Ultrasound Obstet Gynecol 2021; **58**: 111–120
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.23642

Ultrasound and Doppler findings in pregnant women with SARS-CoV-2 infection

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KEYWORDS: COVID-19 pandemic; fetus; infection; obesity; perinatal death; preterm delivery; SGA; small-for-gestational age; ultrasound; vertical transmission

CONTRIBUTION

What are the novel findings of this work?
We observed no differences in ultrasound and Doppler findings between pregnant women who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and those who were negative, matched for age, body mass index, parity and gestational age. There was a higher prevalence of preterm delivery at or before 35 weeks of gestation among SARS-CoV-2-positive pregnant women.

What are the clinical implications of this work?
Additional ultrasound and Doppler evaluations are probably not needed in SARS-CoV-2-positive women with a normally grown fetus. Cervical length evaluation may be indicated in SARS-CoV-2-positive pregnant women. The association between SARS-CoV-2 and perinatal mortality should be explored further.

ABSTRACT

Objectives *To describe and compare ultrasound and Doppler findings in pregnant women who were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with findings in those who were SARS-CoV-2-negative, evaluated during the pandemic period.*

Methods *In this retrospective case–control study, we analyzed data from 106 pregnant women who tested positive for SARS-CoV-2 at the time of, or within 1 week of, an ultrasound scan between 1 May and 31 August 2020. Scans were either performed for routine fetal evaluation or indicated due to a positive SARS-CoV-2 test. Forty-nine women were symptomatic and 57 were asymptomatic. For comparison, we analyzed data from 103 pregnant women matched for maternal age, parity, body mass index and gestational age at the time of the ultrasound scan. These control women did not report symptoms of SARS-CoV-2 infection at the time of the ultrasound scan or at the time of admission for delivery and had a negative SARS-CoV-2 test at admission for delivery. Fetal biometry, fetal anatomy, amniotic fluid volume and Doppler parameters, including umbilical and fetal middle cerebral artery pulsatility indices, cerebroplacental ratio and biophysical profile (BPP), were evaluated as indicated. Biometric and Doppler values were converted to Z-scores for comparison. Our primary outcome, an adverse prenatal composite outcome (APCO) included any one or more of: small-for-gestational-age (SGA) fetus, oligohydramnios, abnormal BPP, abnormal Doppler velocimetry and fetal death. Comorbidities, delivery information and neonatal outcome were compared between the two groups.*

Results *Eighty-seven (82.1%) women who were positive for SARS-CoV-2 had a body mass index $> 25\,kg/m^2$. SARS-CoV-2-positive women had a higher prevalence of diabetes (26/106 (24.5%)* vs *13/103 (12.6%); P = 0.03), but not of pre-eclampsia (21/106 (19.8%)* vs *11/103 (10.7%); P = 0.08), compared with controls. The prevalence of APCO was not significantly different between SARS-CoV-2-positive women (19/106 (17.9%)) and controls (9/103 (8.7%)) (P = 0.06). There were no differences between SARS-CoV-2-positive women and controls in the prevalence of SGA fetuses (12/106 (11.3%)* vs *6/103 (5.8%); P = 0.17), fetuses with abnormal Doppler evaluation (8/106 (7.5%)* vs *2/103 (1.9%); P = 0.08) and fetuses with abnormal BPP (4/106 (3.8%)* vs *0/103 (0%); P = 0.14). There were two fetal deaths in women who were positive for SARS-CoV-2 and these*

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Accepted: 26 March 2021

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women had a higher rate of preterm delivery ≤ 35 weeks of gestation (22/106 (20.8%) vs *9/103 (8.7%); odds ratio, 2.73 (95% CI, 1.19–6.3);* P = *0.01) compared with controls.*

Conclusions *There were no significant differences in abnormal fetal ultrasound and Doppler findings observed between pregnant women who were positive for SARS-CoV-2 and controls. However, preterm delivery ≤ 35 weeks was more frequent among SARS-CoV-2-positive women.* © *2021 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection among pregnant women has been reported to be 14–15%, with most (50–90%) women being asymptomatic[1–4]. Only a small percentage show severe symptoms, mainly during the third trimester of pregnancy[2]; among these women, there is a higher risk of severe complications and death[5,6]. Nevertheless, most pregnant women who are positive for SARS-CoV-2 are asymptomatic and have a low prevalence of perinatal complications. Initially, there was an overreaction concerning the potential complications of SARS-CoV-2 in pregnancy, with an increase in rate of indicated preterm birth in order to avoid fetal exposure to the virus[7]. However, now that clinical experience has accumulated, the general consensus is that only minimal or mild fetal side effects are associated with maternal SARS-CoV-2 infection during pregnancy[8,9], despite evidence of vertical transmission of the virus[10]. Nevertheless, the association between SARS-CoV-2 and preterm birth seems to be reported consistently[11–13]. There is a need for more data on the effect of SARS-CoV-2 during pregnancy, in particular prenatal imaging. The aim of this study was to describe ultrasound and Doppler findings in pregnant women who tested positive for SARS-CoV-2 at the time of obstetric ultrasound evaluation and to compare these with findings in SARS-CoV-2-negative controls.

