Correlation between placental histopathology and perinatal outcome in COVID-19

Devendra Arora¹, KS Rajmohan², Sanjay Singh³, Vinod Nair*, Sanghita Barui², Madhusudan Dey³, Abhijeet Kumar⁴

¹Department of Obstetrics and Gynaecology, Base Hospital Delhi Cantt, New Delhi, India; ²Department of Pathology, Base Hospital Delhi Cantt, New Delhi, India

Abstract

Objectives: An alarming rate of adverse perinatal outcomes as well as maternal deaths has been reported worldwide during this pandemic. It would be prudent to start thinking on the lines of acute or chronic intrauterine fetal hypoxia due to placental microvascular pathology or villitis caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. Autopsy studies of deceased patients with severe COVID-19 have revealed the presence of diffuse pulmonary alveolar damage, thrombosis, and microvascular injuries. It is expected that similar pathological features such as microvascular injuries could be found in the placenta of infected pregnant women. Materials and Methods: Placentas of singleton pregnancies from 42 SARS-CoV-2 positive mothers delivered at term were submitted for histopathological examination. Those with multifetal gestation, hypertensive disorder, fetal growth restriction, structural or chromosomal anomalies in the fetus, thrombophilia, prolonged prelabor rupture of membranes, and placenta accreta spectrum were excluded from the study. Histopathological examination was done by two pathologists independently and only those results concurred by both were reported. Histopathological features and corresponding neonatal outcome were analyzed.

Results: Reports of 42 placentas from patients with SARS-CoV-2, delivered at term (37–40 weeks) were analyzed in our study. Features of maternal vascular malperfusions (MVM) were present in 45% (n = 19) cases. Features of fetal vascular malperfusions (FVM) were present in 23.8% (n = 10) cases. There were 47.6% (n = 20) cases showing at least one feature of acute inflammatory pathology (AIP) and 42.8% (n = 18) showing features of chronic inflammatory pathology (CIP). Neonatal respiratory distress syndrome was found in 19% (n = 8) of the neonates. Correspondingly, nearly all placentas (n = 7) of these neonates showed features of MVM, FVM, AIP and CIP. There was no maternal or neonatal mortality in our study group.

Conclusion: The main findings of our study include maternal as well as fetal vascular malperfusions and placental inflammatory pathology. These findings provide an outline for better understanding of etiological factors and pathogenesis of adverse perinatal outcomes in SARS-CoV-2 infection.

Keywords: COVID-19, Histopathology, Perinatal outcome, Placenta, Pregnancy

Introduction

Coronaviruses are enveloped single-stranded RNA viruses that infect both humans and animals [1]. Human coronaviruses cause a wide spectrum of respiratory illnesses ranging from mild upper respiratory tract infections to severe pneumonia [2-4]. Severe acute respiratory syndrome-coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and SARSCoV-2 in 2019 are the three clinically important Coronaviruses which have caused serious respiratory illness and death in humans [5]. The primary target of SARS-CoV is ciliated epithelial cells. SARS-CoV binds to the cells via angiotensin converting enzyme 2 receptor [6]. Various human tissues that express ACE-2 receptors are cardiovascular, gastrointestinal, adipose, pulmonary and renal tissues. In addition to these, human placenta also expresses ACE-2 receptors [7].
The coronavirus disease-19 (COVID-19) in pregnant women is of particular interest to obstetricians worldwide. There is a growing evidence to suggest human placenta as an immune organ [8]. Placental immune response to various maternal infections and their transplacental transmission are of utmost clinicopathological significance in modern medicine. Several case series and meta-analyses have concluded that SARS infection during pregnancy was associated with severe maternal infection, increased risk of maternal death, and spontaneous abortion [9-15]. Meta-analysis of case reports and case series on vertical transmission of SARS-CoV-2 have revealed negative polymerase chain reaction (PCR) results for SARS-CoV-2 in the neonate, placenta, cord blood, and vaginal secretions in majority of cases [16]. Several studies have already been conducted to find out the pathological features of placentas of pregnant women with COVID-19. Acute or chronic inflammatory changes in these placentas were rarely found. However, microvascular changes and maternal vascular malperusions (MVM) were almost a constant finding [1,17,18].

