HJOG An Obstetrics and Gynecology International Journal

Research

HJOG 2024, 23 (3), 205-217 | DOI: 10.33574/HJOG.0567

The Pathognomonic ultrasonographic findings in fetus with COVID-19 infection

Mohamed Elsherbiny Hamed[1], Mostafa Hassan Ragab[1], Waleed Hitlar Ahmed[2]

[1]Department of Environmental Medical Sciences, Faculty of Graduate Studies and Environmental Research, Ain Shams University, Cairo, Egypt
[2]Obstetrics & Gynecology Department, Faculty of Medicine - Ain Shams University, Cairo, Egypt

Correspondence
Mohamed Elsherbiny Hamed, e-mail: karimabdel2013@outlook.com

Abstract

Aim: The main goal is to identify the pathognomonic sonographic signs for foetal SARS-CoV-2 infection and to determine whether or not transplacental SARS-CoV-2 transmission is possible.

Patients and Methods: In total, 105 pregnant women with positive SARS-CoV-2 PCR swabs during the first trimester with mild or moderate infection without hospitalisation and/or oxygen support were included in this prospective comparative study, which was carried out at the ultrasound and foetal medicine unit of Ain Shams University Maternity Hospital from January 2021 to June 2023. The SARS-CoV-2 positive group was compared to the control group with inclusion and exclusion criteria.

Results: In the COVID-19 group, pathognomonic ultrasonographic results were considerably more common. The COVID-19 group had a considerably higher frequency of placental calcifications and oligohydramnios. In the COVID-19 cohort, patients with positive pathognomonic ultrasonographic results had considerably higher BMIs. In the COVID-19 cohort, gestational age at infection, and BMI ≥30.0 kg/m2 were significant independent risk factors for the development of pathognomonic ultrasonographic abnormalities. Those in the control group who had positive pathognomonic ultrasonographic results were older and had higher rates of hypertension. Significant independent risk variables for the incidence of pathognomonic ultrasonographic findings in the control group included age ≥34.0 years and hypertension.

Conclusion: There is no evidence of a teratogenic effect linked to maternal SARS-CoV-2 infection during the first few months of pregnancy. However, early pregnancy infection with COVID-19 is linked to pathognomonic ultrasonography findings of placental calcifications and oligohydramnios.

Key words: COVID 19 infection during pregnancy, Fetal ultrasonographic findings.

Introduction

In December 2019, Wuhan, China, became the first country to report cases of the new coronavirus, which then spread to other countries worldwide. In February 2020, the WHO named this novel coronavirus disease Coronavirus Disease 19 (COVID-19), and in March 2020, they proclaimed a pandemic (Wang et al., 2021).

Afterwards, the International Committee on Taxonomy of Viruses designated the COVID-19 as SARS-CoV-2, or severe acute respiratory syndrome coronavirus 2. Single-stranded RNA viruses, known as SARS-CoV-2, can cause a variety of illnesses, including the common cold and severe acute respiratory syndrome (SARS) (Pavlyshyn et al., 2023, Lu et al., 2020).

Pregnant women are regarded as a COVID-19 high-risk population, and the novel coronavirus-19 (COVID-19) or SAR-CoV-2 is considered a new global health problem. COVID-19-positive pregnant women are at risk for caesarean delivery and preterm labour (PTL). In order to prevent maternal respiratory impairment, the rate of caesarean sections (CSs) rose among women infected with COVID-19 and was often performed prior to term. PTL and aberrant foetal cardiac pattern are associated with higher risks in cases of maternal fever and hypoxia (Papapanou et al., 2021).

Despite the fact that Ayed et al. determined that transplacental vertical transmission of COVID-19 is possible and Vivanti et al. reported a case of transplacental transmission of the virus. Others (Vivanti et al., 2020; Ayed et al., 2020) came to the conclusion that there isn't much proof of Covid-19 vertical transmission when the infection appears during the third trimester of pregnancy. Despite this, the majority of the afflicted foetuses appear growthily normal following transplacental viral transfer. In addition to intrauterine growth restriction (IUGR), even a mild viral infection in the mother can cause aberrant pathognomonic sonographic abnormalities, such as lung, cardiac, hepatic, and/or cerebral calcifications. Additionally, Bronshtein et al. discovered that foetal hepatic calcification was suggestive of viral infection and congenital foetal abnormalities (Bronshtein et al., 1995).

