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ORIGINAL RESEARCH

Analysis of Fetal Growth and Pregnancy Outcome in Pregnant Women Infected with Novel Coronavirus in Mid-Pregnancy

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Purpose: To investigate whether fetal prenatal ultrasound, fetal growth rate, and pregnancy outcome statistically differ between women infected with novel coronavirus (COVID-19) in mid-pregnancy and an uninfected control group.

Patients and Methods: A retrospective analysis of biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), and z-scores for each among 46 pregnant women diagnosed with COVID-19 in mid-pregnancy between December 01, 2022 and June 31, 2023 was conducted. A control group included 92 pregnant women negative for COVID-19 during the same period and was also analyzed. To examine fetal growth, rate of increase in BPD, HC, AC, FL, and estimated fetal weight (EFW) between second and third trimester scans were analyzed. In addition, pregnancy outcome, maternal comorbidities, and neonatal prognosis were assessed.

Results: The occurrence of gestational diabetes differed significantly between groups, but the fetal growth rate and EFW did not. Similarly, pregnancy outcomes and neonatal prognoses did not differ significantly between groups.

Conclusion: Gestational diabetes was a complication that differed between patients with and without COVID-19 in this study. COVID-19 in pregnant women did not affect fetal development. Therefore, these preliminary data suggest that increased fetal monitoring is not necessary for women infected with COVID-19 during the second trimester, and these women should be reassured of the low risk of adverse fetal outcomes.

Keywords: novel coronavirus, pregnant women, prenatal fetal growth, pregnancy outcome, ultrasound imaging

Introduction

During pregnancy, hormonal and physiological changes significantly affect the respiratory system. As a result, the risk of novel coronavirus (COVID-19) infection has been higher among pregnant women than among the general population.[1] However, approximately 92–95% of pregnant women diagnosed with COVID-19 have not experienced the severe spectrum of this disease.[1–3] Binding of the angiotensin-converting enzyme receptor 2 (ACE-2) is critical for the SARS-CoV-2 virus to gain access to host cells. ACE-2 is also expressed at higher levels in the uterus and placenta of pregnant women.[4,5] Consequently, there is an increased risk of virus entry to the posterior placenta. In addition, an increased incidence of decidual arterial lesions has been observed among pregnant women positive for SARS-CoV-2.[6,7] Thus, it is possible that SARS-CoV-2 may adversely affect placental function. Perinatal mother-to-child transmission of novel coronavirus (COVID-19) and impaired placental function are additional concerns. However, prenatal ultrasound studies conducted of fetuses in pregnant women infected with SARS-CoV-2 remain very limited.[8,9] In December 2022, China eased the strict COVID-related restrictions that had previously been imposed. One of the initial observations made regarding the cases of COVID-19 reported up to that point was the high proportion of pregnant women infected during their second trimester. Duan Li et al[10] studied the effects of COVID-19 infection in late pregnancy on pregnancy outcomes in China, but few reports describe the effects of COVID-19 in mid-gestation on fetuses. Thus, our objective

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was to examine and compare available data from women with and without a confirmed diagnosis of COVID-19 in mid-pregnancy and to identify any statistically significant differences in regard to prenatal ultrasound fetal growth rate or neonatal prognostic outcomes.

Materials and Methods

Study Population

Forty-six pregnant women confirmed to be positive for COVID-19 during their second trimester were admitted to the Third Affiliated Hospital of Zhengzhou University between December 01, 2022 and June 31, 2023 and retrospectively analyzed. All enrolled women had received perinatal care at our institution and were vaccinated. All of the women had their infection confirmed by positive real-time PCR analysis of nasopharyngeal swab specimens. The patients exhibited mild symptoms (cough, fever, loss of taste and smell, sore throat, diarrhea, etc), and were diagnosed with mild COVID-19 that did not require hospitalization.[11] All patients were free of underlying diseases and complications at the time of their second ultrasound examinations. For comparison, 92 pregnant women were identified from hospital records of 4150 women who delivered during the study period. This control group was matched according to maternal age, gestational age, gestational age when ultrasound scanning was performed, and body mass index (BMI). We confirmed that control participants were negative for SARS-CoV-2 infection throughout their pregnancies. Additional inclusion criteria were: (1) gestational age could be determined based on head and hip length at 11–13±6 weeks ultrasound scan, both second trimester and third trimester ultrasound evaluations were performed at our hospital, and delivery took place at our hospital. This study was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Zhengzhou University [(Len) Review No. 2022–248-01)]. Requirement for informed consent was waived because the study was retrospective and the identity of all patients remained undisclosed. This study was performed in line with the principles of the Declaration of Helsinki.