An alarming rate of adverse perinatal outcomes as well as maternal deaths has been reported worldwide during this pandemic. Though many of these adverse pregnancy outcomes have been attributed to a collapsed health care system due to a sudden peak in COVID-19 cases, it would be prudent to start thinking on the lines of acute or chronic intrauterine fetal hypoxia due to placental microvascular pathology or villitis caused by SARS-CoV-2 infection. Viral infections during pregnancy have a wide spectrum of placental pathology [19]. Numerous viruses cause villitis and spontaneous abortions [19-21]. Autopsy studies of deceased patients with severe COVID-19 have revealed the presence of diffuse pulmonary alveolar damage in nearly all cases [22-26]. Thrombosis and microvascular injuries were the other significant findings. It is expected that similar pathological features such as microvascular injuries could be found in the placenta of infected pregnant women.

**Materials and Methods**

The study was conducted from March 2021 to May 2021 at a 1000 bedded tertiary care center which is also a designated COVID hospital. The study was approved by the Institutional Ethics Committee of Base Hospital and Army College of Medical Sciences, Delhi Cantt, vide their letter No. IEC/01/2021/02 dated 18 Mar 2021. All patients with singleton pregnancy at term who have been tested positive for SARS-CoV-2 were included in the study. Those with multifetal gestation, hypertensive disorder, fetal growth restriction (FGR), structural or chromosomal anomalies in the fetus, thrombophilia, prolonged prelabour rupture of membranes, and placenta accreta spectrum were excluded from the study. Written informed consent was taken from each participant. Testing was done by Cartridge Based Nucleic Acid Amplification Test using GeneXpert Dx Xpert Xpress SARS-CoV-2 (Cepheid) system approved by United States-Food and Drug Administration for use under an emergency-use-authorizations. The analytical sensitivity and specificity are reported by the manufacturer as 95.65% (95% confidence interval [CI]: 88.4%-99.6%) and 97.72% (95% CI: 85.2%-98.8%) respectively. Positive SARS-CoV-2 test was considered the foremost criterion for submission of placentas for pathological examination.

In an earlier similar type of study, Shanes et al. (2020) had demonstrated that third trimester placentas of SARS-CoV-2 positive mothers were significantly more likely to show at least one feature of maternal vascular malperfusion (MVM), in which MVM was present in 12/15 cases, significantly higher than historical controls (59/215, \( P = 0.001 \)) [17]. Assuming that similar results could be obtained in our study, a minimum number of 26 patients were considered sufficient enough to deduce statistical significance. However, in order to bring out more substantial evidence, it was decided to recruit 50 patients in the study. Forty-two \((n = 42)\) third trimester placentas of singleton term delivery were finally submitted for histopathological examination from women with COVID-19, delivered between March 2021 and May 2021 as depicted Figure 1.

![Figure 1: Flowchart depicting patient enrolment](https://www.fda.gov/medical-devices/emergency-situations-medical-devices/...
All placentas were examined clinically after delivery before putting into fixatives. Photographs of the maternal and fetal surfaces, measurements, and trimmed weight were taken. The placentas were kept in 10% buffered formalin for the next 48 h, for fixation as well as viral inactivation. Examination of the cut surfaces and sectioning was done after adequate fixation. Sections submitted included 2 of umbilical cord, 2 of membrane rolls, 3 sections from placental parenchyma including 2 full-thickness sections, and representative sampling of any lesions present. Sections underwent routine processing, embedding, sectioning at 4 μm, and staining with hematoxylin and eosin (H and E).

Histologic sections were thoroughly examined to look for features of maternal vascular malperfusions (MVM), fetal vascular malperfusions (FVM), acute or chronic inflammatory pathology (AIP/CIP), and any other relevant findings (microscopic accreta, villous edema, increased perivillous fibrin, intervillous thrombus, membranes with hemorrhage, abnormal or injured maternal vessels, and intervillous thrombi). H and E-stained sections were examined and reported independently by two pathologists and only those findings for which both the pathologists concurred unanimously were reported. Pathological findings were classified according to the current Amsterdam Placental Workshop Group Consensus Statement [27].