Consequently, the purpose of this investigation

Table 1. Demographic characteristics between the study groups

Variables		COVID-19 group (Total=105)	Control group (Total=105)	p-value
Age (years)	Mean±SD	30.4±4.2	31.1±4.4	^0.226
	Range	20.0–40.0	21.0–40.0	
BMI (kg/m2)	Mean±SD	28.6±2.7	28.3±2.5	^0.352
	Range	21.9–35.3	22.0–34.0	
Parity (n, %)	Primi	38 (36.2%)	44 (41.9%)	#0.396
	Multi	67 (63.8%)	61 (58.1%)	
Diabetes mellitus, (n, %)		5 (4.8%)	7 (6.7%)	#0.552
Hypertension, (n, %)		4 (3.8%)	5 (4.8%)	§0.999
Gestational age at examination (weeks)	Mean±SD	21.1±1.2	21.3±1.3	^0.215
	Range	18.0–24.0	18.0–24.0	

BMI: Body mass index. ^Independent t-test. #Chi square test

Table 2. COVID-19 infection characteristics among COVID-19 group

Variables	Mean±SD	Range
Gestational age at infection (weeks)	8.6±2.0	4.0–14.0

Total=105.

was to identify pathognomonic sonographic signs for foetal SARS-CoV-2 infection and to determine whether or not transplacental SARS-CoV-2 transmission is possible.

Patients and methods

This prospective comparative study was carried out at Ain Shams University Maternity Hospital, a tertiary care hospital, from January 2021 to June 2023, with written consent from the patients and approval from the ethical committee. A total of 105 pregnant women with positive SARS-CoV-2 PCR swabs during the first trimester (gestational age between 7-13 weeks) with mild or moderate infection were included in the study, and they were compared to the control group.

Pregnant women aged 20 to 40 who had positive SARS-CoV-2 PCR swabs during the first trimester and had mild to moderate infection. The patients who did not admit to the hospital or receive oxygen support were included in the study group. Pregnant women in the control group were also aged 20 to 40 but did not have any history of symptoms or symptoms suggestive of SARS-CoV-2 infection during the first trimester or throughout their pregnancy.

Women who have congenital foetal abnormalities, severe SARS-CoV-2 infection necessitating respiratory assistance, corticosteroids, or antivirals are excluded. several gestations, cigarette smoking, medical conditions (such as diabetes mellitus, hypertension, autoimmune, or thyroid issues), using thromboprophylaxis for women with diseases other than SARS-CoV-2 (e.g., parvovirus, cytomegalovirus, rubella, or toxoplasmosis) and medications impacting their foetus (e.g., anti-epileptics, corticosteroids).

Study Procedures:

The following was applied to all women:

Polymerase chain reaction (PCR) nasopharyngeal swabs (Cobas 6800 Systems, Roche, Switzerland) were used to diagnose SARS-CoV-2 infection.

In accordance with hospital practice, the participants underwent regular antenatal tests as well as an abdominal obstetric examination to measure the fundal height in relation to LMP and measure their weight, blood pressure, pulse, and breathing rate.

In order to identify congenital foetal anomalies and abnormal sonographic findings other than the intrauterine viral infection (IUGR), which is a common sonographic finding in all intrauterine viral infections, such as intracranial, myocardial, hepatic, and/or lung calcifications, participants were examined by ultrasound at the second trimester for fetal anomaly scan and placental examination at 18-22 weeks gestation (Yan J et al., 2020).

Using the last menstrual period (LMP), which was verified by an ultrasound scan performed during the first trimester, the gestational age was determined.

According to Abdelazim IA et al. (2019), IUGR is defined as a foetal growth rate that is lower below the normal growth potential of a particular newborn based on the fetus's race and gender. Both IUGR and small for gestational age (SGA) are outcomes of different etiological reasons, although they are sometimes used interchangeably.

There are two varieties of IUGR/SGA: symmetrical (type II) and asymmetrical (type I), sometimes known as "head sparing." After placental insufficiency, asymmetrical IUGR (type I) develops in the third trimester for women. When the foetal abdominal circumference (AC) decreased with normal femur length (FL), biparietal diameter (BPD), and

Table 3. Pathognomonic ultrasonographic findings between the study groups

Findings	COVID-19 group (Total=105)	Control group (Total=105)	p-value	Relative risk (95% CI)
Positive	15 (14.3%)	6 (5.7%)	#0.038*	2.50 (1.01–6.19)
Negative	90 (85.7%)	99 (94.3%)		

Data presented as n (%). #Chi square test. *Significant. CI: Confidence interval.

head circumference (HC), it was determined that the IUGR (type I) was asymmetrical (Abdelazim IA et al., 2019; Sharma D et al., 2016).

