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Can Prenatal Ultrasound Predict Adverse Neonatal Outcomes in SARS-CoV-2 Affected Pregnancies?

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Condensation: Pregnancies affected by fetal growth restriction after SARS-CoV-2 infection were associated with an increased risk for adverse neonatal outcomes and may require close surveillance.

Short Title: Ultrasound in SARS-CoV-2 Affected Pregnancies

AJOG MFM at a Glance:

A. Why was this study conducted?

Reports on prenatal sonographic findings and associations with neonatal outcomes following SARS-CoV-2 infection in pregnancy have been inconclusive. We aim to describe the sonographic characteristics of pregnancies after confirmed SARS-CoV-2 infection and assess the association of ultrasound findings with adverse neonatal outcomes.

B. What are the key findings?

In a prospective observational cohort, fetal growth restriction that develops in SARS-CoV-2 affected pregnancies is associated with increased rates of adverse neonatal outcomes, even when controlling for potential confounding factors.

C. What does this study add to what is already known:

Composite adverse neonatal outcomes are high in pregnancies affected by SARS-CoV-2 infection. Pregnancies that develop fetal growth restriction after SARS-CoV-2 infection may be at increased risk for adverse neonatal outcomes and require close surveillance.

Disclosure: The authors report no conflict of interest

Keywords: SARS-CoV-2 infection, pregnancy, ultrasound, fetal growth restriction, adverse neonatal outcome

ABSTRACT

Background: Based on available data, at least one ultrasound assessment of pregnancies recovering from SARS-CoV-2 infection is recommended. Reports, however, on prenatal imaging findings and potential associations with neonatal outcomes following SARS-CoV-2 infection in pregnancy have been inconclusive.

Objective: We aim to describe the sonographic characteristics of pregnancies after confirmed SARS-CoV-2 infection and assess the association of prenatal ultrasound (US) findings with adverse neonatal outcomes (ANO).

Study Design: This is an observational prospective cohort study of pregnancies diagnosed with SARS-CoV-2 by reverse transcription polymerase chain reaction between March 2020 and May 2021. Prenatal US evaluation was performed at least once after diagnosis of infection with the following parameters measured: standard fetal biometric measurements, umbilical and middle cerebral artery Dopplers, placental thickness, amniotic fluid volume, and anatomic survey for infection-associated findings. The primary outcome was composite ANO, defined as one or more of the following: preterm birth, NICU admission, small for gestational age (SGA), respiratory

distress, intrauterine fetal demise, neonatal demise, or other neonatal complications. Secondary outcomes were sonographic findings stratified by trimester of infection and severity of SARS-CoV-2 infection. Prenatal US findings were compared with neonatal outcomes, severity of infection, and trimester of infection.

Results: A total 103 SARS-CoV-2 affected mother-infant pairs with prenatal US evaluation were identified; 3 cases were excluded due to known major fetal anomalies. Of the 100 included cases, neonatal outcomes were available in 92 pregnancies (97 infants); of these, 28 (29%) had a composite ANO. Twenty-three (23%) had at least one abnormal prenatal US finding. The most common abnormalities seen on US were placentomegaly (11/23, 47.8%) and fetal growth restriction (FGR) (8/23, 34.8%). FGR was associated with a higher rate of a composite ANO (25% vs 1.5%; aOR: 22.67; 95% 95% CI, 2.63-194.91; p<0.001), even when SGA was removed from the composite ANO. Cochran-Mantel Haensel test controlling for possible FGR confounders continued to show this association (relative risk, 3.7; 95% confidence interval, 2.6-5.9; p<0.001). Median estimated fetal weight (EFW) and birthweight were lower in patients with a composite ANO (p<0.001). Infection in the third trimester was associated with lower median percentile of EFW (p=0.019). An association between placentomegaly and third trimester SARS CoV-2 infection was noted (p=0.045).

Conclusion: In our study of SARS-CoV-2 affected maternal-infant pairs, rates of FGR were comparable to the general population. However, composite ANO rates were high. Pregnancies with FGR after SARS-CoV-2 infection were associated with an increased risk for ANO and may require close surveillance.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected over 765 million people worldwide and resulted in over 6.9 million deaths to date.[1] Its prevalence among pregnant patients has been reported around 14-15% with over 220,000 cases, with most cases being asymptomatic.[2,3,4,5,6] Newer data report rates of SARS-CoV-2 positivity in asymptomatic patients presenting for labor and delivery ranging from 0.45% to 19.9%.[7,8]

Pregnant patients who develop severe symptoms due to Coronavirus Disease of 2019 (COVID-19) are usually in the third trimester of pregnancy; where there is a higher risk of severe morbidity and mortality.[9,10] Overall, pregnancy increases the risk for severe SARS-CoV-2 infection with higher rates of intensive care unit (ICU) admissions, need for mechanical ventilation, and death as compared to nonpregnant individuals and pregnant individuals without COVID-19, though this research was mostly done prior to universal vaccine availability.[11,12]

