Scientific Publications

Open Journal of Medical Sciences, 2023, 3, 823
www.scipublications.org/journal/index.phpo/ojms
DOI: 10.31586/ojms.2023.823

Systematic Review

Pregnancy outcome in patients with previous infection with COVID-19 and the health of newborns

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Abstract: The study is a follow-up of the study "Coronavirus in pregnant patients and their clinical outcomes – results of a case-control study" conducted by R. Kadriu et al (2023) in which, in addition to the pregnant patients whose outcome is now being investigated, a control group of patients who were not pregnant, conducted with pregnant patients and a control group that were non-pregnant patients. This study was conducted 6 months after the discharge of the patients and their newborns, and highlights the impact of COVID-19 on their health as well as the health of the newborns. The aim of the study is to follow up the patients after 6 months of their hospitalization as COVID-19 patients and after their delivery. In the COVID study, none of the health indicators showed statistically significant differences between the population before and after hospitalization. Patient data were collected at the case level summarized in their respective groups. For secondary objectives, several comparative analyzes were performed regarding comorbidity-related parameters and available risk factors. A significance level (α) of 0. 05 was used for statistical significance. While these results may be reassuring regarding the stability of health status, one should be aware of the limitations of the study, including sample size and specific population characteristics.

Keywords: Pregnancy, COVID-19, consequences

How to cite this paper:
Kadriu, R., Demiri, I., Dimitrov, G., Asani, P., & Demiri-Kadriu, A. (2023). Pregnancy outcome in patients with previous infection with COVID-19 and the health of newborns. *Open Journal of Medical Sciences*, *3*(1), 46–52. Retrieved from https://www.scipublications.com/journal/index.php/ojms/article/view/823

Received: September 27, 2023
Revised: October 28, 2023
Accepted: November 20, 2023
Published: November 22, 2023

1. Introduction

The global outbreak of the novel coronavirus disease 2019 (Covid-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed unprecedented challenges, ever for public health systems around the world. As the pandemic intensifies, concerns about the impact of COVID-19 on pregnant women and the subsequent health of their infants has become an important area of research. Understanding the impact of maternal COVID-19 infection on pregnancy outcome and infant health is essential to guide health care strategies, shape prenatal care protocols, and ensure health outcomes healthy for mothers and babies. Pregnancy represents a unique physiological state in which the maternal immune system undergoes dynamic changes to accommodate the developing fetus. The interplay between the immune response and viral infection during pregnancy is a complex and multifaceted phenomenon, and the SARS-CoV-2 virus adds a new layer of complexity to this delicate balance. At the beginning of the pandemic, concerns were raised about the potential adverse effects of COVID-19 on pregnancy, including the risk of preterm birth, fetal distress, and maternal complications. Therefore, researchers around the world have conducted rigorous investigations to elucidate the relationship between prior maternal COVID-19 infection and pregnancy outcome. Several studies have focused on elucidating the impact of

COVID-19 on pregnancy complications such as preeclampsia, gestational diabetes, and intrauterine growth restriction.

Viral infections during pregnancy have a wide range of placental and neonatal pathology. There have been reports of SARS-CoV-2 infection of the placenta. The placenta is an immunologically privileged place and the detection of viruses is complex due to its structure [1]. Histopathological examination of placental tissue can contribute important information regarding the health of both mother and child and is a valuable method for determining transplacental transmission of virus from an infected mother to the fetus. Although rare, cases of transplacental transmission and reports of SARS-CoV-2 in amniotic fluid, placental samples, and positive nasopharyngeal swabs at birth indicate that intrauterine transmission is possible. Vbivanti et al. reported a case of transplacental transmission of SARS-CoV-2 in a 23-year-old pregnant woman with known SARS-CoV-2 infection. At birth, SARS-CoV-2 was identified by RT-PCR in samples from amniotic fluid, placental tissue, maternal and newborn blood, and the child's nasopharyngeal swab. Immunohistochemistry of placental tissue showed significant invasion of the virus into the trophoblast and coexisting placental inflammation [2].

