

The Effects of Asymptomatic Coronavirus Disease-2019 on Placenta at Third Trimester Pregnancy: A Comprehensive Study

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ABSTRACT Objective: By the time coronavirus disease-2019 (COVID-19) had been announced as pandemic, the disease was shown to have a great risk among pregnant woman if lower respiratory system is involved. We aimed to describe clinical characteristics of deliveries with asymptomatic COVID-19 infection, investigate transplacental transmission, and compare first-line histopathological findings with healthy controls. **Material and Methods:** We conducted a prospective cohort study of consecutive term deliveries at our tertiary hospital's obstetric unit between March and November 2021. Forty-five patients with asymptomatic reverse transcription-polymerase chain reaction (RT-PCR) positivity were matched with 45 controls with negative RT-PCR testing. All newborns of mothers with positive RT-PCR results for COVID-19 underwent a nasopharyngeal swab following delivery, and Apgar scores of the newborns were extracted from pediatric charts. Placentas were transported and fixated in 10% formaldehyde solution before pathological evaluation. **Results:** There were no significant differences in Apgar scores, birth weights, head circumferences, birth height, and genders between the 2 groups. RT-PCR results were negative in all of the newborns, indicating no vertical transmission. Placental focal and global calcification, and choriamnionitis frequencies were similar between the groups, whereas placental fibrin deposits were significantly more frequent in the placentas of infected pregnancies. **Conclusion:** There was no evidence of vertical transmission and any characteristic feature in the placentas of pregnancies with asymptomatic COVID-19 infection. Although no significant clinical implication was found, increased perivillous fibrin deposition in the study group could be a baseline step for the progression of perinatal infection.

Keywords: COVID-19; placental pathology; transplacental transmission; virus infection; pregnancy

By the time coronavirus disease-2019 (COVID-19) had been announced pandemic by the World Health Organization, Turkish Ministry of Health reported the first case in Türkiye.¹ Since then, number of clinical trials indicated an obstetrical practice algorithm. To date, the disease shows a greater risk among pregnant women, particularly if the lower respiratory system is involved. Although most series reported that there is no intrauterine or transplacental viral transmission to the fetus, several placental histochemical analyses of symptomatic cases demonstrated severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) invasion of the placenta.²⁻⁵

Theoretically, placenta functions as lung and kidney in the antenatal period. Thus, focusing on placental structural and functional alterations may provide further information about the process of the infection. In this prospective cohort study, we planned to report characteristics of deliveries with asymptomatic COVID-19 infection, investigate transplacental transmission, and compare first-line histopathological findings with healthy controls.

MATERIAL AND METHODS

We constructed a prospective cohort study of term deliveries at our tertiary hospital's obstetric unit between March and April 2021. We tested the patients

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with universal RNA real-time reverse transcription-polymerase chain reaction (RT-PCR) testing (Cepheid Xpert Xpress, Cepheid, Sunnyvale, California, United States). Patients with positive PCR for SARS-CoV-2 were consulted to infectious diseases clinic, and asymptomatic cases were included accordingly. Pregnancies complicated with hypertension, diabetes, preeclampsia, or eclampsia were excluded. Finally, 45 patients with asymptomatic PCR positivity were matched with 45 patients with negative PCR testing.

All newborns of mothers with positive RT-PCR results for COVID-19 underwent a nasopharyngeal (NP) swab for SARS-CoV-2 following delivery, and Apgar scores of the newborns were extracted from pediatric charts. Placentas were transported and fixed in 10% formaldehyde solution before pathological evaluation. One expert pathologist stained the placenta with hematoxylin and eosin and evaluated the placental tissue following relevant guidelines.⁶ Placental examinations were classified into following findings: perivillous fibrin deposits, focal calcification, global calcification, chorioamnionitis, and no significance (if none were identified).

The study was carried out in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from women. İzmir Kâtip Çelebi University, Faculty of Medicine Ethics Committee approved this study (date: February 25, 2021; no: 22). Patient informed consent form was obtained from each patient.