Reports thus far on fetal and neonatal effects following SARS-CoV-2 infection in pregnancy have been inconclusive. Some studies have reported minimal differences in maternal or neonatal morbidities, while others have suggested an increased risk for fetal death, preeclampsia, preterm birth, and low birthweight infants.[13,14,15,16] Based on available data, at least one US assessment 14 days after symptom resolution in pregnancies affected by SARS-CoV-2 infection is recommended.[17]

With the continued emergence of SARS-CoV-2 variants, cases will continue to accrue in pregnant individuals. The ability to predict adverse pregnancy and neonatal outcomes with existing technology requires further investigation. Given the recommendation for universal US assessment in all pregnancies affected by SARS-CoV-2 infection, we aimed to describe the

sonographic characteristics of pregnancies after confirmed SARS-CoV-2 infection and assess the association of prenatal ultrasound (US) findings with adverse neonatal outcomes (ANO).

MATERIALS AND METHODS

Study Design and Participants

This was a secondary analysis of a prospective observational cohort study of pregnant patients diagnosed with SARS-CoV-2 by reverse-transcription polymerase chain reaction (RT-PCR) between March 2020 and May 2021.[18] Informed consent was obtained from all participants prior to enrollment. Inclusion criteria was laboratory confirmed SARS-CoV-2 diagnosis during pregnancy. Exclusion criteria were age <18 years, spontaneous abortions, deliveries prior to viability, major fetal genetic or structural abnormalities, or confirmed intrauterine infections associated with fetal growth restriction (FGR) other than SARS-CoV-2 infection. If the participating pregnant patient was incapacitated during an acute hospitalization and initial consent was provided by a surrogate decision maker, confirmation of continued study participation was obtained once the patient regained capacity.

All pregnant patients with confirmed SARS-CoV-2 infection by nasopharyngeal (NP) RT-PCR between April 2020 and March 2021 were eligible for inclusion. At our institution, those with SARS-CoV-2 infection in pregnancy were referred for prenatal US evaluation following symptomatic recovery. We included all pregnant patients with confirmed SARS-CoV-2 infection who underwent at least one prenatal US evaluation and had known neonatal outcomes. Within this patient cohort, we reported on sonographic characteristics of pregnancies after confirmed SARS-CoV-2 infection and compared prenatal ultrasound US findings with neonatal outcomes, degree of COVID-19 severity, and trimester of infection.

Ultrasound and Doppler Studies

Prenatal US was performed by maternal-fetal medicine (MFM) subspecialists and included assessment of the following parameters potentially affected by infection in pregnancy: fetal biometry, general morphological evaluation for signs of congenital infection, amniotic fluid index (AFI) assessment, placental thickness measurement, and Doppler evaluation of the umbilical artery (UA) and middle cerebral artery (MCA). Standard fetal biometric measurements included biparietal diameter, head circumference, abdominal circumference, and femur length. Estimated fetal weight (EFW) was derived from these measurements, using the Hadlock formula.[19]

FGR was defined as having an US EFW or abdominal circumference below the 10th percentile for gestational age.[20] Placentomegaly was defined as greater than 4 cm in maximal placental thickness.[21] Ventriculomegaly was defined as the atrial diameter of the lateral ventricle measuring at least 10 mm or more.[22] Microcephaly was defined as a fetal head circumference measurement of less than or equal to three standard deviations below the mean for gestational age.[23] Oligohydramnios was defined as AFI measuring less than 5 cm, while polyhydramnios was defined as AFI measuring greater than or equal to 24 cm.[24] For Doppler evaluation, UA Dopplers were considered abnormal if the systolic to diastolic (S/D) ratio was greater than the 95th percentile for the given gestational age or if there was absent or reversed end diastolic flow. MCA Dopplers were considered abnormal if the peak systolic velocity was above 1.5 multiples of the median.

Maternal characteristics, prenatal US data, and pregnancy and neonatal outcomes were abstracted from the medical record. Each participant was considered as a single case, irrespective of the number of US scans performed. They were categorized as having an abnormal US if any

of the following were identified on at least one US: FGR, placentomegaly, an infection-associated soft marker or structural anomaly (intracranial calcifications, ventriculomegaly, microcephaly, cardiomegaly, intraabdominal calcifications, echogenic bowel, ascites, pleural effusion, pericardial effusion, hydrops), abnormal UA or MCA Doppler measurement, abnormal AFI (oligohydramnios, polyhydramnios), or some other structural anomaly. EFW percentile was used from the last MFM US performed prior to delivery.

Statistical Analysis

Descriptive statistics for baseline clinical characteristics comparing normal versus abnormal US were applied. The primary outcome was a composite ANO defined as one or more of the following: preterm birth, NICU admission, small for gestational age (SGA), respiratory distress, intrauterine fetal demise, neonatal demise, or other neonatal complications (condition requiring additional medical interventions such as intraventricular hemorrhage, hypoglycemia, pneumothorax, or congenital anomaly).

