



## Review Article

## A review of the main placenta histopathological findings reported in coronavirus disease 2019



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### المخلص

أفادت العديد من الدراسات أن النساء الحوامل أكثر عرضة للإصابة بمرض كوفيد-19. ومع ذلك، فإن دراسات عدوى السارز-كوفي-2 محدودة فيما يتعلق بتأثيره على الحمل، ولا سيما آثاره المرضية على الأم والجنين.

توضح هذه المراجعة خصائص المشيمة وآلية الدفاع المناعي ضد العدوى الفيروسية كوفيد-19 ودراسة التغيرات النسيجية المرضية التي توصلت إليها الأبحاث من مشيمة الأمهات المصابات بعدوى سارز كوفي-2 للمساهمة في معرفة طبيعة هذا المرض المشيمي.

كذلك أشارت الدراسة إلى أهمية دراسة جميع حالات الإصابة بعدوى سارز كوفي-2 بين النساء الحوامل وعمل دراسات تعاونية لتحليل المشيمة ودراسة التغيرات على عينة أكبر من العدد الذي تم نشره في التجارب الفردية وذلك لتحسين قابلية التعميم وموثوقية النتائج. كما أن هذه الدراسات ستؤدي إلى تحسين المعرفة حول العلاقة بين الخلل الوظيفي في المشيمة والتغيرات المرضية من عدوى الأم الناتج من سارز كوفي-2. وبالتالي، يمكن أن يساعد ذلك في تحسين تقديم الرعاية الطبية للأم والجنين وتقليل المضاعفات المحتملة أثناء الجائحة.

**الكلمات المفتاحية:** كوفيد-19؛ المشيمة؛ عدوى سارز كوفي-2؛ الحمل

### Abstract

Several studies have reported that pregnant women are more susceptible to contracting the SARS-CoV-2 disease. However, SARS-CoV-2 infection studies have limited evidence regarding its impact on pregnancy, particularly its pathological effects on the maternal

–fetal interface. This review emphasized the placental structures and immunomodulatory defense mechanism against the viral infection COVID and highlighted the spectrum of reported histopathological changes from SARS-CoV-2-infected mothers' placenta to contribute to the knowledge of the nature of this placental pathology. Further studies where collaborations that seek to maximize sample numbers analyzed can be performed to improve the generalizability and reliability of the findings. This can lead to improved knowledge on the relationship between placental dysfunction and pathology from maternal SARS-CoV-2 infection. Consequently, this can help improve maternity care delivery during the pandemic.

**Keywords:** COVID-19; Placenta; Pregnancy; SARS-CoV-2 infection

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### Introduction

The coronavirus disease (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. There has been an estimated 180,413,090 laboratory-confirmed cases of COVID-19 globally, with 3,909,491 resulting in death. In KSA, the reported laboratory-confirmed cases were around 480,702, which resulted in 7,743 deaths.<sup>1</sup> Three novel coronaviruses have been described since 2002, namely, severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East

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respiratory syndrome coronavirus (MERS-CoV) in 2012, and SARS-CoV-2 in 2019.<sup>2</sup>

In recent times, the birth of new vulnerable hosts, as well as immunity decline among previously infected individuals, have challenged the efforts to eradicate SARS-CoV-2. Although there is no fully established durability of immunity to SARS-CoV-2 yet, viral survival was projected to be prevalent in new births. SARS-CoV-2 transfer among humans is highly probable in the future, like any other infectious pathogens.<sup>3</sup>

The first instance of SARS-CoV-2 infection was reported in Wuhan, China, around December 2019.<sup>4</sup> The infection results in the development of various symptoms, such as dyspnea, cough, fevers, myalgias, diarrhea, cytokine storm, pharyngitis, acute respiratory distress syndrome, pneumonia, thrombotic events, endothelial damage, and multisystem organ failure.<sup>5</sup>

Several studies have reported that pregnant women are at higher risk of contracting the SARS-CoV-2 disease, which can result in greater susceptibility to viral pneumonia.<sup>6</sup> Breslin and colleagues found that a majority of pregnant mothers can get either asymptomatic or mild conditions of this disease. Moreover, about 3% required intensive care, and cases of perinatal death and preterm labor were reported among 43 maternity cases.<sup>7</sup>