A genetic condition or intrauterine infection causes symmetrical (type II) IUGR, which is characterized by a proportionate decline in AC, BPD, HC, and FL (Sharma D et al., 2016).

Hepatic, lung, and intracranial calcifications for cytomegalovirus (CMV), myocardial and hepatic calcifications for herpes simplex II, and hepatic calcifications for adenovirus, parvovirus B19, and varicella zoster virus are among the pathognomonic sonographic findings of foetal viral infection (Papapanou M et al., 2021).

Following birth, virology and ultrasonography examinations were used to assess the foetuses with positive sonographic results in order to confirm the foetal SARS-CoV-2 infection.

Outcome measures

The pathognomonic sonographic features for foetal SARS-CoV-2 infection were one of the primary outcomes.

One potential secondary outcome was the potential for SARS-CoV-2 to spread through pregnancy.

Moral Aspects to Take into Account: The patient information was private. Patient confidentiality was maintained and data was presented according to diagnosis rather than the patient's identity. Every participant signed an informed consent form, which was

Table 4. Details of pathognomonic ultrasonographic findings between the study groups

Findings	COVID-19 group (Total=105)	Control group (Total=105)	p-value	Relative risk (95% CI)
Cardiac finding				
Intracardiac echogenic focus	3 (2.9%)	1 (1.0%)	§0.621	3.00 (0.32–28.38)
Pericardial effusion	2 (1.9%)	2 (1.9%)	§0.999	1.00 (0.14–6.97)
CNS finding				
Ventricular dilatation	4 (3.8%)	3 (2.9%)	§0.999	1.33 (0.31–5.81)
GIT finding				
Intestinal calcifications	3 (2.9%)	1 (1.0%)	§0.621	3.00 (0.32–28.38)
Intrahepatic calcifications	2 (1.9%)	1 (1.0%)	§0.999	2.00 (0.18–21.72)
Ascites	1 (1.0%)	1 (1.0%)	§0.999	1.00 (0.06–15.78)
Pulmonary finding				
Lung calcifications	2 (1.9%)	0 (0.0%)	§0.498	Not applicable
Growth				
IUGR	6 (5.7%)	2 (1.9%)	§0.280	3.00 (0.62–14.53)
Placenta				
Placental calcifications	19 (18.1%)	2 (1.9%)	#<0.001*	9.50 (2.27–39.76)
Amniotic fluid				
Oligohydramnios	8 (7.6%)	1 (1.0%)	§0.035*	8.00 (1.02–62.84)

Data presented as n (%). #Chi square test. §Fisher's Exact test. *Significant. CI: Confidence interval.

verified with a date and time in Arabic. By giving each patient's initials a number, confidentiality was maintained and only the investigator was aware of it.

Conflict of interest

The applicant stated that they had no conflicts of interest and that they had covered the study's expenses.

Statistical analysis

Analysis is to be performed using SPSS for windows v20.0, Data to be presented in terms of range, mean and standard deviation (for numeric parametric variables); range, median and inter-quartile range (for numeric non-parametric variables); or number and percentage (for categorical variables). Difference between two independent groups is to be analyzed using independent student's t-test as well as the mean difference and its 95% CI (for numeric parametric variables); or chi-squared test as well as the risk ratio and its 95% CI (for categorical variables). Binary logistic regression analysis is to be performed for estimating the association between good/poor response and the measured variables ROC curves are to be constructed for estimating the validity of measured variables as predictors of good or poor response validity is to be presented in terms of sensitivity, specificity, positive and negative predictive values and their corresponding 95% Cis significance level is set at 0.05.

Results

Recruitment occurred from January 2021 to October 2023 at the ultrasound and foetal medicine unit, Ain Shams University Maternity Hospital. A total of 250 women were enrolled in the current prospective comparative study and 210 of those women completed the study. Of all eligible patients, 28 patients were excluded from the study based on the inclusion criteria and 12 patients refused to participate in of the study.

Table 5. Comparison according to pathognomonic ultrasonographic findings regarding COVID-19 infection characteristics among COVID-19 group

Variables	Pathognomonic findings		
	Positive (Total=15)	Negative (Total=90)	p-value
Gestational age) at infection (weeks	7.3±1.7	8.8±2.0	^0.006*

Data presented as Mean ± SD or n (%). ^Independent t-test. §Fisher's Exact test. *Significant

Ultimately, the analysis was based on the data of 105 pregnant women who had infected with SARs COVID 2 during early pregnancy, compared to 105 healthy pregnant women as a control group.