Prenatal US findings were compared with neonatal outcomes, degree of COVID-19 severity, and trimester of infection using t-test, Mann-Whitney U, and Kruskal-Wallis tests for continuous variables. Chi-squared tests were performed for categorical variables with more than two categories, and Barnard's test was used for binary variables. These statistical analyses were performed on R version 4.1.2. The Cochran-Mantel Haensel (CHM) test in SAS 9 was used to calculate the relative risk of ANO in pregnancies with FGR to those without while controlling for the effects of any hypertension in pregnancy, maternal diabetes, or multiple gestations. $P < 0.05$ was considered statistically significant. This study was approved by our institutional review board (IRB #20-000569).

RESULTS

A total of 103 SARS-CoV-2 affected mother-infant pairs with prenatal US evaluation were identified; 100 met inclusion criteria for study participation (Figure 1). Three cases were excluded for confirmed trisomy 18, major structural congenital heart disease, and confirmed parvovirus B19 infection. Twenty three percent of pregnancies had at least one abnormal prenatal US finding. Neonatal outcomes were known in 92 pregnancies (97 infants) with 28 pregnancies (29%) identified as having a composite ANO. Eight patients delivered at outside medical facilities and neonatal outcome data was not available.

Among the abnormalities noted, the most common seen on US were placentomegaly (11/23, 47.8%) and FGR (8/23, 34.8%). Two cases (8.7%) had both placentomegaly and FGR. In the entire cohort, the prevalence of FGR was 8%. Less common abnormalities included: echogenic bowel (3/23, 13.0%), abnormal Doppler indices (1/23, 4.4%), and abnormal AFI (2/23, 8.7%). The one case of abnormal Doppler indices was the presence of elevated umbilical artery S/D ratio in the setting of FGR. There were two cases of oligohydramnios. There were no cases of abnormal middle cerebral artery Dopplers or polyhydramnios. There was no significant correlation between FGR and SGA in our cohort (r=0.09, p=0.38).

All cases of FGR were diagnosed after SARS-CoV-2 infection. Median length of time from diagnosis of SARS-CoV-2 to diagnosis of FGR was 27.5 days (IQR 14.5, 35.5), which was significantly shorter than the median 47 days from diagnosis of SARS-CoV-2 to any follow-up ultrasound (IQR 23, 82) (p=0.03).

Demographics between groups with abnormal and normal US are seen in Table 1. There were no significant differences between groups when stratified by median maternal age, maternal comorbidity, trimester of infection , and COVID-19 severity. Obstetric and neonatal outcomes in

both groups were also similar for mode of delivery, gestational age at delivery, and rate of preterm birth. The presence of an abnormal US was not significantly associated with the composite ANO (38.1% vs 28.2%, p=0.33). There were no cases of intrauterine fetal demise.

There were three neonatal demises, all in the setting of previable delivery. One was in the setting of previable preterm premature rupture of membranes (PPROM) with maternal BMI 50 kg/m^2. Two were from a patient with a monochorionic-diamniotic twin pregnancy complicated by Stage II twin-twin transfusion syndrome and a short cervix, who had undergone cerclage placement and laser ablation at 18 weeks of gestation complicated by a placental hematoma. The patient developed gram-negative rod bacteremia and underwent previable preterm delivery of both twins. The PPROM case had an abnormal US (oligohydramnios likely due to PPROM); the twin pregnancy did not.

When evaluating specific abnormal US findings, FGR was associated with a higher rate of a composite ANO (25% vs 1.5%; adjusted odds ratio, 22.67; 95% confidence interval, 2.63-194.91; p<0.001) (Table 2).The association remained significant when SGA was removed from the composite ANO (data not shown). Furthermore, a Cochran-Mantel Haensel test was run controlling for possible confounding effects of maternal diabetes, chronic hypertension or hypertensive diseases of pregnancy, and multiple gestation, and the association between FGR and the composite ANO remained significant (relative risk, 3.7; 95% confidence interval, 2.6-5.9; p<0.001).

Lower EFW in grams and percentile were both associated with composite ANO (1316g vs 2815g, p<0.001, 41%ile vs 50.5%ile, p<0.001). Lower birthweight was also associated with the composite ANO (2073g vs 3360g, p<0.001). Placentomegaly and other abnormal US results,

including infection-associated abnormal findings, abnormal Doppler indices, and fluid abnormalities were not associated with ANO.

When stratified by COVID-19 severity (asymptomatic versus mild/moderate versus severe/critical), there was no association between disease severity and US findings (Table 3). A lower median birth weight was noted in infants born to patients with severe/critical infection (1274g) as compared to mild/ moderate (3160g) or asymptomatic disease (3051g) (p=0.002). This was likely impacted by significantly higher rates of preterm delivery in the severe/critical cohort (44.4% vs 14.3% mild/moderate, 0% in asymptomatic; p=0.036).

When stratified by trimester of infection, median EFW percentile was lowest with infection in the third trimester (38%ile) as compared to the second (57%ile) and first (41%ile) (p=0.019) (Table 4). Rates of FGR were higher in patients with third trimester infection however this was not statistically significant (p=0.32). There was a significant association between placentomegaly and third trimester infections (0% first trimester, 7.3% second trimester, 20% third trimester, p=0.045).