METHODS

This was a retrospective case–control study of pregnant women who had an obstetric ultrasound examination as either an outpatient or an inpatient while under the care of the Maternal Fetal Medicine (MFM) Division of the University of Texas McGovern Medical School, Department of Obstetrics and Gynecology, between 1st May and 31st August 2020, during the coronavirus disease 2019 (COVID-19) pandemic. The MFM Division covers 10 outpatient ultrasound units and seven hospitals within the Memorial Hermann Hospital system in the greater Houston area. Outpatient ultrasound units screened for SARS-CoV-2 symptoms using a questionnaire and body temperature. Prior to admission, all labor and delivery units implemented universal screening via SARS-CoV-2 viral RNA polymerase chain reaction (PCR) or SARS-CoV-2 rapid antigen tests of nasopharyngeal samples. Cases included in this study were all patients who were admitted for delivery and tested positive for SARS-CoV-2, and those with a confirmed antepartum outpatient positive SARS-CoV-2 result who were scheduled for an ultrasound appointment. We evaluated 106 SARS-CoV-2-positive pregnant women, of whom 75 had a positive SARS-CoV-2 test result within 7 days after the ultrasound scan and 31 had a clinically indicated ultrasound examination due to a positive SARS-CoV-2 test. Both symptomatic and asymptomatic patients were included. SARS-CoV-2 infection was diagnosed by a positive SARS-CoV-2 viral RNA PCR or SARS-CoV-2 rapid antigen test carried out on nasopharyngeal samples. Symptomatic patients were classified according to their symptoms as mild or severe. All patients with severe symptoms required oxygen supplementation to maintain pulse oximetry above 95%. Mild cases manifested symptoms such as cough, fever, malaise, diarrhea and anosmia/ageusia, but did not require oxygen supplementation. Asymptomatic carriers attended the ultrasound unit for a routine examination and were screened negative based on the questionnaire and temperature reading, but tested positive after the ultrasound examination, on subsequent hospitalization or obstetric triage evaluation.

For each case, we carried out a computer search of our database to select a control patient matched for maternal age, body mass index (BMI), gestational age at the time of ultrasound examination and parity, and with an obstetrical ultrasound examination completed during the pandemic period. These control women screened negative for SARS-CoV-2 symptoms at the time of the ultrasound scan and at the time of admission for delivery and had a negative SARS-CoV-2 test at the time of admission for delivery.

Ultrasound and Doppler studies

Ultrasound examinations of patients known to be positive for SARS-CoV-2 were performed following guidelines and recommendations for optimal protection to reduce the risk of viral transmission between the ultrasound operator and the patient. This included: N95 face mask, shield or goggles, hair cover and gown, along with proper disinfection of the room and ultrasound machine before and after each scan[14,15]. In women for whom the diagnosis of SARS-CoV-2 was not known, the ultrasound scan was performed following the recommendations of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) to reduce the risk of viral transmission[16,17]. The routine ultrasound evaluation included fetal biometry, anatomy evaluation, assessment of amount of amniotic fluid and, in the event of a small-for-gestational-age (SGA) fetus, Doppler examination of the umbilical artery (UA), fetal middle cerebral artery (MCA) and cerebroplacental ratio (CPR). In women with known SARS-CoV-2 infection at the time of the ultrasound scan, whether symptomatic or asymptomatic, fetal biometry, anatomy evaluation, Doppler velocimetry of the UA and MCA, and fetal biophysical

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profile (BPP) were performed. Control cases were evaluated according to their ultrasound indication, and the evaluation always included fetal biometry, anatomy evaluation and determination of amniotic fluid volume. Doppler velocimetry was performed only in SGA fetuses, and BPP was assessed for maternal/fetal indications.

Fetal biometry included measurement of biparietal diameter, head circumference, abdominal circumference and femur length, and calculation of estimated fetal weight (EFW)[18,19]. A fetus was SGA when EFW was $< 10^{th}$ percentile for gestational age according to the Hadlock charts[19]. Doppler velocimetry, including UA pulsatility index (PI), MCA-PI and CPR, were recorded following ISUOG recommendations[20]. Biometric and Doppler values were converted to *z*-scores for comparison. UA-PI was considered abnormal if $> 95^{th}$ percentile (> 1.65 *Z*-score) for gestational age. MCA-PI and CPR were considered abnormal if $< 5^{th}$ percentile (< -1.65 *Z*-score) for gestational age[21]. The BPP included four parameters (fetal movements, fetal tone, fetal breathing and maximum vertical pocket); BPP ≤ 6 was considered abnormal[22,23].

Ultrasound studies performed both at the time of and after SARS-CoV-2 diagnosis were evaluated. Biometric and Doppler values were transformed into *Z*-scores according to reference charts[24] and values were compared between women who were positive for SARS-CoV-2 and those who tested negative. The prevalence of complications, including SGA fetus, abnormal amniotic fluid volume, abnormal ultrasound and Doppler findings and adverse perinatal outcome, i.e. perinatal death, preterm delivery ≤ 35 weeks of gestation, low birth weight ($< 10^{th}$ percentile), 1-min and 5-min Apgar scores ≤ 6, was compared between the two groups. An adverse prenatal composite outcome (APCO), which was defined as the primary outcome, and included any one or more of: SGA, reduced amniotic fluid (defined as amniotic fluid index < 5 and/or maximum vertical pocket < 2 cm), abnormal BPP, abnormal Doppler velocimetry and fetal death, was evaluated and compared between the two groups. Comorbidities, delivery information and neonatal outcome were compared between the two groups. The prevalence of APCO in symptomatic and in asymptomatic SARS-CoV-2-positive women was also estimated.

