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## Controversial of SARS-CoV-2 transmission in pregnant mothers: a review



David Tjahyadi<sup>1\*</sup>

### ABSTRACT

Pregnant women are a population group at high risk of contracting SARS-CoV-2. Several cases have been reported, including diabetic ketoacidosis and hypertension, diabetes mellitus and hypertension, and heart disease associated with COVID-19. In addition, it is also reported that pregnant women are also exposed to SARS-CoV-2. Most pregnant women with COVID-19 show mild symptoms. The placenta is usually an effective barrier to prevent the spread of infection from mother to fetus (vertical transmission). Certain pathogens can overcome this barrier, with effects that are sometimes detrimental to the development of pregnancy. Vertical infection of SARS-CoV-2 from mother to fetus is possible, although there is no adequate evidence. It has been reported that in pregnant women with COVID-19, the vertical transmission of SARS-CoV-2 from mother to fetus is low. The transmission of SARS-CoV-2 from mother to fetus occurs in the third trimester of pregnancy. Although there is vertical transmission of SARS-CoV-2 from mother to fetus, there are no reports of adverse effects in neonates. The results of another study explained that in the case of pregnant women who were confirmed positive for COVID-19, there was an gene expression of the ACE2 receptor, N and S proteins from SARS-CoV-2 in the placenta. This study's results contradict the opinion that ACE2 and TMPRSS2 in the placenta that mediates viral entry can be ignored. Vertical transmission of SARS-CoV-2 during delivery can occur through close contact with infected cervical secretions or perineal tissue. It is more important to note that the angiotensin-converting enzyme (ACE)-2, the SARS-CoV-2 receptor, is significantly elevated during pregnancy, which may contribute to susceptibility to SARS-CoV-2. The selection of drugs that demonstrate superior maternal and fetal safety should be considered for pregnant women with COVID-19.

**Keywords:** Pregnant women, SARS-CoV-2, COVID-19, vertical transmission of SARS-CoV-2.

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### INTRODUCTION

Coronavirus disease-19 (COVID-19) is caused by the 2019 novel coronavirus (2019-nCoV),<sup>1</sup> then, by WHO the virus was given the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>2</sup> This statement is important for the public to understand.<sup>3</sup> In addition, many cases of COVID-19 have been reported during the pandemic, including cases in patients with diabetic ketoacidosis and hypertension.<sup>4</sup> More than that, it is necessary to order the elderly who suffer from hypertension and diabetes mellitus to healthy lives and protect themselves from COVID-19.<sup>5</sup> In addition, people with heart disease are also reminded to be careful to avoid COVID-19.<sup>6</sup> Although it is still necessary to investigate whether there is a relationship between heart disease and aortic enlargement in COVID-19 patients, it has been reported that cadaveric aortic enlargement has been

reported.<sup>7</sup> In addition, it was also reported that SARS-CoV-2 infection induces acute aortic occlusion.<sup>8</sup> Moreover, an acute aortic dissection surgery has also been performed on patients with COVID-19.<sup>9</sup>

Data reported by the COVID-19 Task Force, National Disaster Management Agency (Badan Nasional Penanggulangan Bencana/BNPB) of the Republic of Indonesia as of July 11, 2022, shows 6,111,305 confirmed cases (with the addition of 2,576 cases), 20,535 active cases (0.3% of confirmed cases), 5,933,979 recovered (97.1% of confirmed cases) and 156,791 died (2.6% of confirmed cases). Based on gender, COVID-19 cases in Indonesia showed 47.7% positive cases in men and 52.3% in women. Individuals treated or self-isolated due to COVID-19 were 45.5% males and 54.5% females. The percentage of the number of COVID-19 sufferers who recovered in men was 47.5%, while in women, it was 52.5%. Patients

with COVID-19 who died in men were 52.5%, while in women, 47.5%.<sup>10</sup> However, women are often faced with social and economic problems due to the COVID-19 pandemic compared to men.<sup>11</sup> Due to the COVID-19 pandemic, pregnant women are at high risk of contracting SARS-CoV-2. Although the data available to date suggest that pregnant women are no more susceptible to SARS-CoV-2 infection than those who are not pregnant or the general population.<sup>12</sup> A previous study demonstrated that in Canada, there are 8,786 cumulative pregnancies affected by SARS-CoV-2 (as of October 31, 2021).<sup>13</sup>

This study aimed to analyze the potential for SARS-CoV-2 transmission in pregnant mothers. Although pregnant mothers infected with SARS-CoV-2 tend to have mild symptoms, it can cause metabolic disorders in their bodies. Further research is still needed to prove the existence of vertical infection of SARS-



CoV-2 between pregnant mothers and their fetuses.