COMMENT

Principal Findings

We focused on patients with known SARS-CoV-2 infection in pregnancy and correlating US findings with neonatal outcomes. Our overall rate of FGR was 8%, while the rate of SGA was 7.2%, which is comparable to rates observed in the general population.[20] Despite having these similar baseline rates of FGR and SGA, we had a notably high rate of composite ANO at 29% as compared to 13.2% in studies evaluating neonatal outcomes with FGR alone.[25] Baseline rates of composite ANO in the general population are unknown but are likely even lower. These findings

correlate with previously reported studies demonstrating increased rates of ANO with SARS-CoV-2 infection in pregnancy, including respiratory distress syndrome, low birth weight, and NICU admission.[13,15,16] We had similarly high rates of preterm delivery (17.5%), NICU admission (18.6%), respiratory distress (15.5%), and neonatal complications (17.5%) in our cohort.

Results in the Context of What is Known

Data regarding fetal and neonatal effects following SARS-CoV-2 infection in pregnancy have varied and has largely focused on comparing SARS-CoV-2 positive patients with controls. Some studies have reported higher neonatal morbidities with SARS-CoV-2 infection, while others have reported no significant difference in rates of maternal or neonatal co-morbidities.[13,14,15,16] There are limited publications regarding sonographic findings and their possible association with neonatal outcomes. Soto-Torres et al assessed very similar US parameters and found no significant differences in abnormal fetal US and Doppler indices between SARS-CoV-2 positive pregnant patients and controls. They did note a higher frequency of SGA fetuses and abnormal Doppler parameters in the SARS-CoV-2 positive cohort, but the differences did not reach statistical significance.[26] Rizzo et al also found no increased risk of fetal growth restriction in 49 pregnancies complicated by SARS-CoV-2 infection as compared to controls.[27]

Interestingly, we found that median length of time from diagnosis of SARS-CoV-2 to diagnosis of FGR was 27.5 days, significantly shorter than the median 47 days from diagnosis of SARS-CoV-2 to any follow-up ultrasound. This timeline loosely correlates with 14 days after symptom resolution, which is the current recommendation for a follow-up ultrasound after SARS-CoV-2 infection in pregnancy.[17] Our data supports these existing guidelines in detecting FGR.

Clinical Implications

We could not find any previous reports comparing neonatal outcomes stratified by abnormal versus normal US results specifically in pregnant patients who were SARS-CoV-2 positive. Our results highlight that FGR was associated with higher rates of composite ANO, even when controlling for SGA and possible FGR confounders . This suggests a possible compounding effect of SARS-CoV-2 infection in pregnancies affected by FGR which increase the risk of ANO beyond those noted in FGR alone. Lower EFW and birthweight were also associated with a composite ANO. These findings suggest that special attention should be paid for SARS-CoV-2 affected pregnancies in which the fetus becomes growth restricted.

Our finding that SARS-CoV-2 infection in the third trimester was associated with the lowest median EFW percentile is potentially due to the majority of fetal growth occurring in the third trimester, thus possibly attributing a stronger association between active infection during that period and lower fetal weight. These findings support existing recommendations to obtain a third trimester growth US for patients affected by SARS-CoV-2 during pregnancy.[28] While larger scale studies are necessary to assess the impact of SARS-CoV-2 infection on fetal growth restriction based on trimester, more attention should be paid to patients who become infected in the third trimester.

We observed lower median birthweight in those with severe or critical SARS-CoV-2 infections; however, we suspect this is due to an increased rate of preterm deliveries in the severe/ critical infection cohort.[29] These higher rates are attributed to worsening maternal clinical

status, development of preeclampsia with severe features, and higher rates of preterm labor with SARS-CoV-2 infection.[30,31,32]

Research Implications

Future investigations should include larger patient cohorts with a broad geographic reach, and investigation of notable findings which did not reach significance in our cohort likely due to our smaller sample size, such as echogenic bowel given its association with infections in pregnancy. It would also be important to evaluate the pathophysiology behind placentomegaly and SARS-CoV-2 infection in the third trimester of pregnancy and correlate to postnatal histopathologic evaluation. One hypothesis is that placentomegaly is associated with prior congenital infections as well as preeclampsia and can be a marker for inflammation or impending fetal infection though we have not elucidated the mechanism by which this occurs.[33] Possible explanations include a potential protective effect by which the placenta appears to act as a reservoir for and barrier to infection, potentially explaining why not all maternal primary infection result in fetal infection.[34]

Strengths and Limitations

A strength of our study was its prospective nature in a large, diverse quaternary-care center. In addition, both maternal characteristics and neonatal outcomes were available for evaluation and correlation. There were similar maternal demographics between the abnormal US versus normal US cohorts. Limitations include the smaller sample size and the potential for confounders that were not considered. We did not match SARS-CoV-2 positive patients with controls as we specifically sought to evaluate differences in neonatal outcomes when stratified by US findings within a SARS-CoV-2 positive cohort. This study was also conducted in a quaternary referral

center with MFM and extracorporeal membrane oxygenation capabilities and an urban population. Thus, the findings may not be generalizable to the broader population.