Those patients who had respiratory compromise requiring continuous respiratory support underwent cesarean delivery. General anesthesia was not administered in any of the cases. All deliveries were attended by the neonatologist of the hospital. Those neonates requiring continued respiratory support were immediately shifted to the neonatal intensive care unit (NICU) with a diagnosis of respiratory distress syndrome (RDS).

RESULTS

Majority of the pregnant women who were tested positive for SARS-CoV-2 were either asymptomatic or had mild symptoms. Twelve patients (28.57%) had breathlessness requiring respiratory support. The detailed symptomatology, mode of delivery, placental histopathological features, and corresponding perinatal outcome are expressed in Table 1.

Reports of 42 placentas from patients with SARS-CoV-2 delivered at term (37–40 weeks) were analyzed. Total 8 of 42 placentas weighted above 90th percentile and 3 weighted below 10th percentile for gestational age. One umbilical cord revealed 4 vessels (2 arteries and 2 veins). Three umbilical cords were hyper coiled [depicted in Figure 2a] and one cord was very thin with narrow cord diameter (<8 mm). Marginal cord insertion was noted in 2 cases. One placenta was found meconium stained [depicted in Figure 2b].

Features of MVM were present in 45% (n = 19) cases. Features included central (n = 8)/peripheral (n = 3), villous infarctions/necrosis, increased syncytial knots (n = 5) and accelerated villous maturation (n = 3). Villous agglutination was seen in one case (n = 1) and retroploental hematoma in two cases (n = 2). Decidual arteriopathy occurred in 30.9% (n = 13) cases in the form of mural hypertrophy of membrane arterioles (n = 10) and absent spiral artery remodeling (n = 3). However, no atherosis or fibrinoid necrosis of maternal vessels was noted. Microscopic features of MVM are depicted in Figure 3. Peripheral infarctions, decidual arteriopathy with mural hypertrophy were common findings in our cases. Features of FVM were present in 23.8% (n = 10) cases and one showed clustered avascular villi. One case of mural fibrin and one case of mural hypertrophy of fetal vessels were also identified. Four placentas showed chorangiosis. Microscopic features of FVM are depicted in Figure 4.

Rates of both AIP and CIP were substantially increased in COVID-19 cases in the form of subchorionitis, chorioamnionitis, villousitis/intervillositis and deciduitis. There were 47.6% (n = 20) cases showing at least one feature of AIP and 42.8% (n = 18) showing features of CIP. Varying degree of villous edema was found in most of the cases; 73.8% (n = 31). Perivillous fibrin deposition was seen in 40.5% (n = 17) cases. Microscopic features of inflammatory pathology are depicted in Figure 5.

Neonatal RDS was found in 19% (n = 8) of the neonates. Correspondingly, nearly all placentas (n = 7) of these neonates showed features of MVM, FVM, AIP, and CIP. Placenta of the remaining one neonate with RDS showed features suggestive of villous edema. There was no maternal or neonatal mortality in our study group.