Table (1) shows that no significant statistical differences between the studied groups regarding demographic characteristics; age, body mass index, parity and comorbidities (hypertension and diabetes mellitus as well as gestational age.

Table (2) shows that that Mean ± SD of gestational age at infection (weeks).

Table (3) shows that that Pathognomonic ultrasonographic findings were significantly more frequent in COVID-19 group.

Table (4) shows that Placental calcifications and Oligohydramnios was significantly more frequent in COVID-19 group.

Table (5) shows that among COVID-19 group; cases with positive pathognomonic ultrasonographic findings significantly had lower gestational age at infection.

Table (6) shows that Among control group; cases with positive pathognomonic ultrasonographic findings significantly had high age and more frequent hypertension.

Discussion

There is limited information about the effects of severe acute respiratory syndrome coronavirus 2

Table 6. Comparison according to pathognomonic ultrasonographic findings regarding demographic characteristics among control group

Variables		Pathognomonic findings		p-value
		Positive (Total=6)	**Negative (Total=99)**	
Age (years)		35.8±3.8	30.8±4.3	^0.006*
BMI (kg/m2)		29.1±2.0	28.3±2.5	^0.424
Parity (n, %)	Primi	2 (33.3%)	42 (42.4%)	§0.999
	Multi	4 (66.7%)	57 (57.6%)	
Diabetes mellitus		1 (16.7%)	6 (6.1%)	§0.346
Hypertension		2 (33.3%)	3 (3.0%)	§0.025*
Gestational age at examination (weeks)		21.8±1.2	21.3±1.3	^0.302

Data presented as Mean ± SD or n (%). ^Independent t-test. §Fisher's Exact test. *Significant

(SARS-CoV-2) infection during the first trimester of pregnancy on the risk of major congenital malformations (MCMs) (Brandibur et al., 2023).

Since the consequences of COVID-19 infection in pregnant women and the potential risks of verti¬cal transmission represents major conflict and related research is also controversial, investigate the association between the Covid-19 pandemic and congenital birth anomalies was highlighted as a main point of interest (Heidarzadeh et al., 2022).

Consequently, this study was conducted and aimed to detect the pathognomonic sonographic findings for fetal SARS-CoV-2 infection and to detect whether there is possibility of trans-placental transmission of SARS-CoV-2 or not.

Recruitment occurred from January 2021 to October 2023 at the ultrasound and foetal medicine unit, Ain Shams University Maternity Hospital. A total of 250 women were enrolled in the current prospective comparative study and 210 of those women completed the study. Of all eligible patients, 28 patients were excluded from the study based on the inclusion criteria and 12 patients refused to participate in of the study.

Ultimately, the analysis was based on the data of 105 pregnant women who had infected with SARs COVID 2 during early pregnancy, compared to 105 healthy pregnant women as a control group.

The current study revealed that there were no statistically significant differences between the studied groups regarding demographic characteristics; age, body mass index, parity and comorbidities (hypertension and diabetes mellitus as well as gestational age. The mean gestational age at infection was 8.5±2.0 weeks.

A regard Pathognomonic ultrasonographic findings, our study revealed that Pathognomonic ultrasonographic findings were significantly more frequent in COVID-19 group (p value= 0.038). Placental calcifications and Oligohydramnios were significantly more frequent in COVID-19 group (p value= 0.001, 0.035), while Intracardiac echogenic focus, Pericardial effusion, Ventricular dilatation, Intestinal calcifications, Intrahepatic calcifications, Lung calcifications and IUGR were non-significantly more frequent in COVID-19 group.

Among COVID-19 group, our study results revealed that BMI was significantly higher in cases with positive pathognomonic ultrasonographic findings (p value= 0.009) and the cases with positive pathognomonic ultrasonographic findings significantly had significantly lower gestational age at infection (p value= 0.006).

Among control group, our study results revealed that cases with positive pathognomonic ultrasonographic findings significantly had advanced maternal

age and more frequent hypertension (p value= 0.006, 0.025) respectively. Consequently, maternal age ≥ 34.0 years and hypertension were significant independent risk factors for occurrence of pathognomonic ultrasonographic findings in control group (p value= 0.044, 0.029) respectively.

To the best of our knowledge, there is a paucity of studies in literature evaluating the congenital anomalies associated with early covid-19 infection, and that represents a strength point of our study.

