NEONATES AT BIRTH, THE REASON FOR NICU ADMISSION AND THE OUTCOME

Symptoms at the time of Birth		
	Yes	No

Fever		7 (22.6)		24 (77.4%)
Respiratory Distress		20 (64.6%)		11 (35%)
Cyanosis		0		31 (100%)
Asymptomatic		13 (42%)		18 (58%)
Reason for NICU admission				
Preterm		11 (35%)		20 (64.5%)
Low Birth weight		10 (32.3%)		21 (67.7%
Congenital pneumonia		7 (22.6)		24 (77.4%)
Observation		4 (13%)		27 (87%)
Neonatal sepsis		7 (22.6)		24 (77.4%)
Respiratory Distress		10 (32.3%)		21 (67.7%
Outcome of Neonates				
Discharged early(<7days)	**Expired**	**Discharged late (>7 days)**	**Shifted with Mothers**	**LAMA**
15 (48.4%)	3 (9.7%)	7 (22.6%)	5 (16.1%)	1 (3.2%)

FIGURE II: CASE TIMELINE OF A NEONATE WITH COVID-19 INFECTION AND HEMOLYTIC ANEMIA



DISCUSSION

Due to the risk of development of congenital Covid-19 disease in newborns, data regarding the vertical transmission of this infection needs to be elaborated. The current study evaluated the outcome in neonates of 31 pregnant covid-19 positive mothers. Most literature does not support that Covid-19 can be transmitted vertically from diseased mothers to their neonates. In one study, the vertical transmission of covid-19 was assessed, and the findings revealed no risk of vertical transmission, and the viral markers in the placenta were not detected[13]. However, it was later refuted by **Seymen CM et al.**[14] that the virus can enter the placenta and cause severe pathological changes. Contrary to these findings, 6 (19.4%) neonates were found to be Covid-19 positive in our study.

In a systemic review, it was concluded that there are chances that if the disease occurs in the 3rd trimester of pregnancy, a small number of neonates at Birth may get infected. Furthermore, it was mentioned in the data regarding mothers who got an infection in the first trimester that the outcome of those pregnancies did not show any potential risk for consequent fetal morbidity and mortality[15]. These findings are similar to those of our study. However, we found that one baby who was COVID-19 PCR positive developed severe anemia with positive inflammatory markers strongly suggestive of vertical transmission of infection. The correlation of vertical transmission was further strengthened by negative bacterial culture. However, to confirm vertical transmission, we need to check the COVID variants at the genomic level to identify the similarities in the genome of the mother's and neonates' viral samples, which was a limitation of our study. Regarding the second serological analysis of Covid-19 in three COVID positive neonates, our results were found to be in parallel to the findings of Martínez-Perez O et al., 2020 who reported that when evaluated for the second time after 48 hours, the neonates were covid-19 negative despite being positive in the first PCR. The reason for a negative PCR test in these neonates has not been identified yet.

In our study, there was no relation between the mode of delivery of COVID-19-negative and covid-19 positive mothers. However, neonates born to mothers who underwent Emergency lower segment caesarian section required NICU admission[16]. The most common reasons for NICU admission were preterm delivery, respiratory distress and low birth weight. The same results were documented by **Anand P et al.** [17]. It is established in the research literature that neonates born to Covid-19 mothers with late disease onset, i.e. in the late third trimester, may not develop symptoms

of the disease. It is also highlighted that the neonates should not be kept separately from the mothers, and rooming in should be encouraged with standard precautions [18]. In our study, there was a positive outcome, i.e. out of 31 neonates, 27 (87.1%) were discharged, three expired, and one left against medical advice. Our findings are consistent with those of other studies documented in the research literature[19-21]. Our study found that one covid-19 positive neonate had hemolytic anaemia. To the best of our search, we could not find a similar case elsewhere in the neonatal age group in the online literature. However, similar findings were reported by Kosmeri C et al. in older children secondary to covid-19 infection[22].

CONCLUSION

The possibility of vertical transmission of covid-19 cannot be ruled out, primarily if the mother acquires infection in the last trimester. Even with positive PCR, most neonates had good outcomes, with fewer or no disease-specific symptoms. However, morbidity and mortality seemed to be directly related to prematurity and low birth weight. Furthermore, it is recommended to encourage breastfeeding in neonates born to COVID-positive mothers with standard precautions.

ACKNOWLEDGEMENT:

We appreciate the help of Pediatric postgraduate residents and our dear colleague Dr. Rehana Yasmeen (Gynecologist) for their support in data collection.

Ethical Permission: Ziauddin University ERC letter No. 3300221FZPED, Dated: 12-03-2021.

Conflict of Interest: No conflicts of interest, as stated by authors.

Financial Disclosure / Grant Approval: No funding agency was involved in this research.

Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publically.