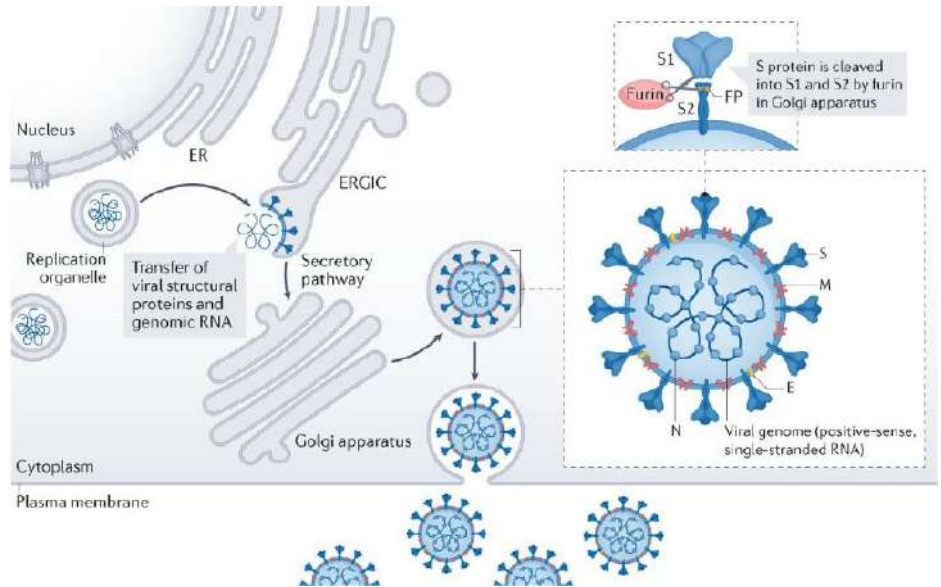
### Genome and infection of SARS-CoV-2

The nucleotides that comprise the SARS-CoV-2 genome are 29,903 nucleotides (nt). The genes that make up the SARS-CoV-2 genome are 5' UTR, ORF 1ab gene, S gene, ORF 3a gene, E gene, M gene, ORF 6 gene, ORF 7a gene, ORF 7b gene, ORF 8 gene, N gene, ORF 10, and 3' UTR genes.<sup>14</sup> Gene mutations in SARS-CoV-2 can occur in all genes that make up the genome of SARS-CoV-2.

Interest in researching SARS-CoV-2 infection became even more interesting with the emergence of Alpha B.1.1.7, Beta B.1.351, Gamma P.1, Delta B.1.617.2, and most recently, the Omicron variant. Infection by SARS-CoV-2 induces perinuclear regions during the formation of new membrane structures. These perinuclear regions constitute the "replication organelles".<sup>15,16</sup> Viral structural proteins and genomic RNA synthesized at the site of replication were then translocated to the "ER-Golgi intermediate compartment" (ERGIC) to assemble new virus particles.<sup>17,18</sup> The N protein bound to the viral genomic RNA is assembled in the virion, while the structural proteins, namely spike protein (S protein), envelope protein (E protein), and membrane protein (M protein), are incorporated in the virion membrane. Protein S mediates major entry steps, including receptor binding and membrane fusion. During biosynthesis and maturation in infected cells, protein S is cleaved by furin or furin-like proprotein convertase in the Golgi apparatus into S1 and S2 subunits, which remain linked.<sup>19</sup> The S1 subunit binds to the receptor, while the S2 subunit binds to the virion membrane, resulting in membrane fusion. Proteins E and M interact with other viral proteins to assemble and bud new viruses.<sup>20,21</sup> The viruses that are formed will enter the lumen of the ERGIC, then reach the plasma membrane. The viruses are released into the extracellular space in the next stage and fuse with the plasma membrane.<sup>22</sup> Mechanisms of SARS-CoV-2 entry into cells showed in Figure 1.

### COVID-19 in pregnant women

Anyone can be infected by SARS-CoV-2 and thus suffer from COVID-19,



**Figure 1.** Mechanisms of SARS-CoV-2 entry into cells.<sup>22</sup>

including pregnant women. A person who has recovered from COVID-19 still has a chance of being re-infected by SARS-CoV-2. No research has demonstrated that someone with COVID-19 cannot be infected by SARS-CoV-2 later in life. In detail, it is stated that SARS-CoV-2 can infect pregnant women in all trimesters. It has also been shown that hormone levels and immunity in each pregnancy trimester differ.<sup>23</sup> In addition, it was explained that pregnant women's immune balance is still unstable in the early trimester of pregnancy. There is a decrease in the regulation of proliferation and activation of lymphocytes in pregnancy, so pregnant women become a vulnerable group to SARS-CoV-2 infection.<sup>24</sup>