Evidence of a high viral load in placental tissue and the presence of SARS-CoV-2 in trophoblast cells support transplacental transmission in this case. Similarly Hosier et al. reported a case in which SARS-CoV-2 was identified in a placental syncytiotrophoblast, although fetal lung, heart, liver, and kidney tissues were negative for SARS-CoV-2. Zamaniyan et al also reported that amniotic fluid collected during a cesarean section of a pregnant woman with COVID-19 was positive for SARS-CoV-2. [3] In a case report from Switzerland, a 26-year-old pregnant woman with a COVID-19 infection presented with premature labor and fetal death at 19 weeks of pregnancy. Fetal tissue was negative for SARS-CoV-2; however, fetal placental surface RT-PCR was positive. Pathology of the placenta was significant for areas of inflammation, increased fibrin deposition, and funisitis. RT-PCR of maternal blood, vaginal secretions and urine were negative for SARS-CoV-2 [4]. A recently published study of 15 placentas from SARS-CoV-2 positive or convalescent mothers showed a statistically significant increase in maternal vascular malperfusion (MVM) compared to controls. Pathologic findings consistent with MVM include decidual arteriopathy, fibrinoid necrosis, and amniotic membrane arteriolar hypertrophy. In a case series of 20 placentas from pregnant women with SARS-CoV 2, fetal vascular malperfusion was the most common pathology (9 cases). Intramural, 6 non-occlusive thrombi were also observed in several placentas. Villitis was detected in four cases. One placenta had chorioamnionitis and funisitis, which were discovered in a pregnant woman with pneumonia and hypoxia. These reports indicate that SARS-CoV 2 infection can induce inflammation and vascular changes in the placenta. Alternatively, SARS-CoV-2 infection may induce hypercoagulability in the placenta as has been shown in other organs. [5] Pregnant women with COVID-19 showed a significant increase and other inflammatory conditions, suggesting that the inflammatory nature of SARS-CoV-2 infection during pregnancy may cause adverse outcomes for both mother and fetus [3].

Evidence for vertical transmission is sparse and mostly based on small case series. If the possibility of intrauterine infection is proven, it is important to determine the moment of pregnancy when the virus can cross the placenta, to determine the possible impact on the organogenesis of the fetus and its overall well-being. Vertical transmission is defined as transmission of an infectious pathogen from mother to fetus/infant during the antepartum, intrapartum, or postpartum period via the placenta in utero, contact with body fluids during delivery, and/or direct contact with breastfeeding after birth. [6] Current studies indicate that the probability of vertical transmission of SARS-CoV-2 from mother to infant ranges from 3% to 8%. A study by Wang et al. showed that, 36 hours after birth, a positive result was obtained from a nasopharyngeal swab in an infant for SARS-Cov-2. However, it was not detected in cord blood, placenta and breast milk samples. In this case, despite the fact that the virus was not detected in the blood from the umbilical

cord, as well as in the tissues of the placenta, intrauterine transmission of SARS-CoV-2 cannot be excluded. In turn, Pietrasanta et al. reported a case of infection of an infant with SARS-CoV-2 from an asymptomatic mother. The child was born prematurely by caesarean section. Immediately after birth, the newborn developed respiratory distress, and the infection with COVID-19 was confirmed at 23 hours of life. Palatnik et al diagnosed COVID-19 in two infants. In one of them, positive results were obtained within 24 hours after birth, while in the other, they were obtained only on the 7th day of life (the child was isolated from the sick mother during this period). In both cases, the maternal placenta showed chronic intervillosis, with the presence of macrophages. In case of intrauterine transmission of the virus from mother to child, attention should be paid to the level of IgM antibodies to SARS-CoV-2 and cytokine IL-6 in the serum of newborns [5]. Dong et al. reported high levels of IgM to SARS-CoV-2 as well as IL-6 and IL-10 in the newborn at 2 hours of life, while the nasopharyngeal swab was negative. Infection during delivery cannot be excluded; however, IgM antibodies do not usually appear until 3–7 days after infection, and in the reported case, higher levels of IgM were found 2 hours after birth. In addition, it should be noted that IgG, but not IgM, antibodies can be transferred to the fetus via the placenta[8]. Therefore, an increased level of IgM antibodies suggests that the newborn may have been infected during pregnancy. [4] Zimmermann & Curtis noted that despite strict infection control and prevention procedures during and after caesarean section, four infants tested positive for SARS-CoV-2 (one healthy infant and three who presented with pneumonia), and three of them had expression of IgM and IgG antibodies at birth, indicating the possibility of vertical transmission. Zeng et al. confirm this with a report of six infants—all born by caesarean section and immediately separated from their mothers—who also had high concentrations of IgG and IgM antibodies immediately after birth, as well as high levels of IL-6. This topic still remains questionable, as Xiong et al. and Alzamora et al. , on the other hand, reported negative IgG and IgM serological results in newborns immediately after birth [7].

