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ORIGINAL PAPER

# Sonographic Signs of SARS-CoV-2 Placentitis. Association with Pregnancy Outcome

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*ABSTRACT*

***Introduction:*** *Being associated with a systemic infection, SARS-CoV-2 affects multiple organs, including the placenta. SARS-CoV-2 placentitis is a new condition that shows the destructive effects of fibrin deposition in the perivillous area, chronic histiocytic intervillositis and trophoblast necrosis after the placenta is infected with SARS-CoV-2. Until now, there have been no published reports regarding the ultrasound signs of massive perivillous fibrin deposition and the recommended monitoring for these cases.*

***Aim:*** *Our aim was to analyze the sonographic appearance of the placenta in a series of SARS-CoV-2 infected pregnant women during their third trimester.*

***Material and method:*** *In all cases included in the present study, we performed serial obstetrical ultrasounds every seven days until delivery, followed by histopathological examination of the placenta postpartum.*

***Results:*** *In women with intrauterine growth restriction (IUGR), sonographic images of the placentas revealed that they matured faster within three weeks of receiving a COVID-19 diagnosis and reached a more rapid senescence. In all cases, there was a gradual increase in placental calcification from week to week, but only in pregnant women with a grade 3 placenta at the moment of inclusion in the study the deterioration was severe, leading to placental insufficiency and subsequently to IUGR.*

***Conclusion:*** *The cases who had an increased placental degree at the time of infection were associated with abnormally rapid placental aging. These aspects can be evaluated sonographically.*

**Keywords**: SARS-CoV-2 placentitis, sonography, IUGR.

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## INTRODUCTION

Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic factor of coronavirus disease 2019 (COVID-19), during pregnancy is linked to unfavorable outcomes. Symptomatic pregnant women with COVID-19 have an increased risk of giving birth prematurely, developing preeclampsia, undergoing a caesarean section and experiencing stillbirth (1). SARS-CoV-2 triggers a systemic infection that affects multiple organs, including the placenta.

The placenta is a fetal organ whose development is highly regulated during pregnancy, a fact that is critical for maintaining normal fetal growth. The significant roles of the placenta include preventing immune rejection of the fetal allograft, transferring nutrients and oxygen from the mother to the fetus and carbon dioxide from the fetus to the mother, and secreting steroid hormones and peptides to regulate maternal and fetal metabolism and ensure normal fetal growth.

Sonography is an integral component of routine prenatal monitoring. Ultrasound examination of the placenta throughout pregnancy is focused on morphology, anatomy, implantation, location, insertion anomalies, size and pulsed Doppler assessment (2). Placenta insufficiency is a general term that describes deterioration in placental functioning, which culminates in decompensated fetal hypoxia and acidosis. At this point, there is no standard method for placental insufficiency diagnosis, but Doppler ultrasound provides useful information on fetal-maternal circulation and, therefore, on the fetal status. There are four parameters used for evaluating placental function: umbilical artery flow, uterine artery velocimetry, middle cerebral artery flow and ductus venosus flow. According to Ohgiya Y *et al* (3), in cases complicated by placental insufficiency there is an increase in the placental thickness to volume ratio.

SARS-CoV-2 placentitis is a new condition reflecting the destructive presence of perivillous fibrin deposition, chronic histiocytic intervillositis and subsequent trophoblast necrosis following SARS-CoV-2 infection of the placenta (4). Although initially there was no association between COVID-19 occurrence during pregnancy and stillbirth, further research revealed that pregnant women infected with SARS-CoV-2 had a greater risk of intrauterine fetal demise (5).

SARS-CoV-2 placentitis is currently a postpartum histopathological and immunohistochemistry-based diagnosis defined by a particular trio of destructive mechanisms. When pregnant women get infected with SARS-CoV-2, syncytiotrophoblast cells are most often affected. This can cause perivillous fibrin deposition, chronic histiocytic intervillositis, and villous trophoblast necrosis, altering placental maternal-fetal oxygen transfer. Acute fetal distress and stillbirth within days are believed to result from these findings. According to the largest study, which included 64 cases of intrauterine fetal death and four cases of early neonatal death in SARS-CoV-2 infected pregnant women (6), stillbirth occurred at an average gestational age of 30 weeks and in all cases a massive perivillous fibrin deposition was found.