There is an extensive continuum of neonatal and placental pathology of viral infections during pregnancy. Villitis and spontaneous abortion can be caused by several viruses. Moreover, multisystem organ damage, sepsis, lifelong disabilities, and death can result from congenital viral infections in the neonate.<sup>5</sup> However, factors bolstering the association between COVID-19 and adverse outcomes during pregnancy remain unclear, despite the increasing research on clinical situations involving infected pregnant women as well as their infants.<sup>8</sup> Given its critical nature as the interface between the fetus and the mother, the placenta serves as a layer of protection for the fetus from infection. However, the adverse environment of the mother can affect its ability to protect the fetus from infection.<sup>9</sup>

Despite limited data on this disease and its consequences on pregnancy, questions, as well as concerns related to maternal and fetal outcomes, have arisen. Likewise, the unclear pathological description of the infection and its outcome in pregnancy, particularly on the maternal–fetal interface, have raised more questions. Therefore, this review study aimed to emphasize the placental structures and immunomodulatory defense mechanism against COVID-19. Moreover, this review highlights the spectrum of reported histopathological changes from the placenta of infected pregnant women for better knowledge of placental pathology and its type.

### SARS-CoV-2 structure and its receptor

Coronaviruses are deemed as sizable, enclosed viruses with a positive-sense single-stranded RNA genome. In particular, one of the key receptors of SARS-CoV being utilized is angiotensin-converting enzyme 2 (ACE2). It has a crucial role in disease infection development.<sup>10</sup> Thus, disease treatment can target the interaction between the receptor and the virus. As a constituent that regulates blood pressure,

ACE2 distribution and expression have been described in kidneys, lungs, heart, and placenta with tissue-specific activity patterns.<sup>11</sup> Moreover, another key enzyme for SARS-CoV-2's entry in host cells was identified in the form of serine protease for virus Spike (S) protein priming, which is referred to as transmembrane protease serine 2 (TMPRSS2).<sup>12</sup>

During pregnancy, TMPRSS2 and ACE2 expression significantly vary at different stages based on the study conducted by Bloise and colleagues.<sup>13</sup> They found a decline in placental TMPRSS2 and ACE2 expression during gestation. Significant reductions in expression levels were observed from the first to the second trimester until it became almost undetectable in the third semester. This means that pregnant women in their first trimester are more vulnerable to contracting SARS-CoV-2 together with its transplacental conveyance. Although mothers were found to be positive for COVID-19, research has rarely mentioned the non-detection of placental virus in first- and second-trimester miscarriages.<sup>8,14</sup> However, a mother who was COVID-19 positive in the third trimester was reported to give preterm birth to an infant with amniotic fluid infected with SARS-CoV-2.<sup>15</sup> This result was different from the theory that infants of COVID-19-positive mothers can be protected from the virus due to placental TMPRSS2 and ACE2 not being detected in the third trimester.

Studies on single-nucleotide polymorphisms (SNPs) have found an association between genetic variation and susceptibility to SARS via such variations' impact on gene expressions that result in disease outcomes. Factors such as age, ethnicity, and selection criteria resulting in contentious outcomes among various population groups affect this association.<sup>12</sup>

The pathogenesis and infectivity of the SARS-CoV-2 virus can be ascertained via its entry into the host cell, which can be facilitated by a virus surface spike protein. This virus can attach to the human ACE2 (hACE2) receptor and is stimulated by human proteases through its receptor-binding domain (RBD). Spike protein aids the virus in efficiently maintaining its ability to enter the host cell, as it avoids immune surveillance. Consequently, these characteristics help the virus propagate in its host.<sup>10</sup>

Receptor binding and virus entry can be initiated by the activation of the spike (S)-protein via cathepsin-mediated cleavage or type-II transmembrane serine proteases (TTSPs). A disintegrin and metalloproteinase 17 (ADAM17) can trim ACE2, which competes with TTSPs for the same receptor. ADAM17 discharges extracellular soluble ACE2 (sACE2), while the ACE2 receptor for binding can be activated using cleavage by TTSPs. Sites that are critically involved in the binding mechanism were found via structural studies on both S-protein and ACE2.<sup>12</sup>