Statistical analysis

Descriptive statistics for baseline clinical characteristics of both groups were applied. Continuous data were evaluated with one way analysis of variance (ANOVA) or Student's *t*-test. Percentages and fractions were compared using Fisher's exact test or the chi-square test. Associations were analyzed using logistic regression models; in addition to the matching process, regression analyses were further adjusted for maternal age, weight and parity. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS statistical software (version 26.0; IBM Corp, Armonk, NY, USA).

This study qualified for exempt status by the Institutional Review Board at the McGovern Medical School at the University of Texas Health Science Center at Houston (HSC-MS-14-0632). Data evaluation complied with the guidelines for human studies, and data collection was conducted ethically in accordance with the World Medical Association and the Declaration of Helsinki, under Institutional Review Board approval (HSC-MS-14-0632). STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies were followed[25].

RESULTS

A total of 106 SARS-CoV-2-positive and 103 SARS-CoV-2-negative pregnant women were analyzed. Maternal characteristics are shown in Table 1. Among the 106 patients who were positive for SARS-CoV-2, 87 (82.1%) had a BMI > 25 kg/m^2, the median gestational age at the ultrasound examination closest to the positive test was $33 + 1$ weeks, the median number of ultrasound scans per patient was two (range, 1–9) and the median gestational age at the time of the SARS-CoV-2-positive test was $32 + 6$ (range, $10 + 6$ to $40 + 3$) weeks. There was a similar number of twin pregnancies in both groups. The median gestational age at delivery and frequency of delivery by Cesarean section were not different between the two groups. Among women who were positive for SARS-CoV-2, 57 (53.8%) were asymptomatic and 49 (46.2%) were symptomatic, of whom 19 had severe symptoms and 30 had mild clinical manifestations (Tables 1 and 2).

The prevalence of maternal comorbidity was higher among SARS-CoV-2-positive women (76/106 (71.7%)) than in controls (50/103 (48.5%); $P = 0.007$), mainly due to a greater number of women with diabetes (26/106 (24.5%) *vs* 13/103 (12.6%); $P = 0.03$) (Table 3). There were no significant differences between the two groups in the prevalence of chronic complications, i.e. asthma, lupus, human immunodeficiency virus and hepatitis C. The prevalence of hypertensive disorders was not significantly different between the groups, although there was a trend towards a higher prevalence of pre-eclampsia in women who tested positive for SARS-CoV-2 (21/106 (19.8%) *vs* 11/103 (10.7%); $P = 0.08$). The high prevalence of complications observed, including pre-eclampsia, can be attributed to the characteristics of this selected population in which more than 80% were overweight and more than 50% obese.

The prevalence of APCO in SARS-CoV-2-positive women was not significantly different from that in controls (19/106 (17.9%) *vs* 9/103 (8.7%); $P = 0.06$) (Table 4) and SARS-CoV-2 positivity was not significantly associated with an increase in APCO (odds ratio (OR), 2.28; 95% CI, 0.97–5.31), compared with controls. There were no significant differences between SARS-CoV-2-positive women and controls in the prevalence of SGA fetuses (12/106 (11.3%) *vs* 6/103 (5.8%); $P = 0.17$), fetuses with abnormal Doppler evaluation (8/106 (7.5%) *vs* 2/103 (1.9%); $P = 0.08$) and fetuses with abnormal BPP (4/106 (3.8%) *vs* 0/103 (0%); $P = 0.14$). There was no difference in the prevalence of abnormal

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Table 1 Clinical characteristics of study group of pregnant women who were positive for SARS-CoV-2 infection and negative controls

Characteristic	*SARS-CoV-2-positive* (n = *106*)	*Negative controls* (n = *103*)	P
Maternal age (years)	28 (15–42)	29 (17–42)	0.27
Gravidity	2 (1–10)	2 (1–7)	1.0
Primigravida	14 (13.2)	9 (8.7)	0.37
GA at ultrasound nearest SARS-CoV-2 test (weeks)*	33 + 1 (11 + 3 to 38 + 4)	30 + 2 (10 + 2 to 39 + 0)	0.34
GA at last scan (weeks)	34 + 3 (18 + 0 to 38 + 4)	35 + 0 (14 + 1 to 40 + 0)	0.20
Body mass index (kg/m^2)	32.6 ± 8.1 (18.0–54.6)	33.1 ± 8.4 (19.0–54.1)	0.70
Body mass index > 25 kg/m^2	87 (82.1)	82 (79.6)	0.47
Body mass index > 30 kg/m^2	58 (54.7)	58 (56.3)	0.89
Nulliparous	33 (31.1)	28 (27.2)	0.54
Singleton pregnancy	100 (94.3)	99 (96.1)	0.71
Twin pregnancy	6 (DCDA, *n* = 3; MCDA, *n* = 3)	4 (DCDA, *n* = 3; MCDA, *n* = 1)	0.74
GA at SARS-CoV-2-positive test (weeks)	32 + 6 (10 + 6 to 40 + 3)	NA	NA
Asymptomatic	57 (53.8)	NA	NA
Symptomatic: mild	30 (28.3)	NA	NA
Symptomatic: severe	19 (17.9)	NA	NA
GA at delivery (weeks)	37 + 5 (23 + 5 to 40 + 1)	38 + 1 (25 + 2 to 40 + 5)	0.09
Vaginal delivery	77 (72.6)	62 (60.2)	0.06
Cesarean section	29 (27.4)†	41 (39.8)‡	0.06

Data are given as median (range), *n* (%), mean ± SD (range) or *n*, unless stated otherwise. *For controls, GA at corresponding ultrasound examination. †Including 11 repeat Cesarean sections, eight with abnormal fetal heart rate (FHR) and 10 with other obstetric indications. ‡Including 15 repeat Cesarean sections, 11 with abnormal FHR and 15 with other obstetric indications. DCDA, dichorionic diamniotic; GA, gestational age; MCDA, monochorionic diamniotic; NA, not applicable.