Until now, there has been no published report regarding the ultrasound signs of massive perivillous fibrin deposition and the recommended monitoring for these cases.

### Aim

Our objective was to analyze the sonographic appearance of the placenta in a series of SARS-CoV-2 infected pregnant women during their third trimester and identify sonographic signs that can be linked to SARS-CoV-2 placentitis and implicitly to an adverse perinatal outcome. Also, we aimed to synthesize our conclusions into a recommended management approach for these cases.

## MATERIAL AND METHODS

We conducted a unicentric prospective study examining 10 third-trimester pregnancies that tested positive for SARS-CoV-2 using reverse transcriptase polymerase chain reaction (RT-PCR) at the time of their inclusion in the study. In all cases, we performed serial obstetrical ultrasounds every seven days until delivery, followed by histopathological examination of the placenta postpartum. We noted basic demographic data such as age, associated comorbidities and fetal outcome. Patients with additional factors for placental insufficiency (multiparity, smoking, known cardiac pathology,

| Case | Gestational age | Form of COVID-19 | Placental grade-inclusion | Percentile growth-inclusion | Placental grade-birth | Percentile growth- birth |
|---|---|---|---|---|---|---|
| Case 1 | 30 weeks | Moderate to severe | Grade 2 | 63$^{th}$ percentile | Grade 3 | 57$^{th}$ percentile |
| Case 2 | 29 weeks | Moderate to severe | Grade 2 | 75$^{th}$ percentile | Grade 3 | 62$^{th}$ percentile |
| Case 3 | 31 weeks | Moderate to severe | Grade 3 | 37$^{th}$ percentile | Grade 3 | 15$^{th}$ percentile |
| Case 4 | 29 weeks | Asymptomatic | Grade 2 | 47$^{th}$ percentile | Grade 3 | 34$^{th}$ percentile |
| Case 5 | 30 weeks | Moderate to severe | Grade 2 | 27$^{th}$ percentile | Grade 3 | 18$^{th}$ percentile |
| Case 6 | 31 weeks | Moderate to severe | Grade 2 | 44$^{th}$ percentile | Grade 3 | 27$^{th}$ percentile |
| Case 7 | 31 weeks | Moderate to severe | Grade 3 | 23$^{th}$ percentile | Grade 3 | 9$^{th}$ percentile |
| Case 8 | 30 weeks | Asymptomatic | Grade 2 | 56$^{th}$ percentile | Grade 3 | 44$^{th}$ percentile |
| Case 9 | 29 weeks | Moderate to severe | Grade 2 | 49$^{th}$ percentile | Grade 3 | 39$^{th}$ percentile |
| Case 10 | 32 weeks | Moderate to severe | Grade 3 | 29$^{th}$ percentile | Grade 3 | 8$^{th}$ percentile |

**TABLE 1.** Summary of cases included in the study

known intrauterine fetal growth restriction) were excluded from the study.

## RESULTS

The mean age of patients involved in our study was 36 years. From the cases analyzed by us, eight (80%) had a moderate to severe form of COVID-19 and two cases were asymptomatic (Table 1). From an obstetrical perspective, seven of all study participants were primiparous. The main symptoms were cough, fever, rhinorrhea and anosmia.

On first evaluation, all fetuses had normal growth, with a normal placental appearance and amniotic fluid subjective evaluation within the normal ranges.

All 10 cases delivered at term, within 37–40 weeks of gestation. In our research group, there were no cases of stillbirth and two cases were complicated by intrauterine growth restriction (IUGR) according to the international guideline's definition (estimated fetal weight below the 10th percentile).