2. Materials and Methods

The study was performed as a prospective non-interventional case-control study. Cases were defined as patients who had 1) a finding confirming their pregnancy (ultrasound finding) available in their documentation or electronic record, 2) a positive test for SARS-CoV-2, based on the PCR method, as well as 3) symptomatology from upper respiratory system or systemic signs. As control patients, they were defined in the same way as the cases, but with the information that they are not pregnant. Pregnant patients who were treated at the University Clinic for Gynecology and Obstetrics Skopje North Macedonia for SARS-CoV-2 infection in the period from 2020 to the end of 2021 were identified as cases of interest. Upon inclusion in the study, each patient's demographic characteristics, date of positivity and time to hospitalization, previous comorbidities, as well as admission characteristics such as vital parameters and peripheral O2 saturation were determined, and symptomatology in the period before hospitalization. In pregnant patients, relevant data on pregnancy and gynecological history were additionally determined. Patients were managed by multiple specialties, including infectious disease specialists and specialties related to patient complications. The patients were treated in accordance with the protocols of the mentioned hospitals, and the treatment consisted of the application of supportive therapy (such as added oxygen), and according to the indication of the prescribing physician, corticosteroids, anticoagulant therapy and antibiotic therapy were given. During the hospital stay, multiple laboratory measurements of peripheral blood parameters, including complete blood count (erythrocytes, leukocytes, platelets, and differential blood count), C-reactive protein, lactate dehydrogenase activity, and d -dimers. This study was conducted as a prospective, non-interventional case-control study and it is a follow-up to a previously conducted study in which the patients were hospitalized,

and it is conducted 6 months after the hospitalization and termination of the pregnancy of the patients in the group.

Table 1. Maternal Health and Pregnancy Outcomes - Variable Summary

Variables	No	Yes
Hypertension during pregnancy	100. 0%	0. 0%
Preeclampsia	100. 0%	0. 0%
Eclampsia	100. 0%	0. 0%
Gestational diabetes mellitus	88. 2%	11. 8%
Known defect of the placenta	94. 1%	5. 9%
Is placenta completely removed?	100. 0%	0. 0%
Pregnancy ending in a live fetus	96. 0%	4. 0%
Pregnancy with premature rupture of membranes	95. 0%	5. 0%
Intrauterine growth restriction (IUGR)	89. 2%	10. 8%

For pregnant patients, additional relevant data on pregnancy and gynecological history were collected.

Routine laboratory measurements of peripheral blood parameters, including complete blood count, C-reactive protein, lactate dehydrogenase activity, and D-dimer concentration, were performed during the hospital stay.

Patient data were collected at the case level summarized in their respective groups. For secondary objectives, several comparative analyzes were performed regarding comorbidity-related parameters and available risk factors. A significance level (α) of 0. 05 was used for statistical significance.

3. Results

Table 2. Frequency of clinical variables in pregnant and non-pregnant women with COVID-19