These findings are in agreement with previous studies. Khoiwal et al., (2022) conducted a hospital-based prospective observational study that enrolled 60 COVID-positive pregnant women, compared with 60 COVID-negative pregnant women and revealed that Oligohydramnios was significantly more frequent in COVID-positive than COVID-negative pregnant women (p = .048) with no congenital anomalies observed. Majority of COVID-positive pregnant women were asymptomatic (81.7%). Eleven patients were symptomatic, out of which 9 (15%) had mild disease and only 2 (3.3%) had severe pneumonia.

Moreover, Sotiriou S et al., (2022) conducted a cohort study included 40 pregnant women consecutively testing positive and revealed that ultrasound examination and placental evaluation showed signs of placental involvement with findings indicating malperfusion, chorangiosis, deciduitis, and subchorionitis, such as fibrin deposits, lakes, subchorionic fibrin deposition, and thrombosis. Cases. The most prominent findings were subchorionic fibrin deposition and placental lakes with perivillous fibrin deposits of at least 30% of the placental mass.

Since SARS-CoV-2 has been detected in the placenta of pregnant women infected by COVID-19, great interest has been seen regarding placenta physiology. Angiotensin-converting enzyme 2 (ACE2) receptor is expressed both by the virus and by numerous endothelia as well (Flores-Pliego et al., 2021). The virus enters cells by binding the spike protein to the receptor of the ACE2, a receptor presents in the lung and small intestine epithelia, as in arterial and venous endothelial cells in all organs (Hoffmann et al., 2020). In the placenta, ACE2 is expressed in the stromal and perivascular cells of decidua, fetal placental vessels, and in cytotrophoblast (Flores-Pliego et al., 2021).

In agreement with our results, Zhang et al., (2023) evaluated the prenatal ultrasonographic findings of the fetus in a pregnant woman with mild COVID-19 and revealed that the placenta was diffusely distributed with punctate echogenic foci, which is extremely rare in the second trimester. This may be related to the multifocal calcification and peri villous fibrin deposition in the pathological examination of the placenta. However, many studies have shown that viral infections during pregnancy lead to numerous intrauterine and fetal effects, especially during the first and second trimesters. For instance, rubella virus and cytomegalovirus infection causes congenital malformations in the first and second trimesters (Bukasa et al., 2018; Mappa et al., 2022).

Movahedi et al., (2023) conducted a prospective cohort study that enrolled 430 pregnant women with definite diagnosis of COVID 19 infection to and revealed that FGR was also observed in 22 patients (5.3%) that was mostly observed with COVID 19 in the third trimester (P = 0.012). Oligohydramnios and fetal distress leading to C/S were observed in 19 patients (4.6%) and 12 patients (2.9%), respectively, with no significant differences between mothers with COVID 19 in different gestational ages regarding oligohydramnios, and fetal distress (P > 0.05).

Furthermore, the prevalence of different pregnancy related complications has been assessed among normal populations and showed that the prevalence of FGR was 3 7%, the prevalence of oligohydramnios was 1 2%, the prevalence of IUFD was 13.9 per 1,000 birth and the prevalence of preterm labor was 10%. It could be observed that the preva-

lence of these complications is higher among mothers with COVID 19 infection but the prevalence of FGR is similar to the general population (Tsakiridis et al., 2019). Therefore, we state that currently, there are no hard evidence that COVID 19 infection during pregnancy could increase risks of FGR which is in harmony with our findings (Movahedi et al., 2023).

The International Registry of Coronavirus Exposure in Pregnancy (IRCEP) was designed by Hernández-Díaz et al., (2022) to estimate the relative risk of adverse perinatal outcomes among women with Coronavirus Disease 2019 (COVID-19) at specific times during gestation and enrolled 92 participants with SARS-CoV-2 infection during the first trimester and revealed that the risk of any major congenital malformations (MCMs) did not differ significantly from that reported by an internal reference group with negative SARS-CoV-2 tests. Consequently, no specific pattern of malformations was identified among the 3 children with congenital anomalies reported after first trimester maternal SARSCoV-2 infection. This is reassuring since most teratogenic exposures identified in the past have been associated with a specific pattern of MCMs (e.g., congenital cytomegalovirus, rubella, thalidomide).

The analysis of MCMs includes women with either a positive SARS-CoV-2 PCR test or a clinical diagnosis of COVID-19 during the first trimester (exposed group) or a negative SARS-CoV-2 test (reference) that enrolled while pregnant (Hernández-Díaz et al., 2022).