DISCUSSION

Significant advances have been made by the medical fraternity in understanding pathological spectrum of SARS-CoV-2 infection and its various systemic effects. However, some lacunae still remain in understanding placental pathology of SARS-CoV-2 infection in pregnant women. In a systematic review and meta-analysis of 42 studies involving 4,38,548 pregnant women, Wei et al. have demonstrated that COVID-19 was strongly associated with preeclampsia (odds ratio [OR] 4.16, 95% CI 1.55–11.15), preterm birth (OR 4.29, 95% CI 2.41–7.63), gestational diabetes (OR 1.99, 95% CI 1.09–3.64) and low birth weight (OR 1.89, 95% CI 1.14–3.12) [28]. In another systematic review of 66 studies by Abdel Massih et al., involving 1787 SARS-CoV-2 positive mother-infant pairs, it was concluded that even though vertical transmission is rare, there is an increased risk of placental insufficiency due to prothrombotic tendency in COVID-19 infection. It was also revealed that 20% of these cases had intrauterine hypoxia due to placental abnormalities suggestive of placental vaso-occlusive involvement [29].
| Case number | POG (weeks + days) | Symptoms and SpO2 on room air | Mode of delivery | Indication for LSCS | Birth-weight (kg) | Placental weight (kg) | Placental histopathology (significant findings) | NICU admission for RDS |
|-------------|-------------------|--------------------------------|----------------|--------------------|-----------------|-------------------|-----------------------------------------------|----------------------|
| 1           | 37+4              | Asymptomatic, SpO2=98%       | VD             | -                  | 3.2             | 0.54              | NAD                                           | No                   |
| 2           | 39+0              | Fever, dry cough, SpO2=96%  | VD             | -                  | 2.6             | 0.35              | NAD                                           | No                   |
| 3           | 38+3              | Asymptomatic, SpO2=100%     | VD             | -                  | 3.4             | 0.53              | Villous edema                                  | No                   |
| 4           | 38+6              | Fever, dry cough, SpO2=94%  | VD             | -                  | 3.0             | 0.48              | NAD                                           | No                   |
| 5           | 37+3              | Asymptomatic, LSCS          | Fetal distress | -                  | 2.4             | 0.40              | MVM, FVM, AIP                                 | Yes                  |
| 6           | 38+6              | Asymptomatic, SpO2=99%     | VD             | -                  | 2.8             | 0.45              | Villous edema                                  | No                   |
| 7           | 37+4              | Breathlessness, SpO2=99%   | LSCS           | Maternal respiratory compromise | 2.9             | 0.50              | MVM, FVM, AIP, CIP                            | Yes                  |
| 8           | 39+5              | Breathlessness, SpO2=86%   | LSCS           | Maternal respiratory compromise | 3.4             | 0.51              | MVM, AIP, CIP                                 | No                   |
| 9           | 39+1              | Asymptomatic, SpO2=99%     | VD             | -                  | 3.6             | 0.60              | NAD                                           | No                   |
| 10          | 37+3              | Asymptomatic, SpO2=96%     | VD             | -                  | 3.1             | 0.48              | NAD                                           | No                   |
| 11          | 38+2              | Breathlessness, SpO2=89%   | LSCS           | Maternal respiratory compromise | 2.8             | 0.45              | MVM, FVM, CIP                                 | No                   |
| 12          | 38+0              | Breathlessness, SpO2=92%   | LSCS           | Previous LSCS      | 3.7             | 0.72              | MVM, AIP, CIP                                 | No                   |
| 13          | 39+6              | Breathlessness, SpO2=90%   | LSCS           | Malpresentation    | 3.5             | 0.70              | MVM, FVM, AIP, CIP                            | No                   |
| 14          | 38+5              | Fever, dry cough, SpO2=94% | LSCS           | Previous LSCS      | 2.5             | 0.30              | Villous edema                                  | No                   |
| 15          | 38+3              | Breathlessness, SpO2=88%   | LSCS           | Maternal respiratory compromise | 2.7             | 0.45              | MVM, FVM, AIP, CIP                            | Yes                  |
| 16          | 37+5              | Asymptomatic, SpO2=97%     | VD             | -                  | 2.8             | 0.45              | Villous edema                                  | No                   |
| 17          | 37+6              | Asymptomatic, SpO2=100%    | VD             | -                  | 2.7             | 0.45              | Villous edema                                  | No                   |
| 18          | 39+2              | Asymptomatic, SpO2=97%     | VD             | -                  | 2.9             | 0.50              | AIP, CIP                                      | No                   |
| 19          | 37+4              | Asymptomatic, SpO2=96%     | VD             | -                  | 3.2             | 0.70              | Villous edema                                  | No                   |
| 20          | 38+5              | Asymptomatic, SpO2=98%     | VD             | -                  | 3.4             | 0.55              | Villous edema                                  | No                   |
| 21          | 37+3              | Asymptomatic, LSCS         | Previous LSCS  | 2.8             | 0.46              | Villous edema                                  | No                   |
| 22          | 38+4              | Asymptomatic, SpO2=99%     | LSCS           | Previous LSCS      | 3.3             | 0.50              | NAD                                           | No                   |
| 23          | 38+5              | Breathlessness, SpO2=98%   | VD             | -                  | 2.9             | 0.48              | MVM, AIP                                      | No                   |
| 24          | 39+2              | Fever, dry cough, SpO2=90% | LSCS           | Previous LSCS      | 3.0             | 0.50              | Villous edema                                  | No                   |
| 25          | 37+6              | Fever, dry cough, SpO2=95% | LSCS           | Fetal distress, MSL | 2.6             | 0.45              | MVM, FVM, AIP, Villous edema                  | No                   |