Conclusions

In our study of SARS-CoV-2 affected maternal-infant pairs, rates of FGR were comparable to the general population; however, composite ANO rates were high. Fetal growth restriction and lower EFW in SARS-CoV-2 affected pregnancies were associated with increased rates of composite ANO. SARS-CoV-2 infections that were acquired in the third trimester were associated with lower percentiles of EFW. While overall fetal surveillance in SARS-CoV-2 affected pregnancies should be individualized, patients with COVID-19 in pregnancy, particularly in the third trimester, may require closer antenatal and neonatal surveillance.

References

[1] Organization WH. WHO Coronavirus (COVID-19) Dashboard.

[2] Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. N Engl J Med 2020; 382: 2163–2164.

[3] Crovetto F, Crispi F, Llurba E, et al. Impact of SARS-CoV-2 Infection on Pregnancy Outcomes: A Population-Based Study. Clin Infect Dis 2021; 73 (10): 1768-1775.

[4] Cosma S, Borella F, Carosso A, et al. The "scar" of a pandemic: Cumulative incidence of COVID-19 during the first trimester of pregnancy. J Med Virol 2021; 93: 537–540.

[5] Pineles BL, Alamo IC, Farooq N, et al. Racial-ethnic disparities and pregnancy outcomes in SARS-CoV-2 infection in a universally-tested cohort in Houston, Texas. Eur J Obstet Gynecol Reprod Biol 2020; 254: 329–330.

[6] COVID Data Tracker. Centers for Disease Control and Prevention. https://covid.cdc.gov/covid-data-tracker/#pregnant-population.Updated July 4, 2022. Accessed July 8, 2022.

[7] Vintzileos WS, Muscat J, Hoffmann E, et al. Screening all pregnant women admitted to labor and delivery for the virus responsible for coronavirus disease 2019. Am J Obstet Gynecol 2020; 223: 284–286.

[8] Fassett MJ, Lurvey LD, Yasumura L, et al. Universal SARS-Cov-2 screening in women admitted for delivery in a large managed care organization. Am J Perinatol 2020; 37: 1110–1114.

[9] Martinez-Portilla RJ, Sotiriadis A, Chatzakis C, et al. Pregnant women with SARS-CoV-2 infection are at higher risk of death and pneumonia: propensity score matched analysis of a nationwide prospective cohort (COV19Mx). Ultrasound Obstet Gynecol 2021; 57: 224–231.

[10] Gracia PV, Caballero LC, Sánchez J, et al. Pregnancies recovered from SARS-CoV-2 infection in second or third trimester: obstetric evolution. Ultrasound Obstet Gynecol 2020; 56: 777–778.

[11] Woodworth KR, Olsen EO, Neelam V, et al. Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy - SET-NET, 16 Jurisdictions, March 29-October 14, 2020. MMWR Morb Mortal Wkly Rep 2020; 69 (44): 1635-1640.

[12] Lokken EM, Taylor GG, Huebner EM, et al. Higher severe acute respiratory syndrome coronavirus 2 infection rate in pregnant patients. Am J Obstet Gynecol 2021; 225(1): 75.e1-75.e16.

[13] Norman M, Navér L, Söderling J, et al. Association of Maternal SARS-CoV-2 Infection in Pregnancy With Neonatal Outcomes. JAMA 2021; 325 (20):2076-2086.

[14] Son M, Gallagher K, Lo JY, et al. Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy Outcomes in a U.S. Population. Obstet Gynecol 2021;138 (4): 542-551.

[15] Gurol-Urganci I, Jardine JE, Carroll F, et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. Am J Obstet Gynecol 2021; 225 (5): 522.e1-522.e11.

[16] Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. CMAJ 2021;193 (16): E540-E548.

[17] Covid-19 and pregnancy. BMJ 2020; 369: m1672.

[18] Foo S-S, Cambou MC, Wong T, et al. The systemic inflammatory landscape of COVID19 in pregnancy: Extensive serumproteomic profiling of mother-infant dyads with in-utero SARS-CoV-2. Cell Rep Med 2021; 2 (11): 100453.

[19] Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology 1991;181 (1): 129-33.

[20] Martins JG, Biggio JR, Abuhamad A, pubs@smfm.org SfM-FMSEa. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction. Am J Obstet Gynecol 2020; 223 (4): B2-B17.

[21] Hoddick WK, Mahony BS, Callen PW, Filly RA. Placental thickness. J Ultrasound Med 1985; 4: 479–482.

[22] Farrell TA, Hertzberg BS, Kliewer MA, Harris L, Paine SS. Fetal lateral ventricles: reassessment of normal values for atrial diameter at US. Radiology 1994; 193 (2): 409-11.

[23] Committee SfM-FMSP. Ultrasound screening for fetal microcephaly following Zika virus exposure. Am J Obstet Gynecol 2016; 214 (6): B2-4.