Table 2 Symptoms in 49 SARS-CoV-2-positive pregnant women

Symptom	n *(%)*
Women with severe symptoms (*n* = 19)	
Oxygen required	19 (100)
Cough	13 (68.4)
Fever	11 (57.9)
Pneumonia	9 (47.4)
Chest pain	5 (26.3)
Anosmia/ageusia	3 (15.8)
Nasal congestion	1 (5.3)
Diarrhea	1 (5.3)
Women with mild symptoms (*n* = 30)	
Cough	15 (50.0)
Anosmia/ageusia	13 (43.3)
Fever	8 (26.7)
Diarrhea	4 (13.3)
Shortness of breath	6 (20.0)
Runny nose	3 (10.0)
Nasal congestion	3 (10.0)
Fatigue	1 (3.3)
Chills	1 (3.3)
Chest pain	1 (3.3)
Sore throat	1 (3.3)
Myalgia	1 (3.3)
Fetal tachycardia	1 (3.3)

amniotic fluid volume or structural anomalies between the two groups (Table 4). SARS-CoV-2 positivity was not significantly associated with an increased rate of SGA fetuses (OR, 1.86 (95% CI, 0.67–5.18); $P = 0.2$) or abnormal Doppler velocimetry parameters (OR, 3.88 (95% CI, 0.80–17.80); $P = 0.08$) compared with controls. Analysis of subsequent ultrasound scans showed no changes over time in fetal size (Figures 1 and 2) or in Doppler velocimetry values among SARS-CoV-2-positive women (Figure 3). There were no differences in fetal biometric and Doppler parameters between SARS-CoV-2-positive women and negative controls (Table 5) or in the frequency of the APCO or of individual adverse outcomes between asymptomatic and symptomatic SARS-CoV-2-positive women (Table 6).

There were two fetal deaths in women who were positive for SARS-CoV-2; both were asymptomatic. One woman had hypothyroidism and her fetus developed early and severe SGA. UA-PI and CPR were abnormal at ultrasound examination. She presented with placental abruption and fetal demise at 24 + 5 weeks of gestation. The second patient had hyperthyroidism and developed a SGA fetus with abnormal CPR. She was followed up with serial Doppler and BPP evaluations, but presented at 34 weeks with fetal demise. No other comorbidities were documented in either patient.

Among all 106 pregnant women who tested positive for SARS-CoV-2 infection, there were no ultrasound findings related to fetal infection such as calcifications of the brain, liver, lung or bowel or areas of increased echogenicity, no fetal hydrops, pericardial effusion, ascites or skin edema. There were no structural abnormalities noted in any fetus. However, most of our cases with SARS-CoV-2 infection occurred in the second or third trimester, after organogenesis was complete. Of note, one fetus had evidence of premature atrial contractions (fetal arrhythmia) at 26 weeks of gestation. This mother was tested for SARS-CoV-2 for other indications and was found to be positive on the same day on which the fetal arrhythmia was detected. A normal fetal heart had been reported in previous ultrasound examinations in this patient.

There was a higher prevalence of preterm delivery ≤ 35 weeks of gestation (22/106 (20.8%) *vs* 9/103 (8.7%); OR, 2.73 (95% CI, 1.19–6.3); $P = 0.01$) in women who were positive for SARS-CoV-2 compared

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Table 3 Comorbidities in pregnant women who were positive for SARS-CoV-2 infection and corresponding morbidities in negative controls

Parameter	*SARS-CoV-2-positive* (n = *106*)	*Negative controls* (n = *103*)	P
Maternal (co)morbidity	76 (71.7)	50 (48.5)	0.007
Pre-eclampsia	21 (19.8)	11 (10.7)	0.08
Hypertensive disorder other than pre-eclampsia	17 (16.0)	18 (17.5)	0.8
Diabetes	26 (24.5)	13 (12.6)	0.03
Anemia	8 (7.5)	7 (6.8)	1.0
Asthma	8 (7.5)	4 (3.9)	0.4
Cholestasis	4 (3.8)	5 (4.9)	0.7
Hypothyroidism	4 (3.8)	2 (1.9)	0.7
Hyperthyroidism	1 (0.9)	0	1.0
Thyroiditis	1 (0.9)	0	1.0
Lupus	2 (1.9)	0	0.5
Other	11 (10.4)*	7 (6.8)†	0.5
Number of comorbidities			
One	52/76 (68.4)	34/50 (68.0)	1.0
Two	21/76 (27.6)	15/50 (30.0)	0.8
Three	3/76 (3.9)	1/50 (2.0)	1.0

Data are given as *n* (%) or *n*/*N* (%). *One case each of: epilepsy, syphilis, Von Willebrand disease, human immunodeficiency virus, hepatitis C, consanguinity, pyelonephritis, bariatric surgery, sickle cell disease, breast cancer and bicornuate uterus. †One case each of: pancreatitis, Von Willebrand disease, breast cancer, epilepsy, gastroenteritis, protein S deficiency and fibroids.