Contd...
The placenta is a unique organ that possesses dual blood circulations, which provide oxygen and nutrients to the fetus. The unimpeded flow of properly oxygenated maternal and fetal blood is critical to placental function. Pathologic conditions affecting the maternal vasculature and circulation can cause significant adverse effects to the fetus. These conditions associated with pathologic maternal blood flow are currently known under the terminology: Maternal vascular malperfusions (MVM), as defined in the Amsterdam consensus [27]. It is already known that MVM is a common finding in pregnancies complicated by preeclampsia and FGR [29-32].

Gross findings of MVM include placental hypoplasia, placental infarction, and retroplacental hemorrhage. Placental hypoplasia is defined as a placental weight below the 10th percentile expected for gestational age and/or a thin umbilical cord, defined as width below the 10th percentile for gestational age or <8 mm at term [33,34]. In our study, 3 placentas weighed below 10th percentile for the gestational age and one umbilical cord measured <8 mm in diameter. In a similar study by Shanes et al., it was found that 5 out of 15 placentas were hypoplastic [17]. In the same study, researchers have found that 80% (n = 12) placentas had one or more features suggestive of MVM. These features include central and peripheral villous infarction, accelerated villous maturation and villous agglutination. Similar results have been obtained in our study.

Table 1: Contd...

| Case number | POG (weeks + days) | Symptoms and SpO2 on room air | Mode of delivery | Indication for LSCS | Birth-weight (kg) | Placental weight (kg) | Placental histopathology (significant findings) | NICU admission for RDS |
|-------------|-------------------|------------------------------|-----------------|---------------------|------------------|----------------------|-----------------------------------------------|----------------------|
| 26          | 37+5              | Asymptomatic                 | VD -            |                     | 2.8              | 0.45                 | NAD                                                          | No                   |
| 27          | 39+2              | Breathlessness               | LSCS            | Fetal distress, maternal respiratory compromise | 2.9              | 0.35                 | MVM, FVM, CIP                                                   | Yes                  |
| 28          | 38+4              | Fever, dry cough             | LSCS            | Malpresentation     | 3.2              | 0.65                 | MVM, AIP                                                       | No                   |
| 29          | 38+3              | Asymptomatic                 | VD -            |                     | 2.9              | 0.60                 | Villous edema                                                   | No                   |
| 30          | 37+4              | Fever, dry cough             | LSCS            | Previous LSCS       | 2.8              | 0.47                 | MVM, AIP, CIP                                                   | No                   |
| 31          | 38+2              | Fever, dry cough             | LSCS            | Previous LSCS       | 3.5              | 0.70                 | MVM, AIP, CIP                                                   | No                   |
| 32          | 39+2              | Fever, dry cough             | VD -            |                     | 2.7              | 0.45                 | Villous edema                                                   | No                   |
| 33          | 39+0              | Asymptomatic                 | VD -            |                     | 2.8              | 0.44                 | Villous edema                                                   | Yes                  |
| 34          | 37+0              | Breathlessness               | LSCS            | Previous LSCS       | 3.0              | 0.49                 | MVM, AIP, CIP                                                   | No                   |
| 35          | 37+2              | Asymptomatic                 | VD -            |                     | 3.1              | 0.50                 | Villous edema                                                   | No                   |
| 36          | 37+1              | Breathlessness               | LSCS            | Maternal respiratory compromise Fetal distress | 2.8              | 0.46                 | MVM, FVM, AIP, CIP                                               | Yes                  |
| 37          | 38+6              | Asymptomatic                 | LSCS            | Fetal distress      | 2.6              | 0.45                 | FVM, AIP                                                        | No                   |
| 38          | 38+5              | Breathlessness               | LSCS            | Maternal respiratory compromise | 3.1              | 0.48                 | MVM, AIP, CIP                                                   | No                   |
| 39          | 39+0              | Asymptomatic                 | VD -            |                     | 2.9              | 0.47                 | Villous edema                                                   | No                   |
| 40          | 38+5              | Fever, dry cough             | VD -            |                     | 2.8              | 0.46                 | NAD                                                            | No                   |
| 41          | 39+0              | Breathlessness               | LSCS            | Maternal respiratory compromise | 2.5              | 0.41                 | MVM, FVM, AIP, CIP                                               | Yes                  |
| 42          | 37+2              | Fever, dry cough             | VD -            |                     | 3.0              | 0.65                 | Villous edema                                                   | Yes                  |