Instruments and Methods

Data Collection

Medical record data were collected for both the study and control women selected for this study. Briefly, these data included: age, number of deliveries, number of pregnancies, BMI, and condition at delivery. Transabdominal ultrasounds were used to determine: fetal biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) data. The Hadlock-4 formula was used to estimate fetal weight.[8,9] Data regarding week of gestation at birth, amniotic fluid volume (AFV), mode of birth, preterm labor occurring at ≤ 37 weeks, low birth weight (10^{th} percentile), positive exposure, 1-min and 5-min Apgar scores ≤ 6, and prognosis of newborns delivered by the women in both groups were also collected. Anemia was defined by hemoglobin levels ≤ 90 g/L.

Fetal Prenatal Ultrasonography

Fetal prenatal ultrasound examinations were performed using Voluson E8 and E10 diagnostic ultrasound machines (GE, Boston, Massachusetts, United States) with an abdominal probe frequency of 3.5–5 MHz. Based on previously reported technical data and in accordance with the recommendations of the International Society of Ultrasonography in Obstetrics and Gynecology (ISUOG), the BPD, HC, AC, FL, and AFV were determined from the images obtained.[12,13] The Hadlock-4 formula was used to estimate fetal body weight.[14,15]

Statistical Methods

Measurements obtained at the second trimester scan and again at 35–37±6 weeks gestation had z-scores determined for them. To calculate growth velocity, differences in the latter were divided by the number of days between the two scans and these values were multiplied by 100. Categorical variables are expressed as percentages (%) and number (n) and were analyzed using the Chi-square test. Continuous variables are expressed as median and interquartile range values. SPSS 27.0 software was used to analyze data. Measures that exhibited normal distribution are presented as mean ± standard deviation, and the *t*-test was applied for comparisons. Measures that did not exhibit normal distribution are presented as M (P25, P75), with the Wilcoxon rank-sum test applied for comparisons. Counts were expressed as cases or instances (%), with the $\chi 2$ test applied for comparisons. P-values less than 0.05 were considered statistically significant.

Results

Clinical Characteristics

Clinical characteristics of the study (n = 46) and control (n = 92) groups of women were retrospectively analyzed (Table 1). No significant differences in number of pregnancies, age, number of deliveries, or BMI were observed between the two groups. Frequency of cesarean section and median gestational age at delivery also did not differ between the two groups. For the SARS-CoV-2 positive group, the mean gestational age when infection was confirmed by PCR test was 23 ± 8 weeks (range: 22 ± 0 to 25 ± 6 weeks).

Incidence of Comorbidities

The incidence of comorbidities in the SARS-CoV-2 positive group compared with the control group was not statistically significant (P = 0.066) (Table 2). Corresponding complications were also examined. Only the occurrence of gestational diabetes differed significantly between groups (Table 2). No significant difference in complications such as gestational hypertension and preeclampsia was observed.

Differences in z-Scores

Z-scores were determined for BPD, HC, AC, FL, and EFW from ultrasound scans performed at mid and late gestation. Between the study group and control group, there were no significant differences in these five parameters (Table 3). Similarly, the growth curves associated with these parameters did not significantly differ (Table 3 and Figure 1).

Table 1 Clinical Characteristics of Positive and Negative Controls for SARS-CoV-2 Infection

Clinical Characteristic	SARS-CoV-2 Infection	Negative Controls	t/Z	P
Maternal age (y)	31.22±4.89	30.97±4.13	−0.315	0.753
Number of pregnancies	2.000(1.0,3.0)	2.000(1.0,3.0)	−1.972	0.049
Number of times produced	0.000(0.0,1.0)	0.500(0.0,1.0)	−1.552	0.121
BMI	27.34(26.14,29.18)	26.57(25.47,27.89)	−1.868	0.062
Week of birth	39.428(38.8,40.1)	39.333(382,4.0.48)	−0.291	0.772
Cesarean section	22(47.83)	47(51.09)	0.130	0.718
Vaginal delivery	24(52.17)	45(48.91)	0.130	0.718
Gestational age at SARS-CoV-2 infection	24.142(22.5,25.0)	Null(null,null)	0	0.000
Gestational age at first ultrasound (weeks)	23.142(22.2,24.6)	23.000(22.2,23.0)	−30.382	0.702
Gestational age at second ultrasound (weeks)	36.571(36.1,37.1)	36.428(35.8,37.0)	−1.547	0.122

Note: Data are presented as median (interquartile range).
Abbreviations: Null, not applicable, BMI, body mass index.