SARS-CoV spike (S) protein exhibited ACE2 expression in autopsy studies of dead patients with SARS pneumonia.<sup>16</sup> The mediation of the viral spike (S) protein upon entry of the virus was found to depend on attachment to an analogous receptor in the target cell site. Nuclear factor-kappa B (NFκB)-driven inflammatory module expression is induced by the S protein's attachment to ACE2. In turn, this produces proinflammatory cytokines such as transforming growth factor-beta 1 (TGF-β1), tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein 1 (MCP-1),

interleukin (IL)-1 $\beta$ , and IL-6, which can be linked to thrombogenesis.

SARS-CoV-2 was linked to increases in IL-8 and interferon (IFN)- $\gamma$ . Further, it boosts T-helper (Th)1 cell-associated proinflammatory cytokines, IL-1 $\beta$ , IL-6, and TNF.<sup>17</sup> On the other hand, a potent antiviral response can be provided by type III IFN at the placenta level via the initiation of a signaling cascade to activate the transcription of genes regulated by IFN. This can be a probable mechanism that protects the fetus from the infection since the virus can induce type III IFN release. Another crucial antiviral defense mechanism is the utilization of trophoblastic microRNAs, which play a key role in trophoblast integrity maintenance and viral invasion restriction.<sup>18</sup>

There was a reduction in inflammation caused by NF $\kappa$ B route inhibition in infected mice lungs. Viral transmission reduction, cell damage, immune response mitigation, tissue limitation, and cytokine storm reduction can be caused by placental immune cell immunomodulatory action.<sup>6</sup>

### Placental physical and structural barrier for SARS-CoV-2

The placenta, which is formed during pregnancy, acts upon the liver, heart, kidneys, and lungs of the fetus and facilitates pathogen transmission prevention from the mother to the fetus. It works as a physiological obstruction between maternal and fetal bloodstream formed by maternal and embryonic component fusion attached to the uterine wall.<sup>10</sup>

While the placenta is crucial in the prevention of maternal-to-fetal transmission of pathogens, maternal factors can have adverse effects on the placenta, which can result in dangerous outcomes. During pregnancy, intrauterine alterations can be caused by systemic diseases in the mother, which can lead to later neonatal and fetal morbidity and mortality.<sup>19</sup>

A unique interchange of modulated immune states can be represented by pregnancy at varying gestational stages. Proinflammatory cytokine production can be induced by the pregnant host, as it responds to viral infection. This, in turn, activates the immune system of the mother as the virus crosses the placenta. Infections in the placenta can prompt an inflammatory response in the fetus itself, which can result in damage in the multiorgan system and have negative consequences for fetal development.<sup>5</sup>

MERS-COV and SARS-CoV virus research showed that it can pose an immense risk to pregnant women compared to non-pregnant ones, as well as raise serious complications during gestation. As SARS-CoV-2 possesses a SARS-CoV-like receptor, the fetuses of COVID-positive pregnant women can be affected by the vertical transmission of the novel coronavirus.

### The COVID-19 mechanism on the placenta

There is a scarcity of data explaining COVID-19 and its impact on placental pathology, specifically among asymptomatic pregnant mothers. Relevant information on pathological changes linked to COVID-19 is only limited to literature reviews, case series, and case reports, with

proposed effects classified as either direct or indirect. Despite the lack of clarity on the exact mechanism that results in various forms of placental injury in COVID-19 infected mothers, there are shreds of evidence and postulated theories available in the literature.<sup>20</sup>

#### *Direct effect of COVID-19 on placenta*

Due to its nature as the maternal-fetal interface, the placenta plays a crucial role in protecting the fetus from infection. However, it can be impacted by an adverse maternal environment. Sustained hypoxia can result from severe COVID-19 infection, which may further result in preeclampsia, stillbirth, and fetal growth restriction. Furthermore, infectious agents can pass through the placenta during pregnancy or childbirth. However, a substantial correlation between infection during pregnancy and the fetal outcome must be established as proof of placental damage and transmission.<sup>9</sup>