Means, standard deviations, and frequencies were used to express data. Student's t-test and chi-square test were used for comparisons.

RESULTS

Ninety pregnant women who were admitted to our hospital for delivery were included. Demographic data of the patients are presented in [Table 1](#), revealing no significant differences among the two groups.

Neonatal outcomes are presented in [Table 2](#). There were no significant differences in the mean Apgar scores at minute 1 and 5, neonatal birth weights, head circumferences, birth height, and sex between the study groups. NPs for SARS-CoV-2 RT-PCR were negative in all of the newborns, revealing no vertical transmission. Small for gestational age and preterm delivery rates were equally distributed between the groups.

Results of the placental evaluation are summarized in [Table 2](#). Placental focal and global calcification, and chorioamnionitis frequency were similar between the two groups. However, placental fibrin deposits were significantly more frequent in the placentas of infected pregnancies. Macroscopic examination showed locally dense placenta with slightly granular shape and pale trabeculae, in line with the histological results of perivillous fibrin deposition particularly in the study group ([Figure 1](#)). Frequency of placentas with no significant finding were significantly higher in the control group, and macroscopic examinations of these specimens showed a normal appearance.

DISCUSSION

Although the current data are limited, histopathological examinations of placenta in COVID-19 may provide valuable information about intrauterine

TABLE 1: Comparisons of baseline obstetric characteristics of asymptomatic COVID-19 cases in third-trimester pregnancy with matched controls negative for COVID-19.

	Negative for COVID-19 (n=45)	Positive for COVID-19 (n=45)	p value
Maternal age	27.75±4.78	27.59±7.14	0.9
Route of delivery			
Vaginal	15 (33.3%)	21 (46.7%)	0.07
Cesarean	30 (66.7%)	24 (53.3%)	
Gestational age delivery	38.41±7.46	39.31±2.04	0.45

Data are presented as mean±standard deviation or frequencies with percentage in parentheses

TABLE 2: Comparisons of pregnancy and neonatal outcomes of asymptomatic COVID-19 cases in third-trimester pregnancy with matched controls negative for COVID-19.

	Negative for COVID-19 (n=45)	Positive for COVID-19 (n=45)	p value
Apgar at minute 1	9±0	8.4±2.24	0.9
Apgar at minute 5	10±0	9.3±2.49	0.9
Birth weight	2863.15±709.81	3005.44±654.06	0.12
Head circumference	33.71±2.41	33.71±2.08	0.9
Birth height	48.15±4.03	48.97±2.89	0.87
Neonatal polymerase chain reaction positivity	-	-	-
Sex of newborn			0.061
Male	26 (57.7%)	33 (73.3%)	
Female	19 (42.3%)	12 (26.6%)	
<10 th percentile for neonatal head circumference	16 (35.5%)	15 (33.3%)	0.9
<10 th percentile for birth weight	14 (31.1%)	15 (33.3%)	0.9
Preterm delivery	1 (2.2%)	1 (2.2%)	1.000
Placental weight	608.6±134.04	582.82±137.68	0.08
Placental characteristics			
No significance	23 (51%)	12 (26%)	0.004
Perivillous fibrin deposits	12 (26%)	25 (55%)	0.003
Focal calcification	6 (13.3%)	11 (24%)	0.065
Global calcification	5 (11%)	5 (11%)	NS1.000
Chorioamnionitis	3 (6%)	1 (2%)	0.35

Data are presented as mean±standard deviation or frequencies with percentage in parentheses.