Table 2 Comorbidities of Positive SARS-CoV-2 Infection and Corresponding Complications in Negative Controls

Condition	SARS-CoV-2 Infection (n=46)	Negative Controls (n = 92)	χ2	P
Maternal (co)morbidity	38 (82.6.0)	40(43.47)	2.193	0.354
Gestational diabetes	16(38.10)	13(14.13)	7.880	0.005
Hypertension in pregnancy	2(4.7)	6(6.5)	0.017	0.898
Preeclampsia	2(1.94)	5(5.43)	6.446	0.232
Hypothyroidism in pregnancy	8(17.4)	14(15.22)	0.108	0.742
Hyperthyroidism	1(2.17)	0(0.00)	-	0.333
SGA	1(2.17)	1(2.17)	-	1.000
Anemia in pregnancy	6(13.04)	5(5.43)	1.494	0.222

Note: Data are expressed as n (%) or n/N (%).
Abbreviation: SGA, small for gestational age.

Table 3 Comparison of Biometrics and Amniotic Fluid Volumes Obtained at Two Ultrasound Examinations in SARS-CoV-2 Positive Pregnant Women and Negative Controls (Z-Scores)

Parameters Examined	SARS-CoV-2 Infection (n=46)	Negative Controls (n = 92)	z	P
First scan				
BPD	−0.10(−0.83, 0.83)	−0.26(−0.68, 0.55)	−0.005	0.996
HC	−0.08(−0.74, 0.88)	−0.26(−0.78, 0.71)	−0.018	0.986
AC	−0.10(−0.94, 0.98)	−0.29(−0.73, 0.88)	−0.098	0.922
FL	−0.10(−0.58, 0.75)	−0.16(−0.75, 0.66)	−0.235	0.814
EFW	−0.21(−0.89, 0.99)	−0.28(−0.70, 0.72)	−0.049	0.961
Amniotic fluid MVP (cm)	41.00(35.0,48)	43.00(35.0,5)	−1.144	0.253
AFI (cm)	125.00(111.0,147.0)	133.00(118.8,160.5)	−1.313	0.189
Second scan				
BPD	0.187(−0.4,0.5)	−0.069(−0.4,0.6)	−0.41	0.682
HC	−0.071(−0.7,0.8)	−0.135(−0.6,0.8)	−0.027	0.978
AC	0.034(−0.8,0.7)	−0.047(−0.6,0.6)	−0.109	0.913
FL	−0.162(−0.6,0.8)	−0.083(−0.5,0.8)	−1.03	0.303
EFW	0.000(−0.7,0.8)	0.033(−0.5,0.5)	−0.049	0.961
Amniotic fluid MVP (cm)	40.00(37.0,46.5)	39.00(32.0,51)	−1.106	0.269
AFI (cm)	122.00(106.5,140.0)	109.00(89.8,136.8)	−1.878	0.06
Growth rate between scans				
BPD	0.339(−0.7,1.0)	0.040(−1.4,1.4)	−0.344	0.731
HC	0.159(−0.9,0.9)	−0.086(−1.1,0.9)	−0.295	0.768
AC	0.319(−1.1,1.1)	−0.181(−1.5,1.2)	−0.453	0.651
FL	0.256(−1.0,1.0)	0.090(−1.6,1.2)	−0.202	0.84
EFW	0.279(−1.1,1.1)	−0.033(−1.4,1.1)	−0.366	0.715

Note: Data are expressed as median (interquartile range).
Abbreviations: BPD, biparietal diameter, HC, head circumference, AC, abdominal circumference, FL, femur length, EFW, estimated fetal weight; amniotic fluid MVP, maximum depth of amniotic fluid, AFI, amniotic fluid index.

