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RESEARCH ARTICLE

The impact of the COVID-19 infection during pregnancy on the placenta and its function-a cross sectional study

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ABSTRACT

This research aims at looking into how the coronavirus is likely to influence pregnancies in terms of placental function-important aspects. Global health is faced with unprecedented challenges by the coronavirus pandemic currently happening; pregnant women are particularly at risk because of the bodily changes and potential changes in their immune systems. Study conducted a cross-sectional investigation (March 2022 - March 2023) in Stara Zagora, Bulgaria, involving 15 healthy (31.1 ± 6.32 yrs) pregnant women and 20 pregnant women (33.1 ± 4.88 yrs) with SARS-Co-2. We aim to elucidate and understand COVID-19's effects on pregnant women and neonates. Gestational age at delivery of groups were 36 ± 0.8 and 37.6 ± 1.1. The newborn weight (g) was 3090.55 ± 400.1 gr for pregnant women with SARS-Co-2 and 3211±500.6 gr for controls (P<0.09). Usually, COVID-19 patients who needed intensive care are taken to NICU, where outcomes found three patients (15%) patients and two women with (13.3%) control. In this study, we assessed the outcomes of SARS-Co-2 pregnant woman and controls according to pathological placental patterns. We found that the placental weight in the SARS-Co-2 pregnant woman was 465 ± 50.5, larger than the controls (P<0.07). The preterm birth was found for six SARS-Co-2 patients (30%). The neonatal weight was 3390±190.1 g for the SARS-Co-2 pregnant woman versus 3720±110.1 g of controls (P= 0.001). Finally, the placental patterns and relationship between the VAS-QL that occur during late gestational age show evidence of vertical trans-placental SARSCoV-2 transmission and significant influence on perinatal results among newborns, especially with serious conditions, was discussed.

INTRODUCTION

The global pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has resulted in over 200 million cases of illness and over 4 million fatalities. Pregnant individuals who contract the virus are more prone to experiencing severe illness [1-3] with an increased risk of premature birth and maternal and fetal mortality. Newborns born to women who are positive for SARS-CoV-2 test negative, but a few display symptoms at an early stage [4,5]. Although the placenta may possess a protective mechanism, it is important to note that not all neonates have a positive test result for the virus. Fortunately, there have been no cases of birth abnormalities reported in newborns who tested positive for SARS-CoV-2 [6-9]. Further research is being conducted on the infection of SARS-CoV-2 during pregnancy and the pathobiology of the placenta [10,11].

During pregnancy, the immune system is modified to accommodate the development of a semi-allogeneic fetus [12]. Individuals suffering from severe COVID-19 experience a significant disruption

of their immune system, characterized by elevated levels of white blood cells, a decrease in the number of lymphocytes, and a condition known as lymphopenia. Severe COVID-19 patients have reduced numbers of natural killer (NK), tumors infiltrating lymphocytes (TILs) CD3+, CD4+, and CD8+ T cells and experience functional exhaustion during SARS-CoV-2 infection [13-15]. They also have reduced levels of cytotoxic T cells. The monocyte/macrophage system undergoes significant changes during pregnancy, similar to those observed in familial haemophagocytic lymphohistiocytosis (HLH) [16-20]. Changes in the innate immune system include changes in pattern recognition receptors, namely Toll-like receptors (TLRs), [21] which can either increase or decrease in number during pregnancy.

Further research is needed to determine whether these changes result in increased susceptibility or immunity to COVID-19 during pregnancy [22-24]. New experiments have found that infection with even mild symptoms of the coronavirus during pregnancy 'depletes' the placenta, exhausting it and damaging its immune response [25,26]. Previous studies have found that this damage can be caused to the placenta regardless of the severity and extent of the symptoms, highlighting that any damage to the placenta, even if minor, affects the placenta. It affects its immunity and then the immunity of the fetus and its ability to get food and oxygen [27].