Variables	M	SD
SPO2 ON RECEPTION, IN	92. 31	9. 18
HEMOGLOBIN ON ADMISSION, G/DL	115. 89	15. 24
RED BLOOD CELLS ON ADMISSION, (X10^6MICROL)	4. 00	0. 65
NEUTROPHILS ON ADMISSION, IN %,	50. 99	28. 74
LYMPHOCYTES AT ADMISSION, IN %%,	15. 39	11. 03
GRANULATED ON RECEPTION, IN %%,	50. 99	15. 34
TOTAL LEUKOCYTES ON ADMISSION, (X10^3 MCL)	17. 38	11. 58
ADMISSION PLATELETS, (X 10^3 MCL)	227. 15	89. 61
D-DIMERS AT INTAKE, (NG/DL)	4490. 58	7901. 18
ADMISSION UREA, MMOL/L	3. 16	SD = 1. 41
CREATININE ON ADMISSION, MMOL/L	39. 29	10. 38
GLYCEMIA ON ADMISSION, MMOL/L	5. 27	1. 79
C-REACTIVE PROTEIN ON ADMISSION, (MG/L)	63. 59	70. 38
LDH AT ADMISSION, (UNITS/L)	348. 21	236. 76
LEUKOCYTES HIGHEST VALUE DURING HOSPITALIZATION OF ALL MEASUREMENTS, (X10^3 MCL)	12. 54	7. 28
NEUTROPHILS, VALUES WHEN MEASURED AND HIGHEST VALUES FOR WBC, IN %%,	56. 4	29. 05
LYMPHOCYTES, VALUES WHEN MEASURED AND HIGHEST VALUES FOR WBC, , IN %%,	14. 23	12. 89
GRANULAR, VALUES WHEN MEASURED AND HIGHEST VALUES FOR WBC, ON ADMISSION, IN %%,	46. 31	16. 78
D-DIMERS, HIGHEST VALUE OF ALL MEASUREMENTS, (NG/DL)	4770. 89	9274. 29
D-DIMERS, FIRST MINUS HIGHEST VALUE	-1191. 98	4772. 35
ADMISSION UREA, HIGHEST VALUE OF ALL MEASUREMENTS, , MMOL/L	4. 56	2. 41
CREATININE ON ADMISSION, HIGHEST VALUE OF ALL MEASUREMENTS, , MMOL/L	43. 41	17. 62
GLYCEMIA, HIGHEST VALUE OF ALL MEASUREMENTS, , MMOL/L	5. 12	1. 48
C REACTIVE PROTEIN, HIGHEST VALUE OF ALL MEASUREMENTS, (MG/L)	68. 43	69. 98
CRP, FIRST MINUS HIGHEST VALUE	-1. 16	11. 91

LDH, (UNITS/L)	274. 67	176. 73

Table 3. Statistical analysis of the data

Variables	F-statistic	p-value
spo2 on reception, in %%,	0. 120	0. 887
Hemoglobin on admission, g/dL	0. 160	0. 695
Red blood cells on admission, (x10^6 microL)	0. 103	0. 915
Neutrophils on admission, in %%,	0. 008	0. 993
Lymphocytes at admission, in %%,	0. 239	0. 631
Granulated on reception, in %%,	0. 008	0. 993
Total leukocytes on admission, (x10^3 mcL)	0. 055	0. 982
Admission platelets, as count (x 10^3 mcL)	0. 263	0. 614
D-dimers at intake, (ng/dl)	0. 148	0. 703
Urea on admission mmol/L	0. 208	0. 809
Creatinine on admission, mmol/L	0. 109	0. 908
Glycemia on admission mmol/L	0. 022	0. 978
C-reactive protein on admission, (mg/L)	0. 090	0. 916
LDH at admission, (Units/L)	0. 059	0. 979
Leukocytes highest value during hospitalization of all measurements, (x10^3 mcL)	0. 115	0. 901
Neutrophils, values when measured and highest values for WBC, in %%, from 0 to 99	0. 032	0. 968
Lymphocytes, values when measured and highest values for WBC, , in %%,	0. 057	0. 979
Granular, values when measured and highest values for WBC, on admission, in %%,	0. 013	0. 987
D-dimers, highest value of all measurements, (ng/dl)	0. 117	0. 900
D-dimers, first minus highest value	0. 174	0. 839
Admission urea, highest value of all measurements, mmol/L	0. 043	0. 965
Creatinine on admission, mmol/L	0. 079	0. 925
Glycemia mmol/L	0. 017	0. 983
C (mg/L)	0. 038	0. 971
CRP, first minus highest value	0. 003	0. 954
LDH, (Units/L)	0. 116	0. 900

** significance level of 0. 05*

4. Discussion

The average age of the patients is 28 years, and the average hospital stay in the sample is 9 days. All women in the database showed no signs of hypertension during pregnancy (100%). Approximately 11. 8% of women had gestational diabetes. According to the collected and analyzed data presented in the Table 1, a remarkable 5. 9% of women had known defect of the placenta.