Fetal Birth and Prognosis

A comparison of gestational week of birth, fetal birth weight, type of delivery, prematurity (<37 weeks), SGA, low birth weight, neonatal prognosis, positive exposure, and Apgar score between the two study groups did not show any significant differences (Table 4).

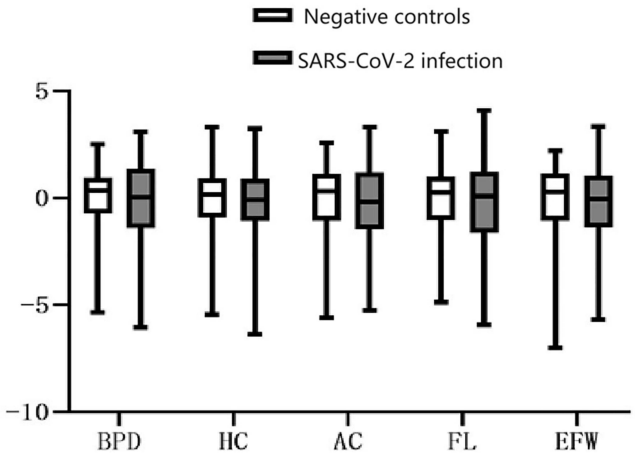

Figure 1 Box-and-whisker plots representing growth rate data for BPD, HC, AC, FL, and EFW of fetuses from SARS-CoV-2-positive pregnant women (black) and SARS-CoV -2-negative pregnant women (white).

Table 4 Perinatal Outcomes of Pregnant Women with and without SARS-CoV-2 Infection In mid-Pregnancy

Perinatal Outcome	SARS-CoV-2 Infection	Negative Controls	t/Z	P
Birth weight at week of birth	3265.174(2873.7,3656.5)	3306.326(2879.5,3733.1.0)	0.549	0.584
Admitted to NICU	6(13.04)	14(15.21)	0.117	0.732
SARS-CoV-2 exposure	0 (0.00)	0(0.00)		
1-minApgar score ≤ 6	4(8.69)	2(2.17)	-	1.00
5-minApgar score≤ 6	5(10.8)	4(4.34)	-	1.00
Low birth weight (<10thpercentile)	0(0.00)	0(0.00)		
<37 weeks	1(2.17)	0(0.00)	1.6	0.206
SGA	1(2.17)	1(1.37)	0.11	0.74
Cesarean section	22(47.83)	47(51.09)	0.130	0.718
Vaginal delivery	24(52.17)	45(48.91)	0.130	0.718

Note: Data expressed as median (interquartile) values.
Abbreviations: NICU, neonatal intensive care unit; SGA, small for gestational age.

Discussion

At the start of the SARS-CoV-2 virus outbreak, there was immediate concern regarding possible effects of SARS-CoV-2 infection on a fetus during pregnancy. As a result, the rate of indicated preterm births increased in an effort to prevent exposure of fetuses to COVD-19 via vertical transmission.[16] However, ongoing research of the pathophysiology of SARS-CoV-2, as well as accumulating clinical experience, suggest that infection with SARS-CoV-2 during pregnancy leads to minimal or mild effects on the fetus, despite possible vertical transmission of the virus.[6,7,17] In parallel, though, the potential for SARS-CoV-2 infection to cause preterm fetal delivery has been consistently reported.[7,18,19] To investigate possible differences in fetal growth rate and pregnancy outcome among women with and without SARS-CoV-2 infection during pregnancy, a retrospective case-control study was conducted to analyze available data from prenatal ultrasound examinations.

Vertical transmission of SARS-CoV-2 virus remains a highly controversial topic. Placental pathology has confirmed the presence of SARS-CoV-2 virus. Neonatal tests have also detected the virus. The ability of SARS-CoV-2 to enter cells is distinct from that of other viruses. Both ACE-2 and transmembrane serine protease 2 (TMPRS-2) receptors are needed. Pique-Regi et al previously reported low levels of expression for these receptors in the placenta of SARS-CoV-2-positive pregnant women, suggesting low potential for vertical transmission.[15,20,21] In the present study, none of the neonates with mothers infected with SARS-CoV-2 virus were positive for the virus. However, placental pathology was not analyzed. Therefore, risk of vertical transmission still needs to be studied.