Sonographic images of the placentas of women with IUGR revealed that they matured faster within three weeks of receiving a COVID-19 diagnosis and reached a more rapid senescence (Figures 1 and 2). In all cases, there was a gradual increase in placental calcification from week to week, but only in the cases with a grade 3 placenta at the moment of inclusion in the study the deterioration was severe, leading to placental insufficiency and, subsequently, to IUGR (Figures 3 and 4).

The specific sonographic signs indicated acute placental maturation, characterized by hyperechoic aspects throughout the entire placental mass (Figures 1 and 2). Until birth, Doppler

**FIGURE 1.** Case 1. Primipara, 28 years old, SARS-CoV-2 positive, 30 weeks of gestation, placenta with normal sonographic appearance – grade 2 placenta

**FIGURE 2.** Case 1. Primipara, 28 years old, SARS-CoV-2 positive, 33 weeks of gestation – grade 3 placenta with calcification in the entire thickness

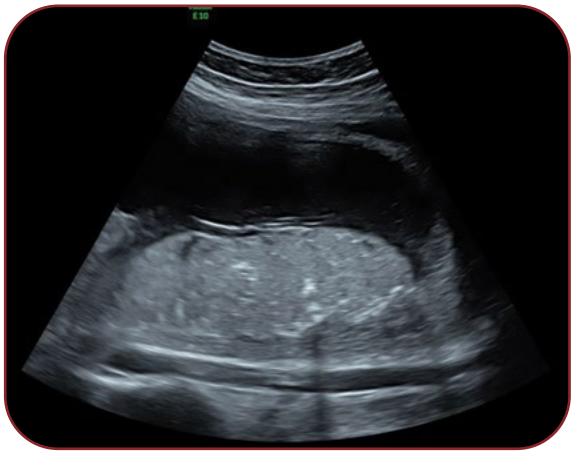

**FIGURE 3.**
Primipara, 32 years old, SARS-CoV-2 positive, 31 weeks of gestation with a grade 3 placenta

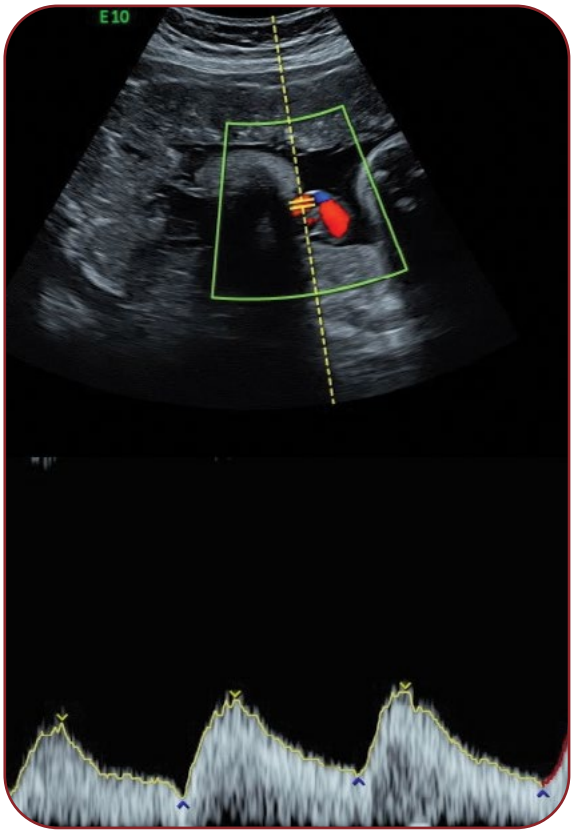


**FIGURE 4.**
Case 2. Primipara, 32 years old, SARS-CoV-2 positive, 33 weeks of gestation – placental deterioration with normal Doppler indices. The mother gave birth at 37 weeks of gestation.