The study employed prenatal magnetic resonance imaging (MRI) to scan 78 placentas and fetuses of pregnant women. The scans were conducted on 20 cases where the pregnant woman had been confirmed to have been infected with SARS-CoV-2 (pre-omicron or omicron variants) and 15 cases where the pregnant woman was healthy. [28]. It can be concluded that the fetuses of infected pregnant women were more likely to develop morbidity and abnormalities in fetal growth (small for gestational age and IUGR) or vascular lesions in the organs and brain [29] early in the epidemic.

Study aim

Evaluate the role of the coronavirus is likely to influence pregnancies in terms of placental function-important aspects.

MATERIALS AND METHOD

This cross-sectional study was conducted in The University Hospital, Professor Dr. Stoian Kirkovich, Stara-Zagora, Bulgaria (June 2021- October 2023) (n=35) among pregnant women who were willing to participate in labor, were admitted to the hospital for delivery and gave their informed consent by signing a consent form.

The researchers gathered complete medical information from the patients, and it included, among other things, histories concerning their illnesses, clinical state, disease signs and symptoms, obstetrical records as well as vaccinations received. The pregnant women stated if they had any signs of flu-like illness, such as coughing and high temperatures, through self-reporting, while gestational age was estimated based on the first day of the last menstrual cycle. On admission, each woman had to be tested by PCR screening test to confirm or exclude SARS-CoV-2 viral RNA infection according to the hospital's COVID-19 protocol during the pandemic period.

The inclusion criteria were: pregnant woman without previous chronic pathologies, singleton pregnancy; body mass index 18–30 kg/m^2; experienced symptomatic Covid-19 infection with (PCR (+)) test, from the >30th gestational week onwards, without COVID-19 vaccine; and the control group without Covid-19 and PCR (−) test, again with singleton and body mass index 18–30 kg/m^2, without COVID-19 vaccine.

Exclusion criteria were: COVID-19-infected pregnant woman with type 2 diabetes (T2DM), heart disease, tumors, lupus erythematosus, kidney transplantation and thyroid disorders, chronic disease, with long-term treatment; previous infectious diseases; body mass index <18 or >30 kg/m2; malnutrition; previous fetal demise.

All Covid-19 pregnant patients enrolled in the study reported severe symptoms (cough (31%), fever ≥ 38.5 °C (50.6 %); respiratory rate ≥ 20 (9%); heart rate ≥ 100 bpm (13%); oxygen saturation SpO_2 less than 92% (7%)) requiring hospital stay and antiviral therapy with Ritonavir and Lopinavir.

The research was conducted according to the Declaration of Helsinki after obtaining approval from the Ethics Committee of the University Multidisciplinary Hospital for Active Treatment "St. Kirkovich" (referenced 10/816 - 12 Oct. 2019). The samples were distributed according to age, where women aged 19-42 years, lying between the 37-40 weeks of gestation, who at the same time are either primary or multiparous. Mothers' weight was recorded to the nearest 100 g using a digital scale, height was measured to the nearest 0.1 cm using a stadiometer, and mothers' body mass index (BMI) was calculated by dividing their weight (kg) by their height (m). Newborns were weighed without nappies and their length from crown to heel was measured to the nearest 0.1 cm using an infant meter (SECA). APGAR (Activity, Pulse, Grimace, Appearance, and Respiration) scores were obtained at 1 and 5 minutes after birth.

Hematological parameters were assessed on whole blood (5 mL) from *v. cubitalis* within 2 hrs of collection using an automated hematology analyzer to measure hemoglobin (Hb), packed cell volume (PCV), red blood cell count (RBC), mean cell volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width coefficient (RDW-CV%), platelet distribution width (PDW).

Ethical approval

The Ethics Committee of the University Multidisciplinary Hospital for Active Treatment "St. Kirkovich" Stara Zagora, Bulgaria, and the Department of Chemistry approved this work. Research approval number 10/816 is dated 13 October 2019.

Statistical analysis

The demographic data and parameters in this study were analyzed according to the statistical analysis program IBM SOFT SPSS 22 and Microsoft Excel 2013. Several techniques were relied upon to analyze the results of this study, which are the mean value and the STD, in addition to frequencies and percentages to the parameters. The quality value was also transferred. Patients' lives and making comparisons to determine the statistical differences and the strength of the statistical relationship between parameters.