[24] Dashe JS, Pressman EK, Hibbard JU. SMFM consult series #46: evaluation and management of polyhydramnios. Am J Obstet Gynecol 2018; 219 (4): PB2-B8.

[25] Roeckner JT, Pressman K, Odibo L, Duncan JR, Odibo AO. Outcome-based comparison of SMFM and ISUOG definitions of fetal growth restriction. Ultrasound Obstet Gynecol 2021; 57 (6): 925-930.

[26]Soto-Torres E, Hernandez-Andrade E, Huntley E, Mendez-Figueroa H, Blackwell SC. Ultrasound and Doppler findings in pregnant women with SARS-CoV-2 infection. Ultrasound Obstet Gynecol 2021; 58 (1): 111-120.

[27] Rizzo G, Mappa I, Maqina P, et al. Effect of SARS-CoV-2 infection during the second half of pregnancy on fetal growth and hemodynamics: A prospective study. Acta Obstet Gynecol Scand 2021; 100 (6): 1034-1039.

[28] Society for Maternal-Fetal Medicine (SMFM). COVID-19 and Pregnancy: What Maternal-Fetal Medicine Subspecialists Need to Know. Washington, DC: SMFM; 2020. Available at: https://www.smfm.org/covidclinical. [Accessed June 20, 2022]

[29] Jamieson DJ, Rasmussen SA. An update on COVID-19 and pregnancy. Am J Obstet Gynecol 2022; 226 (2): 177-186.

[30] Kc A, Gurung R, Kinney MV, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. Lancet Glob Health 2020; 8 (10): e1273-e1281.

[31] Villar J, Ariff S, Gunier RB, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. JAMA Pediatr 2021; 175 (8): 817-826.

[32] Di Mascio D, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2020; 2 (2): 100107.

[33] La Torre R, Nigro G, Mazzocco M, Best AM, Adler SP. Placental enlargement in women with primary maternal cytomegalovirus infection is associated with fetal and neonatal disease. Clin Infect Dis 2006; 43: 994–1000.

[34] Komine-Aizawa S, Takada K, Hayakawa S. Placental barrier against COVID-19. Placenta 2020; 99: 45-49.

Table 1. Maternal characteristics and obstetrical outcomes by prenatal ultrasound findings. *P* values < 0.05 are bolded.

	Abnormal Ultrasound (N=23)	**Normal Ultrasound** (N=77)	**p-value**
Maternal Characteristics			
Age (years), *median (IQR)*	34 (20-42)	33 (18-44)	0.81
Race/ Ethnicity			
White	8 (34.78)	20 (25.97)	0.64
Hispanic	10 (43.48)	34 (44.16)	
Black	1 (4.35)	5 (6.49)	
Asian	4 (17.4)	10 (43.5)	
Other	3 (13.0)	2 (8.7)	
Gravida	2 (1-8)	2 (1-10)	0.72
Nulliparity	12 (52.17)	30 (53)	0.14
Any Maternal Comorbidity[a]	13 (56.52)	35 (45.45)	0.24
Obesity	10 (43.48)	25 (32.47)	0.18
Diabetes mellitus	0	3 (3.9)	0.24
Congenital Heart Disease	0	3 (3.9)	0.24
Asthma	2 (8.7)	11 (14.29)	0.13
Autoimmune Disorders	3 (13.04)	2 (2.6)	**0.038**

Hypertension in pregnancy (chronic or pregnancy-related [b])	7 (30.43)	22 (28.57)	0.5
Trimester of Infection			
First	3 (13.04)	14 (18.18)	
Second	8 (34.78)	35 (45.45)	0.43
Third	12 (52.17)	28 (36.36)	
SARS-CoV-2 Infection Severity			
Asymptomatic	1 (4.35)	5 (3.85)	
Mild/Moderate	18 (78.26)	61 (46.97)	1
Severe/Critical	4 (17.39)	11 (8.47)	
Obstetric and Neonatal Outcomes			
Mode of delivery			
Vaginal delivery	15/21 (71.43)	44/71 (61.97)	
Cesarean delivery	5/21 (23.81)	23/71 (32.39)	0.83
Operative vaginal delivery	1/21 (4.76)	4/71 (5.63)	
Gestational age at delivery (weeks), *median (IQR)*	39 (22-41)	39 (21-41)	0.27
Birthweight	2948 (445-4260)	3190 (309-4780)	0.11
Any composite adverse neonatal outcome[c]	8/23 (38.1)	20/74 (28.17)	0.33
Preterm delivery	6/23 (28.57)	11/74 (15.49)	0.49
Small for gestational age	2/23 (9.52)	5/74 (7.04)	0.49

NICU admission	4/23 (19.05)	14/74 (19.72)	0.51
Respiratory distress	5/23 (23.81)	10/74 (14.08)	0.23
Neonatal demise	1/23 (4.76)	2/74 (2.82)	0.49
Neonatal complications[d]	5/23 (23.81)	12/74 (16.9)	0.34

