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Fetal Biometry and Doppler Assessment of Pregnant Women with COVID-19

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Abstract

Background: The world has changed radically because of the worldwide COVID-19 pandemic. SARS-CoV-2, a unique strain of large, enveloped single-stranded RNA viruses, that has spread around the world. The primary objective of this research was to assess the fetal growth velocity in pregnancies complicated by SARS-CoV-2 infection and those that were not. The secondary objective was to determine if SARS-CoV-2 infection may affect maternal and fetal Doppler readings.

Methods and Results: A total of 250 pregnant women diagnosed with SARS-CoV-2 (Case group) were compared to 300 healthy pregnant women (Control group) in a prospective case-control study in Mosul from February 20 to October 20, 2021. Infections during pregnancy were detected and verified using the real-time reverse transcriptase-polymerase chain reaction (RT-PCR). All ultrasound exams were done from 24 to 40 weeks. Measuring parameters using Doppler ultrasonography included plasticity and resistive indices (PI, RI), as well as cerebroplacental ratio computed according to gestational age. Fetal development in utero was assessed by measuring biometric markers, such as parietal diameter, head size, belly circumference, leg length, and estimated fetal weight every four weeks. The US scans in the second and third trimester of pregnancy showed no evidence of congenital abnormalities (P=0.7047). There was a significant incidence of cesarean delivery (P=0.0000) and lower fetal activity at birth (P=0.0000) in the Case group, compared to the Control group. Anticoagulant treatment during pregnancy was not associated with an increased risk of postpartum hemorrhage in women of the Case group. Also, there were no significant differences in fetal biparietal diameter and femur length between groups in the second and third trimesters, and both fetal and maternal Doppler studies throughout the second and third trimesters of pregnancy yielded no significant differences in the PI and RI indices. (**International Journal of Biomedicine. 2022;12(4):554-559.**).

Keywords: pregnancy • Doppler ultrasonography • COVID-19 • fetal biometry

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Abbreviations

BMI, body mass index; **BPD,** biparietal diameter; **CD**, cesarean delivery; **CPR,** cerebro-placental ratio; **DU**, Doppler ultrasonography; **FL**, femur length; **IUGR**, intrauterine growth restriction; **MCA**, middle cerebral artery; **PI**, pulsatility index; **RI**, resistance index, **UA**, umbilical artery.

Introduction

The world has changed radically because of the worldwide COVID-19 pandemic. SARS-CoV-2, a unique strain of large, enveloped single-stranded RNA viruses, that has spread around the world. As a result of the outbreak of SARS-CoV-2 infections in recent years, the virus has emerged as a significant public health threat.[1] The possible repercussions of these infections on pregnancy are a serious cause of worry for obstetric care professionals.[2-5] Since the outbreak of the pandemic, women who are expecting a child have had a higher risk of developing a life-threatening illness. When comparing nonpregnant women infected with SARS-CoV-2 to pregnant infected women, the pregnant women showed an increased

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chance of severe chest symptoms, need for hospitalization in critical care units, and demand for mechanical ventilators.[6-8]

Pregnant women have a higher concentration of angiotensin-converting-enzyme receptors in the uterus and placenta, making them a perfect target for the transmission of SARS-CoV-2.[9,10] Another piece of evidence supporting this conclusion comes from the higher incidence of indications of decidual arteriopathy in pregnant women infected with SARS-CoV-2, which the researchers say shows that there is a significant association between infection and impaired placental function.[11-13]

Some patients show no symptoms even if their COVID-19 test is positive. Although intrauterine vertical transmission of SARS-CoV-2 has been shown, the most prevalent finding in placental disease is fetal vascular mal perfusion. Maternal-fetal morbidity and death are clearly increased in instances of severe pneumonia, which is often associated with COVID-19. Pregnant women who have been infected should have their prenatal follow-up appointments enhanced, since this may identify a wide range of unfavorable pregnancy outcomes, including miscarriage, IUGR, preeclampsia, and fetal mortality. Consequently, in pregnant women who have recovered from COVID-19, fetal development should be evaluated by ultrasound and Doppler to identify inadequate placental supply, intrauterine growth limitation, and other obstetric problems, among other things. Ultrasound examination of uterine artery, middle cerebral artery (MCA), umbilical artery (UA), and other fetal vessels for fetal well-being, as well as other fetal vasculature, has traditionally been performed in the second and third trimesters of pregnancy to check on the health of the fetus. The assessment of pulsatility index (PI) and resistance index (RI) is a way of measuring uteroplacental perfusion. Variations in vascular resistance are referred to as downstream vascular resistance and are used to predict newborn issues such as IUGR, low birth weight, and intrauterine fetal mortality.