Comorbidities between the study group and control group in our study were not matched since differences in comorbidities and their incidences were a main focus. The incidence of maternal comorbidities in the SARS-CoV -2-positive group did not significantly differ from the control group. Only the incidence of gestational diabetes mellitus differed significantly between groups, as[22] SARS-CoV-2 infection leads to impaired insulin secretion and insulin resistance through the activation of the renin-angiotensin-aldosterone system and the destruction of pancreatic endocrine cells and the microvascular system. This process ultimately leads to the development of diabetes mellitus in predisposed patients. We did observe a trend toward an increased prevalence of preeclampsia among the SARS-CoV-2-positive women. It has previously been reported that pregnant women infected with SARS-CoV-2 exhibit a higher risk of preeclampsia when experiencing pneumonia compared toSARS-CoV-2-infected pregnant women without pneumonia.[18] The occurrence of complications such as gestational hypertension and preeclampsia did not differ significantly between groups in this study. A similar risk of preeclampsia was observed for both study groups in the present study. Thus, it remains to be determined whether SARS-CoV-2 infection increases the risk of preeclampsia independent of other factors.

Vascular endothelin-converting enzyme receptor is expressed at higher levels in both the uterus and placenta.[5] Interactions with this receptor have been demonstrated for SARS-CoV-2. An analysis of placental pathology of SARS-CoV-2-positive pregnant women has shown fetal and maternal vascular malformations associated with meconium arteriopathy.[14–16] This condition may affect placental function and alter fetal hemodynamics.[23] Based on fetal cerebral placental ratio and Doppler

middle cerebral artery pulsatility index values collected from pregnant women infected and not infected by COVID-19, no significant differences were observed between the two groups.[5,24] Fetal growth and development throughout pregnancy is sustained via the blood supply provided by the placenta. We did not observe significant differences in the fetal growth rates between the study group and the control group in the present study. Furthermore, fetal hemodynamics appeared uncompromised. Therefore, consistent with the work of Rizzo et al, placenta function appears unaffected by SARS-CoV-2 infection. In addition, risk of fetal growth restriction does not appear to increase when infection with SARS-CoV-2 occurs during pregnancy, and additional scans to detect growth restriction are not required. However, pregnant women with COVID-19 should strictly control their weight and closely monitor their blood glucose and glycosylated hemoglobin levels to prevent the occurrence of gestational diabetes and reduce the impact on the fetus.

Conclusion

Only data from women infected with SARS-CoV-2 in mid-pregnancy were examined, and this population is not representative of prenatal ultrasound presentations at other stages of pregnancy. Furthermore, the results may have differed if infection had occurred within the first trimester of pregnancy. This has been observed in other studies, indicating that the onset of infection in relation to gestation is a key factor to consider in evaluating risk of placental lesions.[25] Another consideration is that all of our data were obtained from patients exhibiting milder cases of COVID-19. Severe and critically ill patients were not included. Therefore, risk of vasculopathy and pregnancy outcomes may differ in patients experiencing a severe SARS-CoV-2 infection.[20] Regarding the lack of validated evidence for an association between SARS-CoV-2 infection and fetal growth restriction that was observed in this retrospective study, it is possible that pregnant women exhibiting mild symptoms of COVID-19 infection carry a mild viral load. If this is true, it is possible that women experiencing severe cases of COVID-19 may have a higher risk of fetal growth restriction. The sample for this study was small; larger samples and multicenter studies are needed to confirm whether SARS-CoV-2 infection and maternal and fetal growth restriction are associated. Further study of whether adverse fetal-maternal outcomes are associated with the degree of SARS-CoV-2 infection is needed as well. In addition, we did not examine the potential long-term effects of COVID-19 on neonatal health or development; research on these effects is needed.

It remains unclear whether more intensive fetal monitoring of SARS-CoV-2-positive pregnant women is warranted. The results of the present retrospective study suggest that the risk of fetal growth restriction is not increased in pregnant women infected with SARS-CoV-2. Thus, additional ultrasound scanning to assess fetal health is not recommended for normally developing fetuses. The present results should also reassure pregnant individuals regarding the low risk of adverse fetal outcomes despite infection with SARS-CoV-2 in mid-pregnancy, and reduced anxiety during gestation is important for both mother and child.[26,27]

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Disclosure

The authors report no conflicts of interest in this work.

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