SpO2: Oxygen saturation, POG: Period of gestation, LSCS: Lower segment caesarean section, VD: Vaginal delivery, NICU: Neonatal intensive care unit, RDS: Respiratory distress syndrome, MVM: Maternal vascular malperfusion, FVM: Fetal vascular malperfusion, AIP: Acute inflammatory pathology, CIP: Chronic inflammatory pathology, NAD = No abnormality detected, MSL = Meconium stained liquor
FVM is a term applied to a group of placental lesions indicating reduced or absent perfusion of the villous parenchyma by the fetus. The most common etiology of malperfusion is umbilical cord obstruction leading to stasis, ischemia, and in some cases thrombosis. Other contributing factors may include maternal diabetes, fetal cardiac insufficiency or hyperviscosity, and inherited or acquired thrombophilias. Severe or high-grade FVM is an important risk factor for adverse pregnancy outcomes including FGR, fetal CNS injury, and stillbirth [35]. FVM is diagnosed by the presence of vascular lesions in the fetal vessels in the placenta and the resultant changes in the downstream villi [36]. In our study, features of FVM were present in 23.8% \((n = 10)\) placental specimens. Sharps et al., in a structured review have brought out features or diagnoses of FVM in 53 cases (35.3%) of placentas examined, 95% CI 27.7–42.9% by 6 studies [37].

Even though the placental inflammatory response to SARS-CoV-2 is usually expected, most of the studies could not prove this on histopathological examination [16-18]. In our study, 47.6% \((n = 20)\) cases showed acute inflammation and 42.8% \((n = 18)\) showed features of chronic inflammation. Similar evidence was revealed by Sharps et al. in “a structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection” (villitis 8.7% cases, intervillitis 5.3% of cases, and chorioamnionitis 6% of cases) [37].

In our study, all the neonates were tested negative for SARS-CoV-2 reverse transcription-PCR. There were 8 neonates requiring NICU admission for management of RDS. There was no neonatal or maternal mortality in our study. These findings are in conjunction with other reviews and studies conducted by Sharps et al. and Blasco Santana et al. [37,38].