Further analysis and comparison of outcomes at different gestational weeks will provide valuable insights into the relationship between gestational age and pregnancy complications. The average gestational week of termination of pregnancy in patients is 38 weeks. Approximately 10. 8% of pregnancies were associated with intrauterine growth restriction. This condition can lead to low birth weight and other complications, emphasizing the need for careful monitoring of fetal growth during pregnancy. The low incidence of hypertensive disorders is promising, but the presence of gestational diabetes and anatomic placental abnormalities indicates the importance of personalized prenatal

care. Further research and statistical analysis, including correlational studies and logistic regression, could provide deeper insights into the interplay of these factors and their collective impact on maternal and newborn health.

The analysis conducted on a population of 96 women who gave birth and were hospitalized with COVID-19 six months ago provides valuable insights into various health indicators. The examination included parameters such as oxygen saturation (spo2), hemoglobin levels, red and white blood cell counts, inflammatory markers (D-dimer, CRP) and other relevant metrics, as can be seen in the Table 2.

Upon closer examination of the results, a consistent pattern emerges. The F-statistics associated with each health indicator are significantly low, and their respective p-values exceed the conventional significance level of 0. 05. This pattern indicates a lack of statistical significance, implying that there are no substantial differences in means for these health indicators across the population. Starting with spo2, admission oxygen saturation levels showed an F-statistic of 0. 120 with a corresponding p-value of 0. 887. This suggests that the observed variation in spo2 levels among the individuals in the study is likely due to random chance rather than significant differences in their health status. Similarly, hemoglobin levels, red and white blood cell counts, and inflammatory markers such as D-dimer and CRP did not show statistically significant differences. Hence, as can be seen in the processed data and its analysis from the Table 3, the F-statistics associated with these variables ranged from 0. 008 to 0. 263, and their corresponding p-values ranged from 0. 614 to 0. 993. This consistent lack of significance reinforces the notion that, within the study population, these health indicators remained relatively stable over the six-month period following hospitalization for COVID.

In a broader clinical context, these findings imply that trajectories of health recovery, as measured by these indicators, were relatively uniform among postpartum women previously hospitalized with COVID. Although this lack of statistically significant differences may be reassuring in terms of overall health outcomes, it is critical to acknowledge potential study limitations, such as sample size and specific characteristics of the study population. The results of the analysis indicate general homogeneity in health indicators among the population of women who gave birth and underwent a COVID-related hospitalization six months ago. Further research and larger studies would be beneficial to confirm these findings and explore potential factors contributing to the observed patterns in health recovery.

In terms of the health of the newborns, this follow up, all live births after 6 months of delivery are in good health without the occurrence of diseases. It is interesting to mention that in this sample of subjects, vertical transmission was not observed in any patient, that is, from mother to newborn. On the other hand, interviews conducted with mothers during the control examination (6 months after delivery) indicate some consequences of COVID on their mental health, such as an increased level of anxiety, greater anxiety, etc. In addition to this, most of the mothers stated that they gave artificial milk to their children out of fear that they could transmit the virus, and in some mothers due to prolonged isolation from the newborn (immediately after birth, due to the possibility of transmission of the virus, the newborns were separated from their mothers) did not occur or there was significantly little secretion of breast milk. During the period of hospitalization as well as the period of the control examination whose data are analyzed in this follow-up study, none of the patients were vaccinated with the available vaccines against COVID-19.

5. Conclusions

The analysis of the data on gestational and childbirth complications among women who gave birth and were hospitalized with COVID-19 six months ago offers a complete picture of the health status of this group. Important insights can be derived from various aspects of pregnancy, childbirth and the postpartum period. The main results show that

hypertensive conditions were not present in the study population, which could be a potential beneficial influence for the health of the mother and the newborn. We also find that gestational diabetes, although present in 11. 8% of cases, was not predominantly prevalent in the study group. Similarly, we find that 5. 9% of women showed known anatomical abnormalities of the placenta, which raises significant challenges and requires special prenatal care.

All newborns at the control examination show a good state of health without complications, and most of the mothers stated that they feed them with artificial milk both because of the fear of transmission and because of the insufficient secretion of breast milk.

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