Algarroba and colleagues<sup>21</sup> visualized the placental invasion of the virus via electron microscopy. Results showed the presence of extracellular structures that are like those seen within cells with no clathrin-coated vesicles. Placental samples were determined to have the SARS-CoV-2 glycoprotein utilizing the specific antibody. Immunogold electron microscopy was used to immunolocalize the virus, and a real-time polymerase chain reaction (RT-PCR)-specific primer was used to detect the virus in the placenta.

The amniotic fluid, as well as replicated neonatal throat and nasal swabs with positive RT-PCR test results, was determined in a severely infected woman who gave birth at 32 gestational weeks.<sup>15</sup> However, the placenta may phagocytose the virions as immune complexes (IgG-mediated) instead of direct placental tissue invasion.<sup>9</sup>

A study of direct placental expression using immunohistochemistry and in situ hybridization found the highest ACE2 membranous expression on the stromal side of syncytiotrophoblast while TMPRSS2 expression was rarely seen in syncytiotrophoblast. In probable cases of vertical transmission, COVID-19 RNA was primarily found in ST and cytotrophoblast of the placenta indicating rare but possible placental transmission.<sup>22</sup>

#### *Indirect COVID-19 effect on the placenta*

Cytokines have long been presumed to participate in immunopathology during viral infection. To effectively defend against viral infection, a person should have a well-coordinated and rapid innate immune response. Nevertheless, immune damage to the human body can be caused by excessive and dysregulated immune responses.<sup>17</sup> Proinflammatory responses play an important role during virus pathogenesis among severely ill patients. Infected patients were found to have an increment in proinflammatory cytokines, which increases further among critically ill patients.<sup>9</sup>

Epithelial and endothelial cells are directly infected by the virus, followed by heightened amounts of proinflammatory cytokines.<sup>16</sup> There is evidence that it may cause severe systemic inflammatory retort and can be upshot in a hypercoagulable state as well as microthrombi spread in

almost every organ system, which includes the heart, lungs, brain, and kidneys, as corroborated by autopsy examinations.<sup>23</sup> Microvascular platelet-rich thrombotic depositions were found in the small lung vessels as well as in other organs of infected patients upon autopsy. However, indications of schistocytes or hemolysis were not found in the blood film. Further, the platelet count was above the expected count for a case of thrombotic microangiopathy.<sup>24</sup> Similarly, this process can affect the maternal–fetal interface.

Coagulation abnormality is an indirect mechanism during pregnancy that can develop into a definitive thromboinflammatory response in consequence of endothelial, leukocyte, and platelet activation. Similar outcomes were observed among the placenta of women suffering from diabetes, preeclampsia, and hypertensive disorder. Coagulation abnormalities of patients with severe SARS-CoV-2 infection can be imitated by other systemic coagulopathies linked to severe infections, such as thrombotic microangiopathy or disseminated intravascular coagulation (DIC), despite the distinct characteristics of SARS-CoV-2. Its significance has become clearer than more patients with severe SARS-CoV-2 who had developed venous, arterial, or sometimes unrecognized thromboembolic complications.<sup>24</sup>

Fibrin and thrombosis formation in the maternal vasculature coupled with mild maternal malperfusion was found in mildly infected pregnant women. Blood vessel inflammation can cause cardiac muscle inflammation and diffuse microangiopathic thrombi.<sup>25</sup>

#### Intrauterine transplacental SARS-CoV-2 transmission

The probability of transplacental transmission has been supported by limited evidence, as vertical transmission risk is deemed contentious.<sup>9</sup>

The occurrence of inflammatory lesions caused by coronaviruses should be considered substantial, as these are more common in stillbirth and pregnancy loss cases, as reported by Pathak and colleagues.<sup>26</sup> MVM or inflammation can be attributed to earlier pregnancy losses. It has been postulated that systemic inflammation, maternal hypoxemia due to COVID-19, or administration of therapeutic drugs such as corticosteroids may result in placental changes, as these are found to modify the function and turnover of cells in the placenta.<sup>9</sup>