It is possible that SARS-CoV-2 infection in pregnant women affects organogenesis in the fetus and can even cause abortion. However, the effect of SARS-CoV-2 on fetal development during pregnancy still needs to be investigated.<sup>25</sup> The results of previous studies reported that SARS-CoV-2 infection at the time of conception or early pregnancy could increase the risk of neurodevelopmental abnormalities in the fetus.<sup>26</sup> In addition, it has also been reported that SARS-CoV-2 infection can cause neurodevelopmental disorders.<sup>27</sup>

The condition of pregnant women with COVID-19 is indeed diverse. Symptoms that arise among pregnant women with COVID-19 are very diverse and depend on the presence or absence of ballast disease.<sup>28</sup>

For example, obesity in pregnant women with Covid-19 can trigger pulmonary embolism. This is related to prothrombic activation, which triggers clotting in blood vessels and the risk of pulmonary embolism. Embolism can also occur if there is already a bacterial infection in the lungs that causes pneumonia.<sup>29</sup> Of course, the diversity of conditions of pregnant women with COVID-19 determines the success rate of pregnancy, the condition of the fetus, and the health of the mother and baby after giving birth. The results showed that black and Hispanic race, obesity, advanced maternal age and medical comorbidities were risk factors in pregnant women associated with COVID-19.<sup>30</sup>

The first case of COVID-19 occurred in Wuhan, China. The National Health Commission of China identified to 118 pregnant women with COVID-19 from 50 hospitals across the city of Wuhan. The identification was carried out from December 8, 2019, to March 20, 2020. Based on the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment, it was reported that 118 cases of COVID-19 were found, there were 84 (71%), pregnant women, with a positive PCR test result for SARS-CoV-2, and the remaining 34 (29%) shows a picture of pulmonary infiltrates based on CT scan. The number of pregnant women with COVID-19 accounted for 0.24% of the number of COVID-19 cases at that time. Seventy-five (64%) of the 118 cases of

pregnant women with COVID-19 were in the third trimester. It turned out that 112 of the 118 cases of pregnant women with COVID-19 showed symptoms, and 6 of these cases did not show symptoms. The most common symptoms in pregnant women with COVID-19 included high fever (75%), cough (73%), chest pain (18%), fatigue (17%), shortness of breath (7%), diarrhea (7%), and headaches (5%). Based on clinical signs, it was also reported that 44% of the 118 cases of pregnant women with COVID-19 had lymphopenia. A computed tomography scan (CT scan) showed that 79% of the 118 cases of pregnant women with COVID-19 showed multiple patchy nodular opacities bilaterally and ground glass opacity (GGO) in the lungs. Most of the 92% of the 118 cases of pregnant women with COVID-19 were mild cases, 7.15% of the 118 cases were moderate cases, and 1 person or 0.85% of the 118 cases received treatment with a ventilator. There were no maternal deaths in the 118 cases of pregnant women with COVID-19. Most pregnant women with COVID-19 were 68 patients out of 118 cases gave birth by cesarean section, 3 cases of abortion, 2 ectopic pregnancies, and 14 premature births. In this case, it turned out that there were no infants who had neonatal asphyxia.<sup>31</sup> Another study showed that 85% of pregnant women with Covid-19 had mild symptoms.<sup>32</sup> In addition, the other result of research demonstrated that 86% of pregnant women with COVID-19 experienced mild symptoms. It was further stated that the clinical and radiological characteristics of pregnant women with COVID-19 were similar to those of non-pregnant women with COVID-19.<sup>33</sup>

Previous studies have also shown that the main characteristics of COVID-19 in pregnancy are fever, cough, dyspnea, and lymphopenia. Moreover, shortness of breath occurs in 18% of pregnant women with COVID-19. These symptoms are similar to symptoms in non-pregnant women with COVID-19.<sup>34</sup> Initial reports of seven pregnant women with COVID-19 in China showed clinical manifestations of fever (86%), cough (14%), shortness of breath (14%), and diarrhea (14%).<sup>35</sup> Several reports of pregnant women with COVID-19 showing similar

symptoms.<sup>31,36,37</sup> There are also reports of atypical clinical presentations in pregnant COVID-19 patients, including normal temperature and leukocytosis,<sup>38,39</sup> and other symptoms, including nasal congestion, rash, phlegm production, headache, malaise and loss of appetite.<sup>40</sup> Based on research on COVID-19 patients, complaints in pregnant women are similar to those in non-pregnant women. However, it should be noted that fever, gastrointestinal symptoms, dyspnea and fatigue may overlap with those that arise due to changes in physiological adaptations during pregnancy.