RESULTS

The general and obstetric characteristics of the pregnant patients with COVID-19 and healthy pregnant controls are presented in Table 1. Pregnancy, gestational age, birth weight, body mass index and were significantly lower in the pregnant woman with COVID-19 than in the control group ($P < 0.05$). Of the 20 pregnant woman with COVID-19, 7 (35%) had mild pre-eclampsia versus 5 (33.3%) in the controls (P=0.923).

Table 1. General and obstetric characteristics of the pregnant patients with COVID-19 and healthy pregnant controls.

Features	**COVID-19 Patients (n=20)**	**Controls (n=15)**	**P**
Age (yrs)	33.1 ± 4.88	31.1 ± 6.32	0.862
BMI (kg/m^2)	28.9 ± 4.4	26.7 ± 3.3	0.345
Gestational age			

Mean ±SD	36±0.8	37.6±1.1	0.881
Comorbidities N (%)			
Diabetes	3 (15%)	5 (33.3%)	0.89
Preeclampsia	7 (35%)	5 (33.3%)	0.923
Kidney disease	5 (25%)	3 (20%)	0.756
T h	5 (25%)	2 (13.3%)	0.1
Delivery mode N (%)			
VD	15 (75%)	10 (66.6%)	0.837
CS	5 (25%)	5 (33.3%)	
Symptoms N (%)			
Fever	3 (15%)	3 (20%)	
Irritation in the throat	4 (13.3%)	2 (13.3%)	
Nasal congestion	6 (30%)	5 (33.3%)	0.64
Headache	5 (25%)	3 (20%)	
ophthalmic	2 (10%)	2 (13.3%)	
Newborn weight (g)			
mean±SD	3090.55 ± 400.1	3211±500.6	0.09
Smoking			
Yes	2 (10)	4 (26.6)	0.09
No	18 (90)	11 (73.3 0	0.09
Antibiotics added N (%)	7 (35%)	---	
Amniotic Fluid	Clear	---	0.09
Occupation N (%)			
work	5 (25)	3 (20)	0.88
not	15 (75)	12 (80)	0.06

patient's weight, kg (mean±SD)	67.6±3.5	65.4 ± 2.89	0.01

Values are given as mean ± SD (standard deviation), and the P-value between two groups <.05 was considered significant.

Medium labor induction were significantly higher than controls (P < 0.72), Table 2. There were also statistical significant differences between the APGAR at 1 min (P = 0.09) and 5 min in the pregnant patients with COVID-19 (P = 0.006) and in comparison to healthy pregnant controls, (P = 0.89; P < 0.88), respectively.

Table 2. Distribution of the pregnant patients with COVID-19 and healthy pregnant controls, according to labor induction, APGAR score at 5 minutes <7, and NICU admission.

Features	**COVID-19 Patients (n=20)**	**Controls (n=15)**	**P**
labor induction (%)	7 (35)	4 (26.6)	0.72
APGAR 1 min, (mean±SD)	13 (5.87±3.55)	8 (6.1±3.7)	0.89
APGAR score, 5 min (mean±SD)	7 (8.8±1.1)	7 (9.0±1.43)	0.88
NICU admission N (%)	3 (15)	2 (13.3)	0.98

Values are given as mean ± SD (standard deviation), and the P-value between two groups <.05 was considered significant.

A strongly positive correlation was found between circulating oxygen levels (Figure 1) of the pregnant patients with COVID-19 and healthy pregnant controls, 39.3 ± 5.98 versus 25.3 ± 4.33 (r= 0.425, P+0.63).