AUTHOR CONTRIBUTIONS

Zafar F:	Study design, literature review, data collection and drafting of the manuscript
Ehsan S:	Contributed to the idea, data collection and critical review of a manuscript
Khan L:	Contributed to data collection and literature review
Fawad B:	Analyzed data and contributed to data interpretation

REFERENCES

1. Tang JW, Tambyah PA, Hui DSC. Emergence of a novel coronavirus causing respiratory illness from Wuhan, China. J Infect. 2020; 80: 350-371. doi: 10.1016/j.jinf.2020.01.014. Epub 2020 Jan 28.
2. Wu YC, Chen CH, Chen YJ. The outbreak of covid-19: an overview. J Chin Med Assoc. 2020; 83(3): 217-220. doi: 10.1097/JCMA.0000000000000270.

3. Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN *et al*. Aerosol and surface stability of SARSCoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020; 382(16): 1564-7. doi: 10.1056/NEJMc2004973. Epub 2020 Mar 17.
4. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020; 395(10226): 809-15. doi: 10.1016/S0140-6736(20)30360-3.
5. Peng Z, Wang J, Mo Y, Duan W, Xiang G, Yi M et al. Unlikely SARS-CoV-2 vertical transmission from mother to child: a case report. J Infect Public Health. 2020; 13(5): 81820. doi: 10.1016/j.jiph.2020.04.004. Epub 2020 Apr 11.
6. Schwartz DA, Graham AL. Potential maternal and infant outcomes from Coronavirus 2019-nCoV (SARS-CoV-2) infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. Viruses. 2020; 12(2): 194. Published online 2020 February 10. doi: 10.3390/v12020194.
7. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel coronavirus infection in hospitalized infants under 1 year of age in China. JAMA. 2020; 323(13): 1313-14. doi: 10.1001/Jama. 2020.2131
8. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020; 9(1): 51-60. Doi: 10.2103/tp.2020.02.06.
9. Wang L, Shi Y, Xiao T, Fu J, Feng X, Mu D et al. and on behalf of Working Committee on Perinatal and Neonatal Management for the Prevention and Control of the 2019 Novel Coronavirus Infection. Chinese expert consensus on the perinatal and neonatal management for the prevention and control of the 2019 novel coronavirus infection. Ann Transl Med. 2020; 8(3): 47. doi: 10.21037/atm.2020.02.20.
10. Chen Y, Peng H, Wang L, Zhao Y, Zeng L, Gao H et al. Infants born to mothers with a new coronavirus (COVID-19). Front Pediatr. 2020; 8: 104 . Published online 2020 Mar 16. Doi: 10.3389/fped.2020.00104.
11. Khan MA, Kumar V, Ali SR. Vertical Transmission of Novel Coronavirus (COVID-19) from Mother to Newborn: Experience from a Maternity Unit, The Indus Hospital, Karachi. J Coll Physicians Surg Pak. 2020; 30(10): 136.
12. Anand P, Yadav A, Debata P, Bachani S, Gupta N, Gera R. Clinical profile, viral load, management and outcome of neonates born to COVID 19 positive mothers: A tertiary care centre experience from India. Eur J Pediatr. 2021; 180(2): 547-559. Published online 2020 Sept 10. doi: 10.1007/s00431-020-03800-7.
13. Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, Abbasi H, Mirjalili SR, Behforouz A, Ferdosian F, Bahrami R. Vertical transmission of coronavirus disease 19 (COVID-19) from infected pregnant mothers to neonates: a review. Fetal Pediatr Pathol. 2020; 39(3): 246-50.
14. Seymen CM. Being pregnant in the COVID-19 pandemic: Effects on the placenta in all aspects. J Med Virol. 2021; 93(5): 2769-73.
15. Kotlyar A, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O et al. Vertical Transmission of COVID-19: A Systematic Review and Meta-analysis. Am J Obstetr Gynecol. 2020.

16. Martínez-Perez O, Vouga M, Melguizo SC, Acebal LF, Panchaud A, Muñoz-Chápuli M et al. Association between mode of delivery among pregnant women with COVID-19 and maternal and neonatal outcomes in Spain. JAMA. 2020; 324(3): 296-9.
17. Anand P, Yadav A, Debata P, Bachani S, Gupta N, Gera R. Clinical profile, viral load, management and outcome of neonates born to COVID 19 positive mothers: a tertiary care centre experience from India. Eur J Pediatr. 2021; 180(2): 547-59.
18. Yang P, Wang X, Liu P, Wei C, He B, Zheng J et al. Clinical characteristics and risk assessment of newborns born to mothers with COVID-19. J Clin Virol. 2020; 127: 104356.
19. Liu D, Li L, Wu X, Zheng D, Wang J, Liang B et al. Pregnancy and perinatal outcomes of women with COVID-19 pneumonia: A preliminary analysis. Available at SSRN 3548758. 2020 Feb 29.
20. Lowe B, Bopp B. COVID-19 vaginal delivery–a case report. Aust New Zeal J Obstet Gynecol. 2020; 60(3): 465-6.
21. Lowe B, Bopp B. COVID-19 vaginal delivery–a case report. Aust New Zealand J Obstet Gynecol. 2020; 60(3): 465-6.
22. Kosmeri C, Koumpis E, Tsabouri S, Siomou E, Makis A. Hematological manifestations of SARS-CoV-2 in children. Pediatr Blood Cancer. 2020; 67(12): e28745.