In contrast to our results, Heidarzadeh et al., (2022) conducted a retrospective comparative study that enrolled 347839 newborns that to investigate the association between the Covid-19 pandemic and congenital birth anomalies and revealed statistical evidence of association between the Covid-19 pandemic and increased incidence of congenital anomalies.

Published literatures have indicated that viral illness during early pregnancy and several antiviral drugs are associated with an increased risk for neurodevelopmental congenital anomalies of newborn. Although no effective drug has been developed to contain SARS-CoV-2, some antiviral drugs as well as anti-inflammatory agents developed for other viral infections and pathologies are widely used in COVID-19 patients around the world. Many of these drugs have been used for COVID-19 without undergoing proper safety and efficacy tests as we are now facing a serious pandemic (Khan MSI et al., 2020).

Scientific evidences indicate that the causative agent of COVID-19, SARS-CoV-2 seem to cross both placental barrier (viral IgM detected in infants' hours after birth) (Dong et al., 2020) and blood brain barrier (virus detected in cerebrospinal fluid) (Moriguchi et al., 2020). As the virus can enter placenta and nervous system, the virus itself may have some adverse effects on the pathogenesis of NTDs, if pregnant mothers suffer from COVID-19. Also, it appears that coronavirus, SARS-CoV-2, may be transmitted to fetus from mother as the virus use entry receptor, angiotensin-converting enzyme 2 (ACE2) and S protein proteases expressed in developing human embryo (Khan MSI et al., 2020).

Moreover, Heidarzadeh et al., (2022) agreed with our findings in that maternal age and education were significantly associated with congenital anomalies. Advanced maternal age and lower education status are factors that have increased the risk of major congenital anomalies and the overall reported percentage of congenital abnormalities in this study was lower than the international rate (1.5–3%). The high prevalence of prenatal screening methods has led to a significant reduction in the congenital abnormality rate at delivery; most families prefer to abort their abnormal baby during the second trimester.

This study is limited by the retrospective study design which is associated with missed information about the possibility of teratogenicity during the first trimester. The information used in this study is affected by the accuracy of registered data. Also, lack

of information about maternal Covid-19 infection during pregnancy. Therefore, it was not possible for us to assess a direct correlation between Covid- 19 infection and congenital anomalies (Heidarzadeh et al., 2022).

The strength and Limitations of this study

To the best of our knowledge, the present study is one of the pioneer studies that reports specific placental ultrasonographic findings and performing anomaly scan attributed to COVID-19 infection. The prospective study design and having no patients lost to follow-up during the study period represent a strength point of the study.

However, prior to the appraisal of our results, several limitations must be considered. A major limitation is the relatively small number of patients recruited from a single department. One of the main limitations is lack of information about maternal Covid-19 infection during pregnancy. Therefore, it was not possible for us to assess a direct correlation between Covid-19 infection and congenital anomalies. For more reliable information, cohort studies are recommended to accurate risk assessment of covid-19 infected women during their first trimester of pregnancy for the congenital anomalies in their offspring. Assessment of confounding variables such as insufficient prenatal visits and screenings during this pandemic and their effects on congenital abnormalities at delivery would be an interesting topic for future works.

Conclusion

As evident from the current study, no evidence of a teratogenic effect associated with maternal SARS-CoV-2 infection during the first months of pregnancy. However, Pathognomonic ultrasonographic findings of placental calcifications and oligohydramnios are associated with early pregnancy infection with covid-19. Moreover, BMI ≥ 27.6 kg/m2, gestational age at infection ≤8 weeks were significant independent risk factors for occurrence of pathognomonic ultrasonographic findings (oligohydramnios) in patients infected with COVID-19 in early pregnancy. Consequently, early detection of placental changes through the use of specific ultrasound findings could indicate pregnancies that are at an increased risk of fetal complications.

Ultrasound findings including placental calcifications can be used as a diagnostic tool for possible fetal complications, as well as early signs of adverse pregnancy outcomes requiring closer antenatal follow-up.