Data presented as n (%) unless otherwise indicated

Abbreviations: IQR, interquartile range; NICU, neonatal intensive care unit

a. Maternal comorbidity included one or more of the following: chronic hypertension, hypertensive disorders of pregnancy, obesity, diabetes, asthma, autoimmune disease, cardiac disease

b. Hypertensive disorders of pregnancy included: gestational hypertension, preeclampsia with or without severe features, HELLP, and eclampsia

c. Composite adverse neonatal outcome defined as one or more of the following**:** preterm birth, NICU admission, small for gestational age, respiratory distress, neonatal demise, or other neonatal complications

d. Neonatal complication included one or more of the following: condition requiring additional medical intervention (e.g., intraventricular hemorrhage, hypoglycemia, pneumothorax), congenital anomaly, or neonatal demise

Table 2. Prenatal ultrasound findings by composite adverse neonatal outcome

	Composite Adverse Neonatal Outcome[a]		
Ultrasound Result	**Yes (N=28)**	**No (N=69)**	**p-value**
Any abnormal ultrasound finding (n,%)[b]	8 (28.57)	15 (21.74)	0.27
EFW (g), median (IQR)	1316 (827-2396)	2815 (2356-3143)	**<0.001**
EFW %ile, median, (IQR)	41 (10-64)	50.5 (35-77)	**<0.001**
Fetal growth restriction (n, %)	7 (25)	1 (1.45)	**<0.001**
Placentomegaly (n, %)	2 (7.14)	9 (13.04)	0.27
Birthweight (g), median (IQR)	2073 (980-2689)	3360 (3021-3635)	**<0.001**
Infection-associated findings (n, %)			
Intracranial calcifications	0	0	
Ventriculomegaly	0	0	
Microcephaly	0	0	
Cardiomegaly	0	0	
Intraabdominal calcifications	0	0	
Echogenic bowel	0	3 (4.35)	0.17
Ascites	0	0	
Pleural effusion	0	0	
Pericardial effusion	0	0	
Hydrops	0	0	

Abnormal Doppler results (n, %)			
Umbilical artery	1 (3.57)	0	0.13
Middle cerebral artery	0	0	1
Fluid abnormalities (n, %)			
Oligohydramnios	1 (3.57)	1 (1.45)	0.3
Polyhydramnios	0	0	1

Data presented as n (%) unless otherwise indicated

Abbreviations: EFW, estimated fetal weight; IQR, interquartile range

a. Composite adverse neonatal outcome defined as one or more of the following**:** preterm birth, NICU admission, small for gestational age, respiratory distress, neonatal demise, or other neonatal complications

b. "Any abnormal ultrasound finding" includes fetal growth restriction, placentomegaly, infection-associated findings, abnormal Doppler results, or fluid abnormalities.

Table 3. Prenatal ultrasound findings by SARS-CoV-2 infection severity.

	SARS-CoV-2 Infection Severity			
Ultrasound Result	**Asymptomatic (N=6)**	**Mild/ Moderate (N=79)**	**Severe/ Critical (N=12)**	**p-value**
Any abnormal ultrasound finding (n,%)[a]	1 (16.67)	17 (21.52)	5 (41.67)	0.34
EFW (g), median (IQR)	2116 (500-3159)	2789 (2121-3134)	1997 (807-2920)	0.62
EFW %ile, median, (IQR)	75 (58-85)	47 (28-76)	40 (19-56)	0.084
Fetal growth restriction (n, %)	1 (16.7)	7 (8.9)	0 (0)	0.45
Placentomegaly (n, %)	0	10 (12.66)	1 (8.33)	0.73
Birthweight (g), median (IQR)	3051 (2987-3422)	3160 (2810-3548)	1274 (965-3355)	**0.002**

Infection-associated findings (n, %)				
Intracranial calcifications	0	0	0	
Ventriculomegaly	0	0	0	
Microcephaly	0	0	0	
Cardiomegaly	0	0	0	
Intraabdominal calcifications	0	0	0	
Echogenic bowel	0	3 (3.8)	0	1
Ascites	0	0	0	
Pleural effusion	0	0	0	
Pericardial effusion	0	0	0	
Hydrops	0	0	0	
Abnormal Doppler results (n, %)				
Umbilical artery	0	1 (1.27)	0	1
Middle cerebral artery	0	0	0	1
Fluid abnormalities (n, %)				
Oligohydramnios	1 (16.67)	1 (1.27)	0	0.14
Polyhydramnios	0	0	0	1

Data presented as n (%) unless otherwise indicated.

Abbreviations: EFW, estimated fetal weight; IQR, interquartile range

Comparison of various ultrasound findings stratified by degree of SARS-CoV-2 infection severity between asymptomatic, mild/ moderate, and severe/ critical.

a. "Any abnormal ultrasound finding" includes fetal growth restriction, placentomegaly, infection-associated findings, abnormal Doppler results, or fluid abnormalities.

Table 4. Prenatal ultrasound findings by trimester of infection.