Table 4 Fetal ultrasound findings in pregnant women who were positive for SARS-CoV-2 infection and negative controls

Finding	*SARS-CoV-2-positive* (n = *106*)	*Negative controls* (n = *103*)	*Odds ratio (95% CI)*	P
APCO*	19	9	2.28 (0.97–5.31)	0.06
SGA fetus	12	6	1.86 (0.67–5.18)	0.17
Abnormal BPP	4	0	9.08 (0.48–170.90)	0.14
Abnormal Doppler findings	8	2	3.88 (0.80–17.80)	0.08
Oligohydramnios	3	2	1.50 (0.24–8.91)	0.6
Fetal death	2†	0	4.95 (0.23–104.40)	0.3
Premature atrial contractions	1	0	2.94 (0.11–73.00)	0.51
Ventricular septal defect	1	1	0.97 (0.06–15.30)	0.9
Pericardial effusion	0	1	0.30 (0.01–7.96)	0.48
Echogenic bowel	1	1	0.97 (0.06–15.30)	0.9
Placental anomalies	1	1	0.97 (0.06–15.30)	0.9
Placental abruption	1	0	2.94 (0.11–73.00)	0.51
Missed miscarriage	1	0	2.94 (0.11–73.00)	0.51

Data are given as *n*, unless stated otherwise. *Adverse prenatal composite outcome (APCO) included any one or more of: small-for-gestational age (SGA), oligohydramnios (defined as amniotic fluid index < 5 and/or maximum vertical pocket < 2 cm), abnormal fetal biophysical profile (BPP), abnormal Doppler velocimetry and fetal death. †One placental abruption, one severe fetal growth restriction.

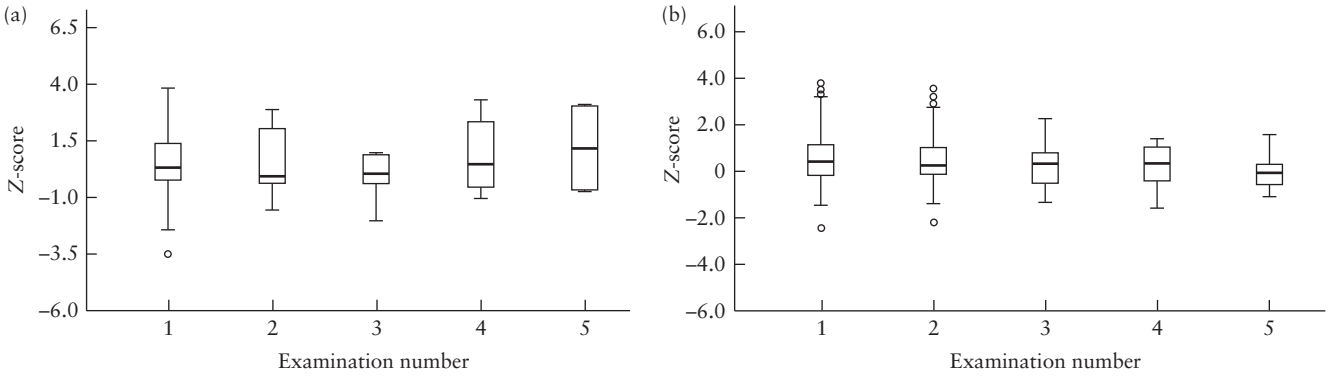

Figure 1 Box-and-whiskers plots of estimated fetal weight *Z*-scores in pregnant women who tested positive for SARS-CoV-2 (a) and in negative controls (b), at first and subsequent ultrasound evaluations. Boxes with internal lines represent median and interquartile range (IQR), whiskers are 1.5 × IQR from upper and lower quartile and circles are outliers.

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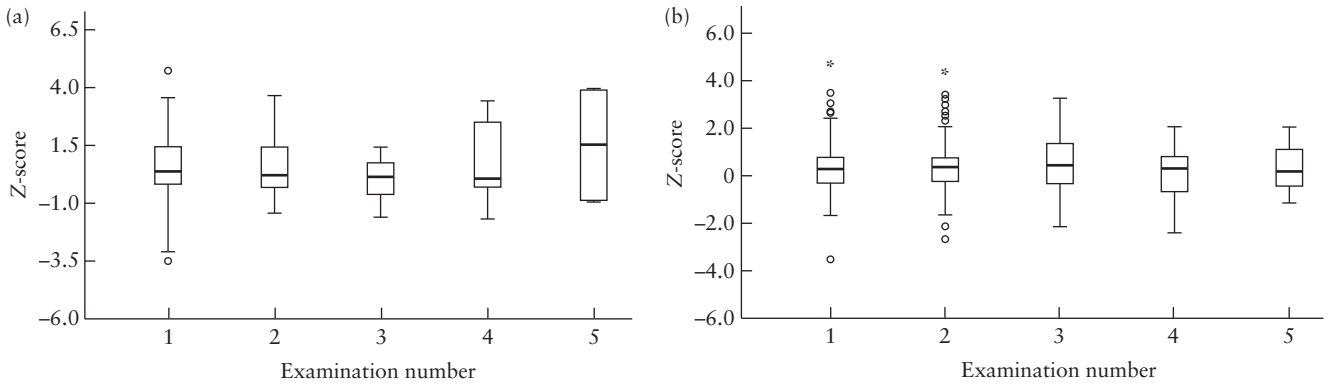

Figure 2 Box-and-whiskers plots of fetal abdominal circumference *Z*-scores in pregnant women who tested positive for SARS-CoV-2 (a) and in negative controls (b), at first and subsequent ultrasound evaluations. Boxes with internal lines represent median and interquartile range (IQR), whiskers are 1.5 × IQR from upper and lower quartile, circles are outliers and asterisks represent an uneven distribution of outliers.