The risk of SARS-CoV-2 infection in pregnant women who have elevated angiotensin-converting enzyme 2 (ACE2) receptors has been linked to hypertension during pregnancy. The binding of the virus to ACE2 causes it to be down-regulated, which can make angiotensin II (Ang-II) more likely to be produced than Ang-(1-7), which can cause vasoconstriction, and which in turn can cause preeclampsia or make it worse[14] (Fig.1). The immune responses of pregnant women to SARS-CoV-2 are unclear at this time; however, data from previous pandemics suggest that pregnancy may increase the risk of disease and mortality when compared to nonpregnant women infected with the virus.[15] When an infection arises during pregnancy, it may have an impact on the mother's immune response, viral clearance, and, eventually, the fate of the child after birth. Because the first and third trimesters are pro-inflammatory in nature, it is necessary to induce implantation and labor at these times.[16] According to the researchers, pregnant women who are infected with SARS-CoV-2 throughout three trimesters may be at increased risk of developing severe viral infections (cytokine storm). Unfortunately, significant quantities of stress and inflammation are produced during delivery, and the physiological changes that occur in a mother's body after the birth of her child may result in poor maternal COVID-19 outcomes following the birth.

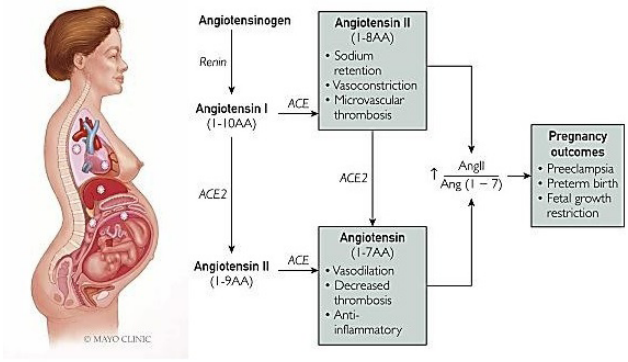

Fig.1. *Pregnancy: COVID-19 and vascular damage pathways.*

Pregnant women with moderate symptoms need postpartum hospitalization for respiratory symptoms.[14] When pregnant, the upper airways get more congested and get more congested from the secretion of mucus the chest wall increases in circumference, and the diaphragm rises higher. These changes in breathing are rather important. They reduce residual volume but increase tidal volume and air trapping. Airway resistance is also reduced significantly while diffusion capacity remains unchanged. Heart output and vascular resistance are both enhanced, and plasma volume decreases by 20% to 50% in hemodynamic alterations.[17] Women who are expecting are more susceptible to respiratory infections because of these abnormalities in their physiology and respiratory alkalosis. Pregnant women with SARS-CoV-2 infection may have symptoms that are similar to physiologic dyspnea, which may cause them to be misdiagnosed and result in more severe sickness. The symptoms of SARS-CoV-2 infection in pregnant women are likely to be more severe than those in nonpregnant women. Although there is a scarcity of data, there have been cases of rapid deterioration in women who initially showed no signs of illness but were subsequently identified with severe COVID-19. Other maternal medical illnesses (hypertension, diabetes, pregnancy cholestasis) were present in some, but not all, patients.[18,19] Cesarean deliveries (CDs) have increased because of the quickly progressing maternal difficulties, which have resulted in either deteriorating maternal status or non-reassuring fetal status as a result of the worsening maternal clinical condition. COVID-19 may increase or exacerbate pregnancy-related complications, including preeclampsia. In addition, both stages have laboratory abnormalities in common, which makes the issue even more complicated. Certain forms of preeclampsia may make it difficult to discern between abnormal test results generated by SARS-CoV-2 infection and those caused by other causes of abnormal results. Examples include thrombocytopenia and decreased liver function, both of which serve as diagnostic criteria for severe preeclampsia and are associated with a worsening COVID-19 score.[20,21] We supposed that placental alterations caused by

this infection might compromise the development of the fetus and hemodynamics in these pregnancies.