Among 38 infected pregnant women, a study by Schwartz<sup>27</sup> reported 1 neonatal death, 9 preterm births, and zero maternal deaths. Another study gathered evidence to show transmission from the mother to the fetus.<sup>28</sup> About 2.7% and 5.3% of neonatal infections were determined from vaginal deliveries and Caesarean sections, respectively. Moreover, the method of delivery, mother-to-infant contact, and breastfeeding did not pose a greater risk for neonatal infection. However, *in utero* infection was not examined for this study.

This research determined the probability of vertical transmission, in contrast to previous reports that did not submit evidence regarding vertical transmission.<sup>29</sup> Plausible mechanisms for viral crossing to the placenta include direct infection and rupture of STB syncytiotrophoblasts (ST),

entry into the intravascular extravascular trophoblasts or other placental cells via endothelial microcirculation, ACE2- and Fc (FcR)-mediated virion transcytosis, ascending vaginal infection, and entry via infected maternal immune cells at the placental barrier.<sup>6</sup>

Electron microscopy revealed the presence of virions in the placental villi, and this study verified transplacental viral transmission with twice the viral load in the placenta than in the blood or nasopharynx of the mother. Heightened placental viral loads boost the probability of the virus prompting placental inflammation, which can further lead to injury.<sup>20</sup>

The presence of substitute proteases and receptors for viral entry into STB cells is being advocated despite the rarity of TMPRSS2 and ACE2 co-expression by the chorioamniotic membranes and human placenta during pregnancy. Recently, CD147 and DPP4 (CD26) receptors have been determined as substitute receptors. Trypsin and furin have been suggested as entry proteases that can be expressed in placental tissues during pregnancy. Another possibility is the SARS-CoV-2 infection of peripheral blood mononuclear cells along with its transmission through the placenta. However, viral replication was found to not exist in this compartment.<sup>6</sup>

Celik and colleagues<sup>30</sup> suggested that the lack of syncytiotrophoblast caveolin causes a lack of vertical viral transmission. As membrane-bound structures, caveolae can endocytose certain viruses. The absence of caveolin may result in inflammation failure, as syncytiotrophoblast remains as a continuous layer wherein the virus cannot enter the placental villi.<sup>30</sup>

Contrary, cases of transplacental transmission of coronavirus were reported to be associated with chronic histiocytic intervillitis and syncytiotrophoblast necrosis. In all of the studied cases, placental syncytiotrophoblast was infected with the virus indicating that placental transmission cannot be dismissed as a risk for fetal infection of SARS-CoV-2.<sup>31</sup>

In a separate study of 50 placentas from SARS-CoV-2 positive mothers, 10% were observed with placental damage which although is not thought to lead to intra uterine fetal death may have been involved in fetal uterine growth limitation. The placental lesions showed perivillous fibrin deposition, and chronic histiocytic intervillitis among others. It was found that 3% of the neonates and about 20% of the placental samples were infected with COVID-19 from their mothers,<sup>32</sup> further suggesting that transplacental transmission can be a possible risk.

#### Histopathological findings of placenta after SARS-CoV-2 infection

Table 1 provides the histopathological changes in the placenta induced by COVID-19. MVM in the form of peripheral infarctions, fibrinoid necrosis and atherosclerosis, decidual arteriopathy, intervillous thrombi, and mural hypertrophy were exemplified in most published cases.