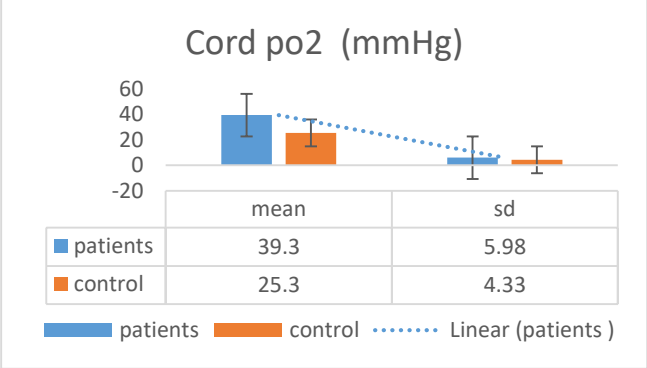

Figure 1. Distribution of the pregnant patients with COVID-19 and healthy pregnant controls, according to measurement of the partial pressure of oxygen.

Pregnancy and neonatal weight, preterm birth, and blood flow to the placentas (Table 3) were significantly higher in the pregnant patients with COVID-19 group than in controls (P <.05).

Table 3. Characteristics of the pregnant patients with COVID-19 and healthy pregnant controls, according to pathological placental patterns.

Variable	COVID-19 Patients (n=20)	Control (n=15)	P
Weight, g	465±50.5	277.6±66.6	0.07
Preterm birth	6 (30)	2 (1.3)	
Neonatal weight, g	3390±190.1	3720±110.1	0.001
Impaired blood flow to the placenta's villous trees, N (P%)	2 (10)	1 (6.6)	0.88
Infarction	2 (10)	0	0.01
Increased previous fibrin deposition	1 (5)	1 (6.6)	0.00
Delayed villous maturation	2 (10)	1 (6.6)	0.9
Phagocytosis of meconium in the amniotic membranes	1 (5)	1 (6.6)	0.00

Values are given as mean ± SD (standard deviation), and the P-value between two groups <.05 was considered significant.

There was considerable elevation (P ≤ 0.1) in Hg, WBC, and platelet (Table 4), whereas a considerable decrease was detected in blood Ferritin level, in RBC, in the neutrophils to lymphocyte ratio pregnant patients with COVID-19 as paralleled to the controls (P ≤ 0.01).

Table 4. Biochemical results of the pregnant patients with COVID-19 and healthy pregnant controls.

Variable	COVID-19 Patients (n=20)	Control (n=15)	P
Hg, (mean ± SD)	11.1±2.2	8.9±1.1	0.44
WBC, (mean ± SD)	12.5±1.8	7.7±2.8	0.37
Ferritin, (ng/mL)	40.8±59.9	45.4±66.5	0.08

platelet	260.6±70.9	230.1±79.54	0.1
RBC, (106/µl)	3.99 ± 0.69	3.77 ± 0.89	0.22
neutrophils to lymphocyte ratio	3.82± 1.79	4.1±2.1	0.32

Values are given as mean ± SD (standard deviation), and the P-value between two groups <.05 was considered significant.

DISCUSSION

The role of the placenta as a barrier against SARS-CoV-2 infection had been suggested during the COVID-19 pandemic. The placenta is a unique organ and a mystery: [30] It is necessary for a developing fetus to reach its maximum potential, and any alteration in placental function can affect the trajectory of pregnancy or have repercussions on the offspring's health from birth to childhood. [31] The placenta also serves as a barrier, limiting the passage of agents that infect the mother to the fetus. [32,33] While the glandular tissue of the chorionic villi is lined with trophoblast cells and, macrophages are found in the villous stroma and decidua. However, various infectious agents have been shown to cross the placenta, including some strains of the coronavirus. [34,35] The placenta is a potential target for the pathophysiological processes of SARS-CoV-2 infection due to the increased thrombotic inflammatory activation and inadequate uteroplacental perfusion and oxygenation, potentially causing intrauterine growth restriction.

According to different studies [36, 37], the entry and spread of the virus around the human cell are encouraged by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers that upregulate ACE2 receptors. ACE2 receptors are found in all cells of one's body and are especially in abundance in the lungs. Furthermore, this receptor is present in the reproductive organs, placenta, uterus, and maternal-fetal interface, and heart and liver of the fetus. Additionally, these receptors are massively expressed in the liver and cardiovascular system of a developing fetus.

ACE2 receptors could enable the transmission of COVID-19 from a mother to her growing fetus, while there is yet no conclusive evidence of vertical transmission. SARS-CoV-2 has the potential to result in mortality during the initial stages of pregnancy.