The primary objective of this research was to assess the fetal growth velocity in pregnancies complicated by SARS-CoV-2 infection and those that were not. The secondary objective was to determine if SARS-CoV-2 infection may affect maternal and fetal Doppler readings. This study also aimed to examine fetal biometric measurements for fetal growth evaluation and Doppler velocimetry in pregnant women infected with SARS-CoV-2.

Materials and Methods

A total of 250 pregnant women diagnosed with SARS-CoV-2 were compared to 300 healthy pregnant women in a prospective case-control study in Mosul from February 20 to October 20, 2021. Infections during pregnancy were detected and verified using the real-time reverse transcriptase-polymerase chain reaction (RT-PCR).

Inclusion criteria were a) singleton pregnancy, b) fetal viability, c) BMI <30kg/m^2, d) no history of diabetes mellitus, hypertension, including pregnancy hypertension, antepartum bleeding, autoimmune disorders, clinical hyperthyroidism/hypothyroidism, hematological diseases, e) negative TORCH test, f) no history of IUGR, g) informed consent from the participants.

Exclusion criteria were moderate and severe COVID-19.

A detailed history was taken, including gestational age at infection diagnosis, medical treatment for COVID-19, the time interval between Doppler measurement and COVID-19 diagnosis, and examinations including general examination, vital signs, complete obstetric examination, and BMI calculation.

All ultrasound exams were done from 24 to 40 weeks (based on the last menstrual period or early ultrasound), and by a single ultra-sonographer who was blinded to the patient's medical history. A Mindray DC-30 Full HD Ultrasound System (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) with wideband convex transducer was used.

At 24 weeks of pregnancy, the UA and MCA were checked with Doppler flowmetry. The examinations were done twice during the study, once in each trimester. Measuring parameters using Doppler ultrasonography included plasticity and resistive indices, as well as cerebroplacental ratio computed according to gestational age. Fetal development in utero was assessed by measuring biometric markers, such as parietal diameter, head size, belly circumference, leg length, and estimated fetal weight every four weeks. In addition, the amniotic fluid index was determined for each patient under consideration.

Statistical analysis was performed using statistical software package SPSS version 23.0 (SPSS Inc, Armonk, NY: IBM Corp). Baseline characteristics were summarized as frequencies and percentages for categorical variables. For descriptive analysis, results are presented as median (Me), first quartile (Q1) and third quartile (Q3). The Mann-Whitney U Test was used to compare the differences between the two independent groups Group comparisons with respect to categorical variables are performed using chi-square tests or, alternatively, Fisher's exact test when expected cell counts were less than 5. A probability value of $P<0.05$ was considered statistically significant.

Results

A total of 250 pregnant women with a positive history of COVID-19 infection (Case group) and 300 pregnant women without infection (Control group) were examined in our private clinic by a gynecologist and radiologist with over a decade of expertise. Maternal age ranged from 17 to 45 years in both control and infected cases. The pregnancy and maternal characteristics of both groups are presented in Table 1, which demonstrates no difference in maternal age, parity, gravidity, or gestational age at birth.

The US scans in the second and third trimester of pregnancy showed no evidence of congenital abnormalities (P=0.7047). There was a significant incidence of CD (P=0.0000) and lower fetal activity at birth (P=0.0000) in the Case group, compared to the Control group. Anticoagulant treatment during pregnancy was not associated with an increased risk of postpartum hemorrhage in women of the Case group. Also, there were no significant differences in fetal biparietal diameter and femur length between groups in the second and third trimesters (Table 1), and both fetal and maternal Doppler studies throughout the second and third (35-37 weeks) trimesters of pregnancy yielded no significant differences in the PI and RI indices (Table 2).