Histopathological results of placentas from infected pregnant mothers during the second and third trimesters have been reported in 29 studies. As reviewed by Sharps and

**Table 1: Placental histopathological findings in COVID-19-positive mothers.**

Study	Number of pregnant women in the study	Gestational age	Mode of delivery <sup>a</sup>	COVID-19 positive	Placental histological finding	Patient or fetal outcome
Algarroba et al., 2020 <sup>21</sup>	1	28 ± 5 weeks	CS	Yes	Decidual vasculopathy, mature chorionic villi with focal villous edema; single virion in microvillus, single virion in syncytiotrophoblast, single virion in the terminal villous core.	Mother recovered and was discharged 10 days post-operation; infant tested negative for COVID-19 on the 2nd and 3rd day of life.
Algeri et al., 2020 <sup>33</sup>	5	27 ± 4 to 38 ± 4 weeks	4 CS, 1 VD	Three cases upon admission, two cases determined after delivery.	N/A	Four among 5 mothers reported to have stabilized condition or have recovered 2 months post-delivery. All neonates were well with 4 among 5 infants testing negative for COVID-19.
Singh et al., 2021 <sup>34</sup>	50	40.3 weeks	92% VD	All positive	Histological examination showed heightened syncytial knotting, increased microcalcifications, heightened fibrin, villous agglutination, and small fibrotic villi.	Maternal and fetal outcomes were stable or asymptomatic of common COVID-19 symptoms.
Shanes et al., 2020 <sup>35</sup>	15	34–40 weeks	NA	13 were positive with COVID-19	Accelerated villous maturation, villous agglutination, and central and peripheral villous infarctions decidual arteriopathy ensued involving mural hypertrophy of membrane arterioles and fibrinoid necrosis and atherosclerosis of maternal vessels.	There were no maternal deaths and all infants tested negative for COVID-19.
Menter et al., 2020 <sup>36</sup>	5	40–41 weeks	CS	3 were positive with COVID-19	Outcomes depended on the state of the infection. The inflammatory response was evident as well as detection of viral RNA in the umbilical cord, placenta, and decidua. Maternal and fetal malperfusion were present.	COVID-19 was not transmitted to all neonates; four out of five infants presented no abnormalities.

<sup>a</sup> CS = Caesarean section; VD = Vaginal delivery; NA = not applicable.

colleagues,<sup>9</sup> about 20 studies revealed no pathognomonic histological patterns in the placenta of infected mothers.

### Pathophysiology of placental infection in pregnancy

Vascular, thrombotic, and inflammatory changes, which are like other inflammatory conditions, have been observed in the placenta of infected pregnant women.<sup>37</sup> Consequently, these inflammatory conditions can result in adverse obstetric and neonatal events. Acute infection among women during pregnancy indicates maternal inflammation instead of direct viral pathology. A common finding among infected pregnant women is the presence of microvasculopathy in the placenta, which can manifest as fetal and/or maternal

malperfusion. Acute infection can affect the prominence of fetal and maternal malperfusion as well as lymphohistiocytic villitis.<sup>35</sup>

In a separate report, early studies associating malperfusion and SARS-CoV-2 infection of pregnant mothers have not been supported by later research. Instead, recent reviews mention indicators of placentitis in cases with confirmed placental coronavirus infection. Placental inflammation due to coronavirus infection is infrequent but often characterized by the presence of histiocytic intervillitis, perivillous fibrin deposition, and trophoblast necrosis. SARS-CoV-2 placentitis is hypothesized to have begun with the accumulation of C4D in the syncytiotrophoblast ultimately leading to the three aforementioned conditions.<sup>38</sup>

A case study involving a 25-year old patient reports a placenta with massive perivillous fibrin deposition, trophoblast necrosis and histiocytic intervillitis. Further examination of the sample revealed that the syncytiotrophoblast layer of chorionic villi expressed high COVID-19 spike glycoprotein and ACE2 concentrations. The study concludes with the preferential localization of SARS-CoV-2 to fibrin-encased, hypoxic trophoblastic cells additionally mentioning that infection of placental villous tissue indicates transplacental transmission.<sup>39</sup>

The SARS-CoV-2 infection can also cause hypoxemia. Substantial increases in the occurrence of subchorionic thrombi and villous agglutination have been evident in the placenta of infected pregnant women. Consequently, it can result in the accumulation of lactic acid and oxygen free radicals, variation in electrolytes and intracellular pH, and extended cellular damage. Furthermore, sustained hypoxia can result from severe COVID-19 infection that may further lead to stillbirth, preeclampsia, and fetal growth restriction.<sup>9</sup>