**CONCLUSION**

Vertical transmission of SARS-CoV-2 from infected pregnant mother has always been a point of discussion since the beginning of COVID-19 pandemic. Numerous studies have already been conducted to bring out evidence regarding placental pathology in SARS-CoV-2 infection and resultant vertical transmission of the disease to the fetus. However, concrete evidence in this regard is still lacking. Interestingly, in most of the studies, only miniscule number of newborns has been tested positive for SARS-CoV-2, despite the high positivity rate of placentas. Further studies are required to understand the immunological response and barrier function of the placenta in response to SARS-CoV-2 infection. Several studies depicting histopathological examination findings of placenta in SARS-CoV-2 infection are available on literature search. In almost all of these studies, the infection to delivery interval was very short. Hence, chronic inflammation of placenta and resultant pathological effect could not be studied. Further, since these studies are being conducted during a pandemic, comparison with appropriate controls is nearly impossible. Here, we have reported histopathological examination findings of 42 placentas from SARS-CoV2 positive pregnant women in an Indian scenario. The main findings of our study include maternal as well as fetal vascular malperusions and placental inflammatory pathology. These findings provide an outline for a better understanding of etiological factors and
pathogenesis of adverse perinatal outcomes in SARS-CoV-2 infection. Our study is single institutional and is limited by its small sample size and lack of comparison with appropriate controls. We recommend larger multicentric studies with appropriate controls in the near future for generalization of our findings.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. MulveY JJ, Magro CM, Ma LX, Nuovo GJ, Baerger RN. Analysis of complement depositions and viral RNA in placentas of COVID-19 patients. Ann Diagn Pathol 2020;46:151530.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a Report of 72 314 cases from the Chinese Center for disease control and prevention. JAMA 2020;323:1239-42.
5. Sharma A, Tiwari S, Deb MK, Marty JL. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): A global pandemic and treatment strategies. Int J Antimicrob Agents 2020;56:106054.
6. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care 2020;24:422.
7. Li M, Chen L, Zhang J, Xiong C, Li X. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One 2020;15:e0230295.
8. PrabhuDas M, Bonney E, Caron K, Dey S, Erlebacher A, Fazleabas A, et al. Immune mechanisms at the maternal-fetal interface: Perspectives and challenges. Nat Immunol 2015;16:328-34.
9. Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: Maternal coronavirus infections and pregnancy outcomes. Arch Pathol Lab Med 2020;144:799-805.
10. Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) coronavirus 2019-nCoV infecting pregnant women: Lessons from SARS, MERS, and other human coronavirus infections. Viruses 2020;12:194.
11. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, 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;2:100107.
12. Liu D, Li L, Wu X, Zheng D, Wang J, Yang L, et al. Pregnancy and perinatal outcomes of women with coronavirus disease (COVID-19) pneumonia: A preliminary analysis. AJR Am J Roentgenol 2020;215:127-32.
13. Yang H, Sun G, Tang F, Peng M, Gao Y, Peng J, et al. Clinical features and outcomes of pregnant women suspected of coronavirus disease 2019. J Infect 2020;81:e40-4.
14. Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: A retrospective, single-centre, descriptive study. Lancet Infect Dis 2020;20:559-64.
15. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand 2020;99:823-9.
16. Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of coronavirus disease 2019: A systematic review and meta-analysis. Am J Obstet Gynecol 2021;224:35-53.e3.
17. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in COVID-19. Am J Clin Pathol 2020;154:23-32.
18. Baerger RN, Heller DS. Placental pathology in covid-19 positive mothers: Preliminary findings. Pediatr Dev Pathol 2020;23:177-80.
19. Horn LC, Röse I. Placental and fetal pathology in intrauterine viral infections. Intervirology 1998;41:219-25.