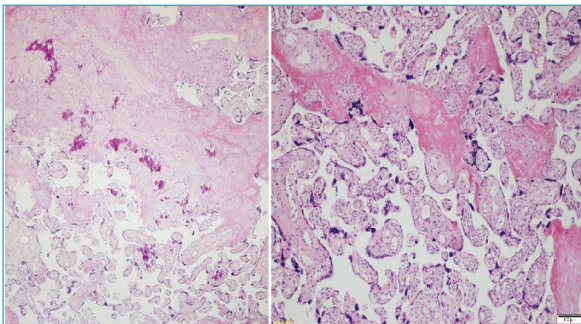


FIGURE 1: Placental fibrin deposits in a COVID-19 positive pregnancy with asymptomatic infection. Hematoxylin eosin stain (magnification X10), hematoxylin eosin stain (magnification X20).

transmission, fetal infection progression, and neonatal outcome. In this study, we found no characteristic inflammatory placental feature that could suggest SARS-CoV-2 invasion. Chen et al. examined 3 infected placentas and revealed fibrin deposition inside and all over the villi with local syncytial nodule increments in all of the 3 placentas.⁷ The newborns in their study had also negative NP swab testing, but all pregnant people were symptomatic in the pre- or postpartum period. We did not reveal any pathological changes such as villitis or chorioamnionitis in

asymptomatic cases, partially confirming results by Chen et al.⁷ These results may suggest that SARS-CoV-2 does not exhibit chronic inflammatory aberrations such as villitis, intervillitis and funisitis in the placenta on the contrary to *Cytomegalovirus*, *Toxoplasma*, and Rubella virus infections.^{8,9}

In our current study, RT-PCR test was negative in the newborns of pregnancies with asymptomatic COVID-19. Thus, we showed no maternal-fetal COVID-19 vertical transmission in late pregnancy. On the other hand, few histopathological studies on disease demonstrated placental infection.^{2,4,10} Their findings suggest that important chronic histiocytic intervillitis frequently occurs, and this feature may be evidence of transvertical transmission. Since most cases in those studies were severely symptomatic, viral load and lower respiratory tract involvement may have influence on the possibility of placental invasion.

Various amount of perivillous fibrin deposition occur in almost every placenta. Clinical reflection of the minor fibrin deposition is negligible. However, Mongula et al. associated perivillous fibrin storage to fetal distress.¹¹ On the other hand, there was no rela-

tionship between placental findings and neonatal outcome in our study. There are two possible explanations for this discrepancy: first, coagulopathy is known to be triggered by the virus and second, existing cofactors such as preterm delivery and diabetes might have increased perivillous fibrin storage.

The mechanism and effects of perivillous fibrin deposition is not clear. A histopathological evaluation study reported that hypoxic respiratory disease causes increased intervillous and subchorionic fibrin deposition associated with disturbances in maternal placental blood flow.¹² Extension of the deposition might be linked to placental blood flow; however, this may not be relevant to asymptomatic cases, considering to the results of our study with no evidence of maternal and fetal hypoxia. Baergen et al. reported the presence of focal increase in perivillous fibrin deposition in asymptomatic COVID-19 cases. The authors concluded that COVID-19 infection might be associated with tendency for thrombosis in the fetal circulation, and associated placental pathologies would have clinical effects for both the mother and the infant.¹³

Our study was conducted to late third-trimester pregnancies with asymptomatic COVID-19 infection. Theoretically, the transvertical transmission of COVID-19 could be influenced by gestational week at infection, since protective strength of the placenta develops through increasing gestational age. Comprehensive series of pregnancies with symptomatic and asymptomatic COVID-19 disease at different trimesters are needed.

CONCLUSION

The current study shows no proof of vertical transmission and characteristic feature in the placentas of pregnancies with asymptomatic COVID-19 infection in the third trimester. Although no significant clinical implication was found, increased perivillous fibrin deposition in the study group could be a baseline step for the progression of perinatal infection.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mustafa Şengül; **Design:** Mustafa Şengül, Halime Şen Selim; **Control/Supervision:** Hüseyin Aydoğmuş; **Data Collection and/or Processing:** Mustafa Şengül; **Analysis and/or Interpretation:** Mustafa Şengül; **Literature Review:** Serhat Şen; **Writing the Article:** Mustafa Şengül, Halime Şen Selim; **Critical Review:** Halime Şen Selim; **References and Fundings:** Mustafa Şengül; **Materials:** İrfan Öcalı Ceren Çıralı.

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