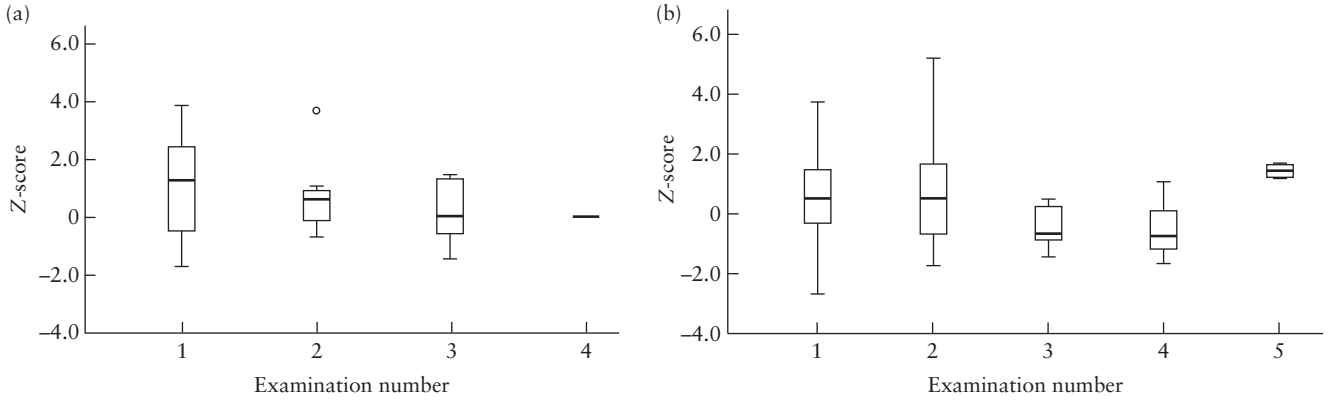

Figure 3 Box-and-whiskers plots of umbilical artery pulsatility index *Z*-scores in pregnant women who tested positive for SARS-CoV-2 (a) and in negative controls (b), at first and subsequent ultrasound evaluations. Boxes with internal lines represent median and interquartile range (IQR), whiskers are 1.5 × IQR from upper and lower quartile and circles are outliers.

Table 5 Fetal biometry and Doppler values (*Z*-scores) in 106 pregnant women who were positive for SARS-CoV-2 infection and 103 negative controls

Parameter	*SARS-CoV-2-positive*	*Negative controls*	P
Biparietal diameter	0.6 ± 1.1	0.2 ± 1.08	0.94
Head circumference	0.4 ± 1.08	−0.1 ± 1.03	0.21
Abdominal circumference	1.5 ± 3.4	0.3 ± 1.06	0.14
Femur length	−0.1 ± 0.49	−0.07 ± 0.8	0.41
Estimated fetal weight	1.2 ± 2.7	0.4 ± 1.04	0.29
Umbilical artery pulsatility index	0.67 ± 1.49	0.4 ± 1.6	0.22
Middle cerebral artery pulsatility index	−0.43 ± 1.18	−0.3 ± 1.2	0.9
Cerebroplacental ratio	−0.64 ± 1.07	−0.6 ± 2.3	0.38
Amniotic fluid MVP (cm)	4.9 (0–9.7)	5.1 (2.9–9.5)	0.22
Amniotic fluid index (cm)	14.2 (0–29.1)	13.6 (3.6–30.7)	0.7

Data expressed as mean ± SD or median (range). MVP, maximum vertical pocket.

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Table 6 Adverse prenatal composite outcome (APCO)* and individual adverse perinatal outcomes in 106 pregnant women who were positive for SARS-CoV-2 infection, according to COVID-19 symptoms

Outcome	*Asymptomatic (n = 57)*	*Symptomatic (n = 49)*	P	*Mild symptoms (n = 30)*	*Severe symptoms (n = 19)*
APCO	10 (17.5)	9 (18.4)	1.0	3	6
Abnormal Doppler findings	5 (8.7)	3 (6.1)	0.72	1	2
SGA fetus with or without abnormal Doppler findings	7 (12.3)	5 (10.2)	0.8	2	3
Fetal death	2 (3.5)	0	0.5	0	0
Oligohydramnios	1 (1.8)	2 (4.1)	0.6	1	1
Abnormal BPP	2 (3.5)	2 (4.1)	1.0	1	1
Preterm delivery ≤ 35 weeks	9 (15.8)	13 (26.5)	0.23	9	4
Low birth weight (< 10th centile)	7 (12.3)	5 (10.2)	0.77	2	3
1-min Apgar score ≤ 6	7 (12.3)	5 (10.2)	0.8	4	1
5-min Apgar score ≤ 6	3 (5.3)	2 (4.1)	1.0	1	1

Data are given as *n* (%) or *n*. *APCO included any one or more of: small-for-gestational age (SGA), oligohydramnios (defined as amniotic fluid index < 5 and/or maximum vertical pocket < 2 cm), abnormal fetal biophysical profile (BPP), abnormal Doppler velocimetry and fetal death.