Table 1.
***The pregnancy and maternal characteristics of both** groups.*

Variable	Case group (n=250)	Control group (n=300)	*P*-value
Maternal age, years	30.04 (17-45)	30.35 (17-45)	0.43
Gravity	4.96 (3-7)	4.78 (2-6)	0.07
Parity	4.28 (3-6)	4.16 (2-6)	0.29
Second trimester US examination, weeks	20.91 (19-23)	21.01 (19.5-22)	0.39
Third trimester US examination, weeks	36.43 (35.5-37)	36.51 (35.9-37)	0.61
Gestational age at birth, weeks	37.97 (37-39)	38.13 (38-40)	0.15
Lower fetal activity at birth	64 (25.6%)	30 (10%)	0.0000
CD rate	72 (28.8%)	43 (14.3%)	0.0000
Anticoagulant treatment during pregnancy	102 (40.8%)	70 (23.3%)	0.0000
Postpartum hemorrhage	6 (2.4%)	7 (2.3%)	1.0000
Congenital abnormality	2 (0.80%)	4 (1.3%)	0.7047

Table 2.

Fetal and maternal Doppler studies in study groups

Variable	Case group (n=250)	Control group (n=300)	*P*-value
Second trimester DU			
BPD, mm	47.01 (45.4-48.5)	46. 91 (39.4-48.4)	0.08
FL, mm	36.08 (34.2-37.6)	36.00 (34.4-37.2)	0.26
UA-PI	1.06 (0.53-1.59)	1.05 (0.54-1.6)	0.59
Third trimester DU			
BDD, mm	88.34 (83.5-93.4)	88.05 (81.1-92.1)	0.25
FL, mm	71.27 (68.4-74.1)	70.27 (69.2–71.3)	0.08
UA-PI	0.72 (0.67-0.77)	0.73 (0.66-0.79)	0.63
UA-RI	0.51 (0.40-0.61)	0.52 (0.52-0.62)	0.07
MCA-PI	2.76 (2.60-2.92)	2.74 (2.51-2.70)	0.09
CPR	1.02 (0.51-1.55)	1.01 (0.53-1.52)	0.51

Discussion

The pathophysiology of SARS-CoV-2 infection during pregnancy and its association with co-morbid disorders remain unknown.[22] This case-control research is one of the few that examines the relationship between intrauterine placental flow and fetal death.[23] The US and Doppler outcomes for SARS-CoV-2 in infected and non-infected pregnant women were compared. As the results showed, there was no significant difference in terms of maternal age (17-45 years), parity, second trimester US examination (19-23 weeks), third trimester US examination (35-37 weeks), or gestational age at birth (37-40 week), while there was a significant difference between the groups in terms of fetal movement at the time of delivery and decreased fetal movement at birth (*P*=0.0000). That some pregnant women report transitory reductions in fetal movement despite the lack of substantial vascular abnormalities seen by Doppler,[24] could be explained by high doses of systemic corticosteroid given to treat the main manifestations of COVID-19, changes in maternal perception because of the fear of disease, maternal pyrexia during acute infection, or transplacental transmission of inflammatory mediators and tiny micro thrombi at the placental bed.[25] SARS-CoV-2 infection may also explain the considerable increase in the rate of CD under regional anesthesia in pregnant women having an urgent medical or obstetric cause for termination of pregnancy. Additionally, there was a statistically significant increase in the usage of prenatal and postpartum anticoagulant medication in the case group, compared to the control group, for thrombus treatment and prophylaxis without differences in postpartum bleeding, which was comparable to a study done by Anuk et al.[25] found that delivery in the maternity hospital with active management in the third stage of labor, in addition to the manipulation or discontinuation of the anticoagulant therapy at an appropriate time during labor, is the cause behind the absence of difference in the rate of postpartum hemorrhage between the groups.