References

1. Abdelazim IA, Abu-Faza M, Hamed MES, Amer OO, Shikanova S, Zhurabekova G. Prenatal diagnosis of single umbilical artery complicated by intrauterine growth retardation and preterm labor: Case report. J Family Med Prim Care. 2019;8(6):2151-2154. doi: 10.4103/jfmpc.jfmpc_394_19.
2. Abdelazim IA, Abufaza M, Munaifi S. COVID-19 Positive Woman Presented with Preterm Labor: Case Report. Gynecol Obstet Reprod Med. doi:10.21613/GORM.2021.1170. published on-line 21-2-2021.
3. Soma-pillay P and Botha H . College of Obstetricians and Gynaecologists of South Africa - Recommendations for COVID-19 vaccination in pregnancy. Obstetrics and Gynaecology Forum 2021; 31, 2. https://hdl.handle.net/10520/ejc-medog_v31_n2_a5
4. Barišić A. Conceived in the covid-19 crisis: Impact of maternal stress and anxiety on fetal neurobehavioral development. J Psychosom Obstet Gynaecol. 2020;41(3):246
5. Brandibur, T. E., Kundnani, N. R., Boia, M., Nistor,

D., Velimirovici, D. M., Mada, L., Neagu M. N & Popoiu, C. M. (2023). Does COVID-19 Infection during Pregnancy Increase the Appearance of Congenital Gastrointestinal Malformations in Neonates?. Biomedicines, 11(12), 3105.

6. Bronshtein M, Blazer S. Prenatal diagnosis of liver calcifications. Obstet Gynecol. 1995;86(5): 739-43. doi: 10.1016/0029-7844(95)00278-Y
7. Buheji M, da Costa CK, Beka G, Mavric B, De Souza YL, da Costa Silva SS, et al. The extent of covid-19 pandemic socio-economic impact on global poverty: a global integrative multidisciplinary review. Am J Econ. 2020; 10:4.
8. Bukasa A, Campbell H, Brown K, Bedford H, Ramsay M, Amirthalingam G, Tookey P. Rubella infection in pregnancy and congenital rubella in United Kingdom, 2003 to 2016. Euro Surveill. 2018;23(19):17–00381.
9. Degani S. Sonographic findings in fetal viral infections: a systematic review. Obstet Gynecol-Surv. 2006;61(5):329-36. doi: 10.1097/01.ogx.0000216518.85796.88.
10. Deprest J, Choolani M, Chervenak F, Farmer D, Lagrou K, Lopriore E, et al. Fetal diagnosis and therapy during the COVID-19 pandemic: guidance on behalf of the international fetal medicine and surgery society. Fetal Diagn Ther. 2020; 47:9.
11. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020;323:1846-8. Medline:32215581 doi:10.1001/jama.2020.4621
12. Dotters-Katz S, Hughes L. Coronavirus (COVID-19) and pregnancy: what maternal-fetal medicine subspecialists need to know. Washington, DC: The Society for Maternal-Fetal Medicine. 2020;4(11):1-7.
13. Flores-Pliego, A.; Miranda, J.; Vega-Torreblanca, S.; Valdespino-Vázquez, Y.; Helguera-Repetto, C.; Espejel-Nuñez, A.; Borboa- Olivares, H.; Espino YSosa, S.; Mateu-Rogell, P.; León-Juárez, M.; et al. Molecular Insights into the Thrombotic and Microvascular Injury in Placental Endothelium ofWomen with Mild or Severe COVID-19. Cells 2021, 10, 364.
14. Heidarzadeh, M., Taheri, M., Mazaheripour, Z. et al. The incidence of congenital anomalies in newborns before and during the Covid-19 pandemic. Ital J Pediatr 48, 174 (2022). https://doi.org/10.1186/s13052-022-01368-6.
15. Hernández-Díaz, S., Smith, L. H., Wyszynski, D. F., & Rasmussen, S. A. (2022). First trimester COVID-19 and the risk of major congenital malformations–International Registry of Coronavirus Exposure in Pregnancy. Birth defects research, 114(15), 906-914.
16. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.;Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020, 181, 271–280.
17. Khan MSI, Nabeka H, Akbar SMF, Al Mahtab M, Shimokawa T, Islam F, Matsuda S. Risk of congenital birth defects during COVID-19 pandemic: Draw attention to the physicians and policymakers. J Glob Health. 2020 Dec; 10(2):020378. doi: 10.7189/jogh.10.020 378. PMID: 33274057; PMCID: PMC7690649.
18. Khoiwal K, Agarwal A, Gaurav A, Kumari R, Mittal A, Sabnani S, Mundhra R, Chawla L, Bahadur A, Chaturvedi J. Obstetric and perinatal outcomes in pregnant women with COVID-19: an interim analysis. Women Health. 2022 Jan;62(1):12-20. doi: 10.1080/03630242.2021.2007199. Epub 2021 Dec 7. PMID: 34875976.
19. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus

origins and receptor binding. Lancet. 2020;395(10224):565-574. doi: 10.1016/S0140-6736(20)30251-8.