### *Third-trimester placental injury*

Histopathological aberrations, such as malperfusions and inflammatory conditions, have been widely reported with differing frequencies. The frequency of these lesions was estimated to be uncertain due to the bulk of reported studies not using control groups as well as the unblinded examination of the clinical condition. Thus, there are no comparisons between infected and non-infected pregnant women in terms of the presence of lesions in the placenta.<sup>9</sup>

Adverse pregnancy outcomes, such as placental abruption, preterm delivery, and stillbirth, are linked to placental maternal vascular malperfusion (MVM) lesions, with a higher prevalence in infected pregnant women as compared to a control group.<sup>40</sup> MVM lesions may be associated with the duration, timing, and severity of the infection, which, in turn, can result in preterm deliveries.<sup>20</sup> There is a recognizable pattern of placental injury associated with abnormal uterine perfusion. Moreover, this can result in countless pathological variations, such as villous infarction, Tenney–Parker change, intervillous thrombosis, decidual vasculopathy, heightened intervillous and perivillous fibrin deposition and accelerated villous maturation.<sup>41,42</sup> Consequently, these can lead to significant clinical outcomes, such as preterm birth, fetal demise, and fetal growth restriction. Subsequent hypoxic-ischemic placental injury and uterine under perfusion may be induced by maternal hypoxia arising from severe lung infection due to COVID-19.

On the other hand, four studies on the placenta of pregnant women affected by COVID-19 reported the occurrence of fetal vascular malperfusion (FVM) due to diminished vascular supply.<sup>36,43–45</sup> FVM can be associated with certain conditions, such as abnormal cord insertion, maternal hypercoagulable state, umbilical cord hyper cooling, and fetal vascular thrombosis.<sup>46,47</sup> Vascular endothelial dysfunction can be caused by viral endotheliotropic behavior via the ACE2 receptors present on endothelial cells. Consequently, COVID-19 infected patients can have

a complement-induced coagulopathy state, which predisposes them to microthrombi formation.<sup>48</sup>

Placentas with focal subchorionic fibrin, prominent intervillous fibrin, increased capillarization, and syncytial nuclear aggregates (SNAs) were found as evidence of MVM and FVM. Ischemic lesions, such as villous agglutination or villous infarcts (microinfarcts), were found to have a combination of intervillous space collapse and trophoblast necrosis. Maternal placental blood flow disturbance due to hypoxic respiratory disorder can be associated with heightened microcalcifications and thrombi. Dysregulation of coagulation cascade has been attributed to causing such phenomenon, which can lead to the formation of fibrin clots, to the coronavirus. Moreover, in a study, there was a substantial increase in fibrin thrombi and microcalcifications among the COVID-positive group as compared to the negative control, as evidenced in 90% of microscopic examinations of placentas that were coronavirus positive.<sup>34</sup>

Due to the unclear etiology of the increasing occurrence of FVM, Golden and Simmons<sup>49</sup> suggested an intermittent or partial umbilical blood flow obstruction in cases of stem villous vessels or chorionic plate occlusion and localized thrombosis. Altered flow may be reflected through endothelial damage instead of thrombosis itself. They presumed that this may be due to indirect systemic damage, which can either be immune- or viral-mediated, instead of local pathophysiologic shifts. In contrast, fetal vascular thrombosis was mentioned in situations of FVM and may be attributed to a COVID-19-induced hypercoagulable state.<sup>50,51</sup>

Fetal endothelial cell breakdown and/or damage within the villous stroma can be a consequence of villous stromal-vascular karyorrhexis. As recognized in one case of infected pregnancy, it can pose a risk to oligohydramnios, fetal growth restriction and demise, and non-reassuring fetal heart rate depending on the nature and severity of obstruction.<sup>52</sup>