Table 7 Perinatal outcome of pregnant women who were positive for SARS-CoV-2 infection and negative controls

Outcome	*SARS-CoV-2-positive (n = 106)*	*Negative controls (n = 103)*	*Odds ratio (95% CI)*	P
GA at delivery (weeks)	37 + 5 (23 + 5 to 40 + 1)	38 + 1 (25 + 2 to 40 + 5)	—	0.004
Birth weight (g)	2896 (490–4300)	3106 (750–4660)	—	0.056
Low birth weight (< 10th centile)	12 (11.3)	15 (14.6)	0.74 (0.33–1.68)	0.48
1-min Apgar score ≤ 6	12 (11.3)	7 (6.8)	1.75 (0.66–4.63)	0.26
5-min Apgar score ≤ 6	5 (4.7)	1 (1.0)	5.04 (0.57–43.9)	0.14
Admitted to NICU	39 (36.8)*	15 (14.6)	3.41 (1.73–6.70)	0.004
Admitted to NICU not due to maternal SARS-CoV-2 exposure	29 (27.4)†	15 (14.6)‡	2.20 (1.10–4.40)	0.02
Term delivery	84 (79.2)	94 (91.3)	0.36 (0.15–0.83)	0.01
Term delivery and SGA	7/84 (8.3)	14/94 (14.9)	0.51 (0.20–1.36)	0.9
Preterm delivery ≤ 35 weeks	22 (20.8)	9 (8.7)	2.73 (1.19–6.3)	0.01
Preterm delivery ≤ 35 weeks and SGA	5/22 (22.7)	1/9 (11.1)	2.35 (0.23–23.6)	0.46

Data are given as median (range) or *n* (%), unless stated otherwise. *Ten due to SARS-CoV-2 exposure. †Admitted mainly for prematurity. ‡Nine admitted due to prematurity and six for complications during delivery. GA, gestational age; NICU, neonatal intensive care unit; SGA, small-for-gestational age.

with controls (Table 7). Among SARS-CoV-2-positive women, the prevalence of preterm delivery was similar between women with (13/49) and those without (9/57) COVID-19 symptoms ($P = 0.23$) (Table 6). There was no difference in low birth weight between neonates of SARS-CoV-2-positive women and those of control women (12/106 (11.3%) *vs* 15/103 (14.6%); OR, 0.74 (95% CI, 0.33–1.68); $P = 0.48$). Most (14/15) low birth-weight newborns of SARS-CoV-2-negative women were born at term, of which only six (40%) were diagnosed before delivery. This is likely to be related to the time at which ultrasound examination was performed and subsequent development of a SGA fetus. Among SARS-CoV-2-positive women, the higher identification of SGA fetuses may be related to a more detailed evaluation by the ultrasound operator.

DISCUSSION

There were no significant differences in the prevalence of abnormal ultrasound and Doppler findings between SARS-CoV-2-positive pregnant women and negative controls, or between SARS-CoV-2-positive women with mild and those with severe clinical symptoms, or between SARS-CoV-2-positive pregnant women with and those without comorbidity. While there was a higher frequency of SGA fetus and of fetus with abnormal Doppler parameters in SARS-CoV-2-positive pregnant women compared with controls, these differences did not reach statistical difference. Nevertheless, our results add to the increasing number of publications showing a higher prevalence of obesity, diabetes, thyroid disease and preterm delivery among pregnant women who test positive for SARS-CoV-2[26–30].

SARS-CoV-2 is the third of a group of known coronaviruses, including Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV)[31]. Despite the initial assumption of severe adverse side effects, it is now agreed that maternal and perinatal repercussions from SARS-CoV-2 are less severe than those from MERS-CoV and SARS-CoV infections[32]. Nevertheless, data from single-center reports, systematic reviews and

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meta-analyses[33–35] have shown that SARS-CoV-2 infection may indeed have perinatal complications, although whether this is due to worsening maternal condition, interactions with maternal comorbidity or vertical transmission of the virus remains unknown. Vertical transmission of SARS-CoV-2 has been demonstrated by the presence of the virus in maternal, placental and neonatal samples[10,36]; however, this seems to be a rare event[37]. Cell invasion by SARS-CoV-2 differs from that of other viruses in that SARS-CoV-2 invasion depends on ACE-2 (angiotensin-converting enzyme 2) and TMPRS-2 (transmembrane serine protease 2) receptors[38–40]. Pique-Regi *et al.*[41] reported low expression of these receptors in placentae from SARS-CoV-2-positive women, suggesting a low likelihood of vertical transmission, although they suggested that SARS-CoV-2 may interact with other proteins to use alternative routes to invade cells. It may also be possible that comorbidities, such as chronic hypertension and those related to chronic inflammation, such as obesity and diabetes, can affect the renin-angiotensin-aldosterone system and facilitate the vertical transmission of SARS-CoV-2[42–45].