Diffuse perivillous fibrin deposition with infarction and acute and chronic intervillositis was shown through a placental histological test. Strong cytoplasmic positivity of villous trophoblastic cells was detected using antibodies for the SARS-CoV-2 N protein in the placental tissues [38]. Also found a preterm neonate with SARS-CoV-2 infection that presented severe acute respiratory distress syndrome immunohistochemically. There has been much research and debate on the effects of coronavirus infection in the placenta and its ability to perform during pregnancy. Pregnant women are believed to be at increased risk of developing severe coronavirus disease compared to their non-pregnant counterparts. This increased risk has led to fears that the placenta and fetal development could be damaged by the virus.

There have been studies indicating COVID-19 can cause problems in the placenta, such as inflammation and the formation of clots, although further research is still being done. Such changes may interfere with oxygenation and feeding capacity, affecting on fetal growth and development [39]. Furthermore, it has been shown that contracting COVID-19 while pregnant might raise the chances of preterm labor, besides other related problems. Therefore, it is important that medical teams track closely high-risk women who have this infection so that there will be favorable results for both the mother and the baby.

In addition, in this study, we investigate the typical factors decreasing the QL in COVID-19-infected pregnant patients: low back pain, the psychological aspect (fear of COVID-19, advanced maternal age, high parity women, physical changes causing limitations, physical activity limitations, fear of labor,), low social, economic status (educational level, prenatal care, partner satisfaction, poor sleep quality,

headache or migraine) anxiety and depression [40 - 46]. We detected a positive correlation in COVID-19-infected pregnant patients with typical factors frequently indicating a poor VAS QL during pregnancy in comparison to controls (P = 0.01; P < 0.05; P < 0.001; P < 0.05). Reznik et al., 2020 [47] commented that COVID-19 is a source of fear, stress, and anxiety, and at the same time, is an important factor affecting mental health and quality of life in COVID-19-infected pregnant mothers. A significant association was found between the infection of COVID-19 and the pregnancy-related quality of their mental life; the greater the fear of COVID-19 infection in pregnant women, the lower their mental quality of life and the more likely placental damage. Our results are consistent with other studies [46-48].

Table 5. Assessment outcomes of study according to visual analogue scale – the quality of life (VAS QL).

Variable	COVID-19 Patients (n=20)	Control (n=15)	P
Pain	66.4±55	39.9±7.97	0.01
The psychological aspect	59.9±4.45	36.6±3.87	0.05
Social side	55.5±6.97	41.1±3.589	0.001
Anxiety	54.4±3.8	38.8±4.2	<0.05

Values are given as mean ± SD (standard deviation), and the P-value between two groups <.05 was considered significant.

In conclusion, there is still a need for more studies to be done concerning the impact of COVID-19 on the placenta as well as its role in pregnancy. For now, pregnant women should adhere strictly to guidelines prescribed in order to control infection by the virus and turn to health professionals for directions or assistance.

One of the limitations of this study is the small (35) number of participants and the relatively few components examined. The inconvenience of collecting the blood samples and talking to the COVID-19-infected mothers was the other limitation of this study, which reduces the possibility of a more complete generalization of the results. One of the strengths of this investigation is that it is being conducted for the first time in Bulgaria during the spread of COVID-19 and in pregnant patients, which can provide health professionals involved in prenatal care with the necessary background information.

CONCLUSION

Researchers are currently studying how COVID-19 infection during pregnancy affects the placenta's function and health, including how it affects maternal well-being as well as the fetal well-being. Previous research has demonstrated that COVID-19 causes placental inflammation, vascular changes, and reduced blood circulation, which may affect the growth of the baby. It is important that people who have COVID-19 while they are pregnant are watched closely by their doctors or other healthcare professionals who care about them during pregnancy in order to keep serious problems from happening with how well their placentas work and make sure that their babies do as well as they can when they're born. Moreover, more studies need to be conducted on it to find out what happens to it later after a patient.

Declaration of competing interest- None declared.

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