	Trimester of Infection			
Ultrasound Result	**First (N=16)**	**Second (N=41)**	**Third (N=40)**	**p-value**
Any abnormal ultrasound finding (n,%)[a]	3 (18.75)	9 (21.95)	11 (27.5)	1
EFW (g), median (IQR)	2047 (1272-2813)	2711 (1610-3001)	2855 (2416-3152)	**0.01**
EFW %ile, median, (IQR)	41 (36-70)	57 (42-79)	38 (19-71)	**0.019**
Fetal growth restriction (n, %)	1 (6.3)	1 (2.4)	6 (15)	0.12
Placentomegaly (n, %)	0	3 (7.32)	8 (20)	**0.045**
Birthweight (g), median (IQR)	3117 (2872-3625)	3260 (2701-3544)	3051 (2692-3506)	0.74

Infection-associated findings (n, %)				
Intracranial calcifications	0	0	0	
Ventriculomegaly	0	0	0	
Microcephaly	0	0	0	
Cardiomegaly	0	0	0	
Intraabdominal calcifications	0	0	0	0.39
Echogenic bowel	0	0	0	
Ascites	1 (6.25)	2 (4.88)	0	
Pleural effusion	0	0	0	
Pericardial effusion	0	0	0	
Hydrops	0	0	0	
Abnormal Doppler results (n, %)				
Umbilical artery	0	0	1 (2.5)	0.58
Middle cerebral artery	0	0	0	1
Fluid abnormalities (n, %)				
Oligohydramnios	1 (6.25)	0	1 (2.5)	0.37
Polyhydramnios	0	0	0	1

Data presented as n (%) unless otherwise indicated.

Abbreviations: EFW, estimated fetal weight; IQR, interquartile range

Comparison of various ultrasound findings stratified by trimester of maternal SARS-CoV-2 infection, between first, second, and third trimester.

a. "Any abnormal ultrasound finding" includes fetal growth restriction, placentomegaly, infection-associated findings, abnormal Doppler results, or fluid abnormalities.

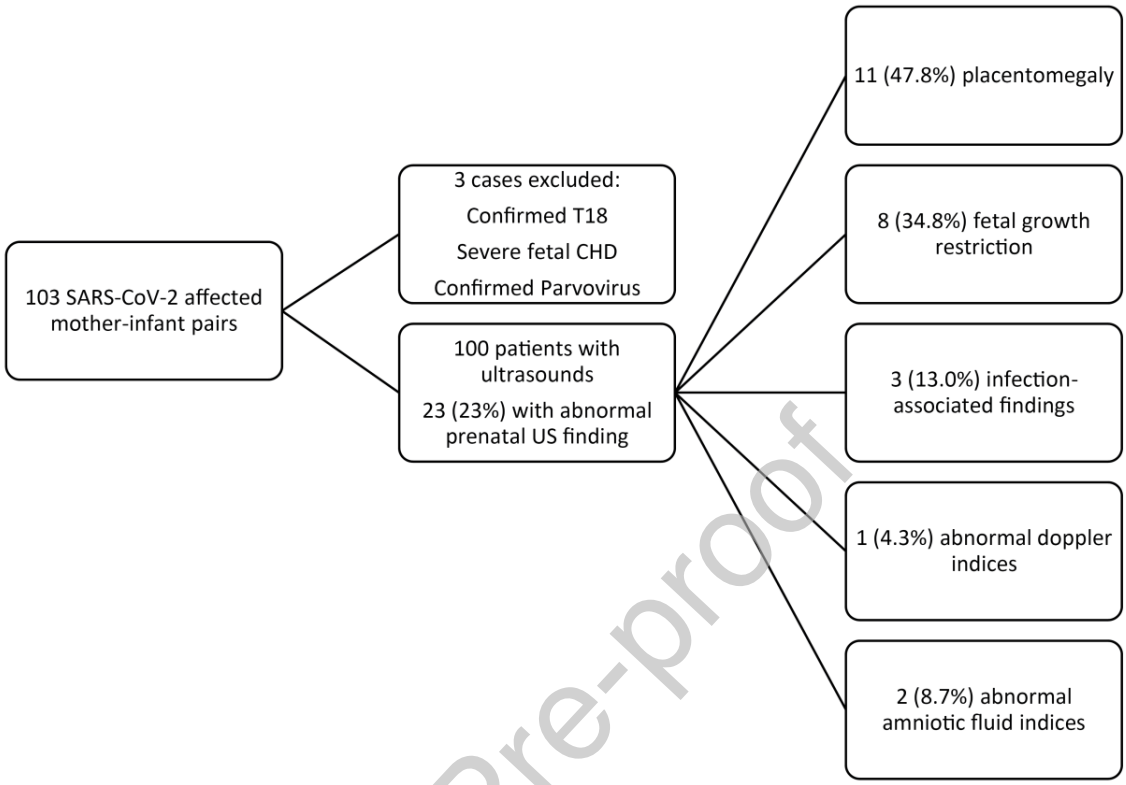

Figure 1. Flow diagram of ultrasound results.

Abbreviations: US, ultrasound; CHD, Congenital Heart Disease

Flow diagram of patients included in study and rate of various abnormal prenatal ultrasound findings. Of note some patients have more than one abnormal ultrasound finding.

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