Chronic inflammatory pathologies, including chronic deciduitis,<sup>36</sup> chronic histiocytic intervillitis,<sup>43,53–56</sup> and lymphohistiocytic villitis,<sup>36,45,46,57,58</sup> can be linked to SARS-CoV-2 placental infections, which are comparable to other RNA viral infections<sup>59</sup> during pregnancy. About one-third of the infected placentas were reported to have maternal inflammatory responses, such as acute stage-2 chorioamnionitis and stage-1 subchorionitis/chorionitis as verified in 11 studies. On the other hand, acute chorioamnionitis was present in 1.7% of the non-infected placentas of pregnant women.<sup>60</sup> One consistent finding in several studies was the rise in intervillous macrophage infiltration,<sup>43,45,53–56,61</sup> which aligned with the findings of lung tissue autopsy among dead patients with severe COVID-19. Macrophage influx is presumed to aid in the containment of local viral transmission and propagation as well as to mediate exuberant immune response, which can result in unnecessary tissue destruction in the COVID-19-infected placenta. Despite macrophages and monocytes being considered viral dissemination vectors,<sup>62,63</sup> fetal infections can be caused by the virus present in the fetal vascular monocyte cytoplasm. To prevent immunopathology linked to the SARS-CoV-2 infection,

vigorous therapeutic approaches can be implemented to impede the differentiation and migration of macrophages and monocytes.

### Second-trimester placental injury

Histopathological characteristics of placentas in COVID-19-infected mothers in their second trimester, which ranges from 16 to 24 gestational weeks, have only been studied in the selected literature.<sup>8,52,58,61,64</sup> However, two studies only focused on the virus detection and not on its effect on the histopathological characteristics of the placenta.<sup>61,65</sup> Hosier and colleagues determined  $3 \times 10^7$  virus copies (number of copies of a virus gene in the genome of an organism) per mg and  $2 \times 10^3$  virus copies per mg in the placenta and umbilical cord, respectively.<sup>64</sup> On the other hand, fetal tissues other than the umbilical cord and placenta did not exhibit the presence of SARS-CoV-2 for a 19-week-old stillbirth, as exemplified by Baud et al.<sup>8</sup>

Three studies revealed the presence of heightened subchorionic and perivillous fibrin depositions.<sup>8,43,52</sup> At 22 gestational weeks, clinical abruption was observed for a 35-year-old infected pregnant woman.<sup>64</sup> Although further study is required on this, it is hypothesized that the early onset of severe preeclampsia can be instigated by COVID-19-related placental inflammation.<sup>66</sup> A gestationally diabetic mother gave birth to 24-week-old twins, who were dichorionic and diamniotic, with chronic histiocytic intervillitis as well as related ischemic necrosis of adjacent villi.<sup>52</sup> Moreover, a 28-year-old infected mother had preterm labor, resulting in the stillbirth of a 19-week-old with acute subchorionitis and fetal vasculitis.<sup>8</sup>

### Conclusion

Given that the placenta is vital to fetus maintenance and development, clear-cut research on COVID-19's impact on outcomes from pregnancy and placental tissue collection and assessment is deemed necessary. A review on the direct placental invasion of the virus shows the SARS-CoV-2 glycoprotein utilizing the specific antibody while coagulation abnormality provides an indirect mechanism for thromboinflammatory response similar to coronavirus characteristics during pregnancy. Vertical transmission of SARS-CoV-2 was determined a possible risk despite contrary reports. This is mainly possible through direct transmission, infection of syncytiotrophoblasts, and mediated virion transcytosis among other pathways. There are numerous reports of maternal vascular malperfusion occurring as a histopathological change in the placenta induced by coronavirus infection. Despite this, placentalitis characterized by histiocytic intervillitis, perivillous fibrin deposition, and trophoblast necrosis are deemed more indicative as a histopathological feature of SARS-CoV-19 infection.

SARS-CoV-2's key receptors are the enzymes ACE2 and TMPRSS2 which are observed to decrease in levels from the first to the third semester of gestation indicating higher infection vulnerability in the early stages of pregnancy. Future research with an increased population size should help provide a better understanding of the nature of the SARS-CoV-2 mechanism on maternal transmission, its

pathological characteristics, and its effect on the mother and fetus.

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### Conflict of interest

The author has no conflict of interest to declare.

### Ethical approval

No ethical approval was indicated, as the present study was a review study. It did not involve any ethical issue or patient's data or treatment intervention.

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