Our results did not show a higher prevalence of abnormal ultrasound and Doppler findings in pregnant women who were positive for SARS-CoV-2 compared with controls. We could not find any previous reports comparing ultrasound and Doppler parameters between pregnant women who were SARS-CoV-2 positive with those who tested negative. The main perinatal complication reported in the literature associated with SARS-CoV-2 infection in pregnancy is preterm delivery. However, several studies have highlighted the occurrence of fetal death among SARS-CoV-2-positive women. In a study from Brazil, five fetal deaths occurring between 21 and 38 weeks of gestation in women who were positive for SARS-CoV-2 were reported[46]; in two cases, the authors confirmed vertical transmission by PCR analysis of placental samples, in two cases, PCR of placental samples was not performed and, in one case, the PCR result was negative. All five cases showed histopathological signs of placental infection, including chorioamnionitis and villitis. The authors concluded that fetal death might have been related to SARS-CoV-2 infection. Di Mascio *et al.*[47] performed a systematic review and meta-analysis of the outcomes of coronavirus spectrum infections during pregnancy, including SARS-CoV, MERS-CoV and SARS-CoV-2 infections. They included 41 patients with SARS-CoV-2 infections, reporting that, among these, there was a 41.1% prevalence of preterm delivery < 37 weeks, 14.6% had pre-eclampsia, 18.8% had preterm prelabor rupture of the membranes and in 7% there was perinatal death. A different report from the same authors[48], analyzing 266 pregnant women who were positive for SARS-CoV-2, from 73 different centers and 22 countries, showed a prevalence of 26.3% ($n = 70$) for preterm delivery, 2.3% ($n = 6$) for stillbirth, 4.1% ($n = 11$) for perinatal death and 3.8% ($n = 10$) for fetal growth restriction. They explained that the increased rate of perinatal mortality was most probably related to prematurity. In Sweden, Ramaeus *et al.*[49] reported their findings in 67 women (with 68 fetuses) who were positive for SARS-CoV-2, showing a prevalence of 19% ($n = 13$) for preterm delivery (< 37 weeks) and two perinatal deaths, one in a normally grown fetus and one in a growth-restricted fetus. All this information has led to the conclusion that preterm delivery and stillbirth might be more common among pregnant women infected with SARS-CoV-2. The two fetal deaths seen in our population occurred in asymptomatic women, both having thyroid comorbidities and placental complications (i.e. one with placental abruption and one with severe fetal growth restriction). Unfortunately, findings regarding the presence of SARS-CoV-2 infection in the placentae or stillbirths were inconclusive. In our cohort there was one fetus with premature atrial contractions whose mother tested positive for SARS-CoV-2 on the same day as the ultrasound scan. Since completion of our analysis, we have seen three more similar cases, in which premature atrial contractions were noted with a concurrent SARS-CoV-2-positive test. Whether this is a sporadic finding or a related complication is unclear and requires further investigation. The association between SARS-CoV-2 and preterm delivery has been described in several studies, with the reported prevalence of PTD in positive pregnancies being higher than 20%[29,47]. Our results, showing a rate of preterm delivery ≤ 35 weeks of 20.8%, almost two and a half times higher than that in control women, are in accordance with these reports.

Whether prenatal care should be modified in SARS-CoV-2-positive pregnant women is still unknown. However, it seems that ultrasound and Doppler velocimetry do not provide additional information, unless the fetus is SGA, which, in turn, can be associated with comorbidities such as hypertensive disorders and diabetes. The lack of specific fetal ultrasound signs in SARS-CoV-2-positive pregnant women suggests that increasing the frequency of scans or using Doppler velocimetry in a normally grown fetus may not be indicated.

Strengths and weaknesses

It is a strength of our study that we included a relatively large number of women with a SARS-CoV-2-positive test, and performed longitudinal evaluations in most cases. In addition, we analyzed the association of SARS-CoV-2 infection and maternal comorbidities and compared our results with control women with similar clinical characteristics. A weakness of our study is that we did not test all women attending the ultrasound unit; most of the positive cases in our study did not know if they were infected at the time of the ultrasound examination, but all had a positive SARS-CoV-2 test result within 7 days after the ultrasound scan. It has been estimated that, after viral exposure, 4–5 days is the average latency period prior to seroconversion and a positive test[50]. We therefore considered that fetuses had already been exposed to the virus at the time of the ultrasound evaluation. Pregnant women who were positive for SARS-CoV-2 and negative

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controls were matched by age, gestational age, BMI and parity; however, we did not match for other variables that may affect results, such as tobacco use or socioeconomic status. We did not match for complications in pregnancy, as one of our main aims was to document differences in the prevalence of comorbidities between women who were positive for SARS-CoV-2 and those who were negative. Our results showed that only diabetes was significantly more frequent among SARS-CoV-2-positive pregnant women. We did not test the placentae after birth. Finally, our study was a retrospective analysis of cases and controls, rather than a prospective cohort study.

Conclusion

There were no significant differences in ultrasound and Doppler findings observed between pregnant women who were positive for SARS-CoV-2 and controls. However, a higher prevalence of preterm delivery ≤ 35 weeks was documented among women who were positive for SARS-CoV-2.

ACKNOWLEDGMENT

We are very grateful to all Registered Diagnostic Medical Sonographers (RDMS) of the University of Texas McGovern Medical School Department of Obstetrics and Gynecology, who performed ultrasound scans during the COVID-19 pandemic at risk to their own health.

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