20. Giakoumelou S, Wheelhouse N, Cuschieri K, Entrican G, Howie SE, Horne AW. The role of infection in miscarriage. Hum Reprod Update 2016;22:116-33.
21. Oliveira GM, Pascoal-Xavier MA, Moreira DR, Guimarães VS, Aguiar RA, Miranda DM, et al. Detection of cytomegalovirus, herpes virus simplex, and parvovirus b19 in spontaneous abortion placentas. J Matern Fetal Neonatal Med 2019;32:768-75.
22. Alberca RW, Pereira NZ, Oliveira LM, Goezzi-Silva SC, Sato MN. Pregnancy, viral infection, and COVID-19. Front Immunol 2020;11:1672.
23. Angeles Montero-Fernandez M, Pardo-Garcia R. Histopathology features of the lung in COVID-19 patients. Diagn Histopathol (Oxf) 2021;27:1237-3.
24. Hariri LP, North CM, Shih AR, Israel MA, Maley JH, Villalba JA, et al. Lung histopathology in coronavirus disease 2019 as compared with severe acute respiratory syndrome and H1N1 influenza: A systematic review. Chest 2021;159:73-84.
25. Pandey P, Agarwal S, Rajkumar. Lung pathology in COVID-19: A systematic review. Int J Appl Basic Med Res 2020;10:226-33.
26. Borczuk AC, Salvatore SP, Seshan SV, Patel SS, Bussel JB, Mostyka M, et al. COVID-19 pulmonary pathology: A multi-institutional autopsy cohort from Italy and New York City. Mod Pathol 2020;33:2156-68.
27. Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundaler MA, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. Arch Pathol Lab Med 2016;140:698-713.
28. 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:E540-8.
29. Abdel Massih A, Fouda R, Essam R, Negm A, Khalil D, Habib D, et al. COVID-19 during pregnancy should we really worry from vertical transmission or rather from fetal hypoxia and placental insufficiency? A systematic review. Egyptian Pediatric Association Gazette 2021;69:12.
30. Roberts DJ, Post MD. The placenta in pre-eclampsia and intrauterine growth restriction. J Clin Pathol 2008;61:1254-60.
31. Salafia CM, Peruzzolo JC, López-Zeno JA, Simmons S, Minor VA, Vintzileos AM. Placental pathologic features of preterm preeclampsia. Am J Obstet Gynecol 2021;224:35-53.e3.
32. Salafia CM, Vintzileos AM, Silberman L, Bantham KF, Vogel CA. Placental pathology of idiopathic intrauterine growth retardation at term. Am J Perinatol 1992;9:179-84.
33. Pinar H, Sung CJ, Oyer CE, Singer DB. Reference values for singleton birth weight and placental pathology. Placenta 2013;34:62-6.
34. Proctor LK, Fitzgerald B, Whittle WL, Mokhtari N, Lee E, Machin G, et al. Umbilical cord diameter percentile curves and their correlation to placental pathology of idiopathic intrauterine growth retardation. Am J Obstet Gynecol Scand 2020;99:823-9.
35. Mostyka M, et al. COVID-19 during pregnancy should we really worry from vertical transmission or rather from fetal hypoxia and placental insufficiency? A systematic review. Egyptian Pediatric Association Gazette 2021;69:12.
36. Roberts DJ, Post MD. The placenta in pre-eclampsia and intrauterine growth restriction. J Clin Pathol 2008;61:1254-60.
37. Salafia CM, Peruzzolo JC, López-Zeno JA, Simmons S, Minor VA, Vintzileos AM. Placental pathologic features of preterm preeclampsia. Am J Obstet Gynecol 2021;224:35-53.e3.
38. Salafia CM, Vintzileos AM, Silberman L, Bantham KF, Vogel CA. Placental pathology of idiopathic intrauterine growth retardation at term. Am J Perinatol 1992;9:179-84.
39. Pinar H, Sung CJ, Oyer CE, Singer DB. Reference values for singleton and twin placental weights. Pediatr Pathol Lab Med 1996;16:901-7.
40. Proctor LK, Fitzgerald B, Whittle WL, Mokhtari N, Lee E, Machin G, et al. Umbilical cord diameter percentile curves and their correlation to birth weight and placental pathology. Placenta 2013;34:62-6.
41. Redline RW, Ravishankar S. Fetal vascular malperfusion, an update. APMS 2018;126:561-9.
42. Ravikumar G, Mascarenhas D, Sunan Rao PN, Crasta J. Fetal vascular malperfusion (FVM): diagnostic implications and clinical associations. J
37. Sharps MC, Hayes DJL, Lee S, Zou Z, Brady CA, Almoghrabi Y, et al. A structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection. Placenta 2020;101:13-29.

38. Blasco Santana L, Miraval Wong E, Álvarez-Troncoso J, Sánchez García L, Bartha JL, Regojo-Zapata RM. Maternal and perinatal outcomes and placental pathologic examination of 29 SARS-CoV-2 infected patients in the third trimester of gestation. J Obstet Gynaecol Res 2021;47:2131-9.