20. Mappa I, De Vito M, Flacco ME, di Mascio D, D'Antonio F, Rizzo G. Prenatal predictors of adverse perinatal outcome in congenital cytomegalovirus infection: a retrospective multicenter study. J Perinat Med. 2022; 51(1):102–10.
21. Masjoudi M, Aslani A, Khazaeian S, Fathnezhad-Kazemi A. Explaining the experience of prenatal care and investigating the association between psychological factors with self-care in pregnant women during COVID-19 pandemic: a mixed method study protocol. Reprod Health. 2020; 17:1.
22. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020;94:55-8.
23. Movahedi, M., Siahafshari, K. M., Hajhashemi, M., Khorvash, F., Saeidi, M., & Allameh, Z. (2023). Evaluation of maternal and fetal outcomes in pregnant women with COVID-19 based on different trimesters. Advanced Biomedical Research, 12(1), 165.
24. Papapanou M, Papaioannou M, Petta A, Routsi E, Farmaki M, Vlahos N, et al. Maternal and Neonatal Characteristics and Outcomes of COVID-19 in Pregnancy: An Overview of Systematic Reviews. Int J Environ Res Public Health. 2021;18(2):596. doi:10.3390/ijerph 18020596.
25. Pavlyshyn, G., Sarapuk, I., & Saturska, U. (2023). MATERNAL STRESS IN VIETNAM DURING THE COVID-19 PANDEMIC. Neonatology, Surgery and Perinatal Medicine, 12 (3(45), 42–47. https://doi.org/10.24061/2413-4260.XII.3.45.2022.6
26. Phoswa WN, Khaliq OP. Is pregnancy a risk factor of COVID-19?. Eur J Obstet Gynecol Reprod Biol. 2020; 252:605-609. doi: 10.1016/j. ejogrb.2020.06.058.
27. Samara AA, Koutras A, Floros T, Kontomanolis E, Sotiriou S. Placental Ultrasonographic Findings Due to COVID-19 Infection During Pregnancy: A Case Report. Cureus. 2022 Apr 18;14(4):e24265. doi: 10.7759/cureus.24265. PMID: 35607566; PMCID: PMC9123338.
28. Sass L, Urhoj SK, Kjargaard J, Dreier JW, Strandberg-Larsen K, Andersen AMN. Fever in pregnancy and the risk of congenital malformations: a cohort study. BMC Pregnancy Childbirth. 2017; 17:1.
29. Sharma D, Shastri S, Farahbakhsh N, Sharma P. Intrauterine growth restriction - part 1. J Matern Fetal Neonatal Med. 2016;29(24): 3977-87. doi: 10.3109/14767058.2016.1152249.
30. Sotiriou S, Samara AA, Tsiamalou IA, Donoudis C, Seviloglou E, Skentou C, Garas A, Daponte A. Placental Ultrasonographical Findings during SARS-CoV-2 Infection. Diagnostics (Basel). 2022 Apr 13;12(4):974. doi: 10.3390/diagnostics12040974. PMID: 35454021; PMCID: PMC9032574.
31. Tsakiridis I, Dagklis T, Zerva C, Mamopoulos A, Athanasiadis A, Papazisis G. Depression in pregnant women hospitalized due to intrauterine growth restriction: Prevalence and associated factors. Midwifery 2019;70:71 5.
32. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020;11(1):3572. doi: 10.1038/s41467-020-17436-6.
33. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020;11(1):3572. doi: 10.1038/s41467-020-17436-6.

34. Wang CL, Liu YY, Wu CH, Wang CY, Wang CH, Long CY. Impact of COVID-19 on Pregnancy. Int J Med Sci. 2021;18(3):763-767. doi: 10.7150 /ijms.49923.
35. Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020;223(1): 111.e1- 111.e14. doi: 10.1016 /j.ajog.2020.04.014.
36. Zhang, M., Hou, L., Guo, L. et al. Intrauterine transmission of SARS-CoV-2 to and prenatal ultrasound abnormal findings in the fetus of a pregnant woman with mild COVID-19. BMC Pregnancy Childbirth 23, 723 (2023). https://doi.org/10.1186/s12884-023-06053-y.
37. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733. doi: 10.1056/NEJMoa2001017.

Received 6-5-2024
Revised 18-5-2024
Accepted 1-6-2024