No congenital anomaly was discovered post-delivery in the pregnant women diagnosed with SARS-CoV-2. According to Rizzo et al.,[26] SARS-CoV-2 infection during the second half of pregnancy without congenital anomaly indicates that the patients have passed the key time of organogenesis. However, Khalil et al.[3] compared stillbirth rates during the pandemic to the pre-pandemic era and found that the frequency of stillbirth was much greater during the pandemic. Anuk et al.[25] found that the Doppler indices were significantly changed during the pandemic. Due to the study group's features, concomitant comorbidities like diabetes, chronic hypertension, advanced age, or a higher BMI in pregnant women with COVID-19 aggravate the disease's effects. But in our study, the presence of all the listed conditions were exclusion criteria. As the long-term effects of this viral infection and its consequences during pregnancy are still being investigated, we discovered that infected women attend antenatal care more often because they are fearful of potential problems.[27]

We studied SARS-CoV-2 impact on fetal development. The primary objective of this research was to use Doppler ultrasonography to assess fetal growth and circulation throughout the second and third trimesters of pregnancy. The results of our study suggest that fetal development and growth velocity, as measured by biparietal diameter and femur length, are similar in SARS-CoV-2 infected and not infected pregnant women. The fetal and maternal Doppler studies showed no significance in the PI and RI throughout the second and third trimesters. These data suggest that infection with SARS-CoV-2 during pregnancy does not increase the risk of IUGR and hence does not need increased fetal surveillance.[26-28] It should be noted that this study included only pregnant women with mild symptoms of infection. A second point to note is a restriction on when an evaluation can be done. If an infection happened early in the pregnancy, it could have a different outcome. Even though there is a lot of evidence that the SARS-CoV-2 virus can spread during pregnancy, many unanswered concerns remain, such as how the virus may damage the fetus and placenta. SARS-CoV-2 infection can be transmitted vertically; however, this is still up for discussion. Early in the outbreak, it was claimed that transmission from mother to fetus was very low.[29] In contrast, more recent and larger studies have found that there is a higher risk of transmission from mother to child.[25] A recent review of 39 studies that looked at 936 newborns born to mothers who had COVID-19 found that 3.2% of them had SARS-CoV-2 in their nasopharyngeal swabs.[30] A subgroup analysis that looked at the effect of the location of the research revealed that the rate of vertical transmission was almost the same whether the trial was conducted in China or elsewhere (2.0% vs 2.7%).[31] Although much progress has been made, the hazards of vertical transmission and the long-term consequences it may have on a developing fetus remain poorly known. Recent research has raised questions regarding the true danger of transmission of SARS-CoV-2, which was found exclusively in the placenta but not in neonates.[28]

Among other things, placentas from pregnant women infected with SARS-CoV-2 revealed evidence of arterial necrosis, fibrinoid necrosis, and mural enlargement of the decidual arterioles.[2,27] In our research, we were unable to address this question because of the absence of an examination of placental pathology. A reduced placental function, growth limitation, or stillbirth may occur even when there is no evidence that the mother has been infected with SARS-CoV-2 or any other sickness that causes maternal vascular hypo perfusion.[3] Contrary to common opinion, the findings of this study reveal that pregnancies complicated by SARS-CoV-2 infection do not increase the likelihood of fetal growth limitation.[32] It is no longer required to do repeated scans during pregnancy to rule out certain conditions. One potential clarification for the absence of a link between women infected with COVID-19 and IUGR is that only women with moderate symptoms were included in the study, which may have represented the slighter range of COVID-19 symptoms only.[33] However, it cannot be ruled out that women with more severe COVID-19 may be at risk for IUGR. The amount of time a woman has been infected may have an impact on her likelihood of having placental lesions.[11,34] One of the most disputed issues in the treatment of pregnant women with SARS-CoV-2 infection is whether these women should be exposed to more intensive prenatal surveillance. Because there is no evidence of a relationship between illness and impaired fetal development, the results of the current study do not sustain a strategy of increased US screenings to ensure the safety of the fetus. Furthermore, it has been established that the incidence of stillbirth in women infected with SARS-CoV-2 is no different from the incidence of stillbirth in the baseline pregnant population that was not infected with the virus.[35] Gravid women infected with SARS-CoV-2 should rest assured that the risk of poor consequences for their unborn child is very minimal,[36,37] but more focused studies need to be done to confirm this finding.

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Competing Interests

The authors declare that they have no competing interests.

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