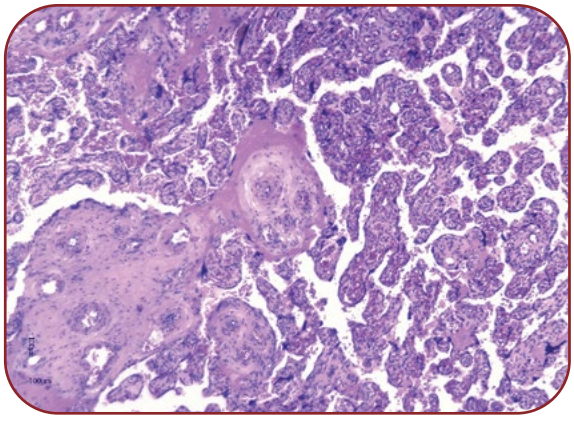

**FIGURE 5.**
Correspondent for case 2 (sonographic image Figures 3 and 4). Intensely acidophilic perivillous fibrinoid deposits around some stem villi. HE stain 10x

indices remained reassuring (Figures 3 and 4). Women with IUGR exhibited a lower biophysical profile, characterized by oligohydramnios, reduced fetal movements and low variability on cardiotocography monitoring.

In term of management, low molecular weight heparin was administered for thromboprophylaxis in all cases.

The simple hematoxylin-eosin (HE) histopathological examination was concordant with the sonographic changes (Figure 5).

## DISCUSSIONS

Stillbirth is a complication with acute psychologic trauma on both the mother and her family, with an estimated incidence of 2-6 million cases per year. The primary identifiable cause of stillbirth is a placental insufficiency, followed by placental malperfusion (7). Concerning the impact of SARS-CoV-2 infection on fetal outcomes and its correlation to stillbirth, research utilizing immunohistochemistry has revealed that infected placentas were displaying a distinct pattern, regardless of the neonate's infection status (8). These findings include chronic histiocytic intervillositis, villous trophoblast necrosis and increased fibrin deposits cumulating in a destructive process. These processes can occur independently and unproportionally with the severity of maternal infection, affecting all cellular types: syncytiotrophoblasts, cytotrophoblasts, Hofbauer cells and endothelial cells (9). Prior to the COVID-19 pandemic, it was already established that chronic histiocytic intervillositis and significant perivillous fibrin deposition were present in placentas of pregnancies with adverse perinatal outcomes. The occurrence of these findings in cases of stillbirth was reported to be less than 1% (10). Until now, there have been published reports with substantial information on the effect of SARS-CoV-2 infection on the placenta, but no studies on prenatal diagnostic criteria or suggestive signs of placental deterioration have been published so far (11).

In our small study, we noticed an accelerated placental maturation in some of the pregnant women diagnosed with COVID-19. Placental maturation is a physiologic process that occurs after 36 weeks of gestation and is characterized by calcification (12). Premature placental calcification was associated with fetal growth restric-

tion and a higher risk for neonatal intensive care unit admission.

Specifically, in our study, subjects who had premature placental calcification at the time of the SARS-CoV-2 infection experienced intrauterine growth restriction (IUGR). We assume that the overlap of a second risk factor, such as SARS-CoV-2 infection, increases the risk of deterioration in the already affected placental tissue.

Despite the small size of our study group, our findings open the way for further research. We believe that close monitoring in cases with accelerated preterm placental calcification is critical to preventing stillbirth. We propose a weekly complete sonographic evaluation for cases exhibiting accelerated placental maturation, as this process may signal the onset of SARS-CoV-2 placentitis and a heightened risk of stillbirth. ❑

## CONCLUSION

Pregnant women represent a risk group for various infection, as the outcome can be unfavorable for both the mother and fetus. The true impact of SARS-CoV-2 infection on neonatal outcomes was clarified only after the immunohistochemistry test on the placenta showed a specific pattern now defined as SARS-CoV-2 placentitis. This is a postnatal diagnosis with a high incidence of stillbirths. Our study showed that the cases with an increased placental degree at the time of infection were associated with abnormally rapid placental aging. These aspects can be evaluated sonographically. Thus, cases with marked placental maturation after infection can be monitored accordingly in tertiary centers, in order to prevent the adverse prognosis, implicitly intrauterine fetal death. ❑

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