### Effects of covid-19 on pregnant mothers

In non-pregnant women, COVID-19 has been associated with cardiovascular diseases (CVD), such as myocarditis, acute myocardial infarction, cardiomyopathy, arrhythmias, and venous thromboembolic events.<sup>41</sup> A previous study demonstrated 154 pregnant women patients with COVID-19. Fifteen patients (9.7%) of the 154 pregnant women with COVID-19 had a myocardial injury (myocardial injury), and were delivered by cesarean section. Sixty percent of the babies born by cesarean section were born prematurely. The laboratory tests showed high levels of troponin and B-type natriuretic peptide. Unfortunately, there were two death patients. This case shows that pregnant women with COVID-19 trigger myocardial injury, whereas previously, all these patients were normal, and there were no cardiovascular risk factors.<sup>42</sup> Recent research results show that pregnant women infected with SARS-CoV-2 include cesarean delivery and premature birth.<sup>13</sup>

### Vertical infection of SARS-CoV-2 from mother to fetus during pregnancy

Vertical transmission of SARS-CoV-2 from mother to fetus is possible during delivery or to the neonates after delivery. In detail, vertical transmission of SARS-CoV-2 during pregnancy can occur through the placenta. Vertical transmission of SARS-CoV-2 during delivery can occur through close contact with infected cervical secretions or perineal tissue. In addition, vertical transmission of SARS-CoV-2 from the mother can occur to the baby during

postpartum, namely during breastfeeding. The placenta is usually an effective barrier to prevent the spread of infection from the mother to the fetus (vertical transmission). In reality, certain pathogens can overcome this barrier, with effects that sometimes undermine the development of pregnancy. Vertical infection of SARS-CoV-2 from mother to fetus is very likely, although there has been no adequate evidence.<sup>31</sup>

During the current COVID-19 pandemic, it is necessary to educate about preventing the transmission of COVID-19 from mother to fetus during pregnancy.<sup>43</sup> However, the reality is that the number of covid-19 sufferers is still high during the COVID-19 pandemic. The high number of patients with pregnant women with COVID-19 allows an increase in vertical infection of SARS-CoV-2 from pregnant women to their fetuses. Concrete actions on educating pregnant women about SARS-CoV-2 and its transmission to the fetus have been carried out. This education is expected to increase the knowledge of pregnant women about SARS-CoV-2 and its transmission to the fetus.<sup>44</sup> In addition, in the context of preventing and controlling COVID-19, efforts have also been made to increase public knowledge about COVID-19.<sup>45,46</sup> In order to prevent and control COVID-19, the Ministry of Health of the Republic of Indonesia has issued a health protocol. The health protocol is stated in the Decree of the Minister of Health of the Republic of Indonesia Number HK.01.07/MENKES/382/2020. The general public, including pregnant women, is expected to be able to implement these health protocols to avoid COVID-19.<sup>47</sup>

It has been reported in pregnant women with COVID-19 that the vertical transmission of SARS-CoV-2 from mother to fetus is low, around 1.6%,<sup>48</sup> 3.2%,<sup>49,50</sup> and 6.3%.<sup>51</sup> The report also stated that transmitting SARS-CoV-2 from mother to fetus occurs in the third trimester of pregnancy. Although there is vertical transmission of SARS-CoV-2 from mother to fetus, there are no reports of side effects in neonates.<sup>49,50</sup> The results of other studies showed that in the case of pregnant women who were confirmed positive for COVID-19, it turned out that there was an expression of the ACE2

receptor gene in the placenta, N and S proteins from SARS-CoV-2.<sup>52</sup> The results of this study contradict the opinion which states that the ACE2 and TMPRSS2 in the placenta that mediates viral entry can be neglected.<sup>53</sup> So far, no studies have shown the effect of COVID-19 on mothers with neonatal babies. Nonetheless, isolating mothers with COVID-19 from neonatal infants is important in stopping the disease transmission.<sup>54</sup>

Based on the research results, it has been interpreted that the transmission of SARS-CoV-2 from mother to fetus, most likely occurs through fetal mononuclear cells infected with the virus. It was also stated that placental infections are associated with the recruitment of maternal inflammatory cells in the intervillous space.<sup>52</sup> The results of other studies showed the presence of SARS-CoV-2 RNA in maternal and fetal tissues. Detection of SARS-CoV-2 was carried out with qRT-PCR from samples of the placenta, umbilical cord, maternal saliva and maternal urine. Sars-CoV-2 genome sequencing was performed on placental samples from various races. In more detail, it is shown that SARS-CoV-2 is present in most syncytiotrophoblast cells in the materno-fetal interface of the placenta. Histological observations of the placenta revealed dense macrophage infiltrates, but there was no evidence of vasculopathy normally associated with preeclampsia. There is no doubt that the case shows the invasion of SARS-CoV-2 in the placenta, so it has great potential for the morbidity of pregnant women with COVID-19.<sup>55</sup> The detection of SARS-CoV-2 RNA in placental was reported as proof of vertical transmission in pregnant women.<sup>52,56</sup> It should be noted that testing for the presence of SARS-CoV-2 with reverse transcriptase PCR repeatedly failed to identify the presence of viral genomes in maternal and infant specimens, including the placenta, blood from the umbilical cord, amniotic fluid or tire swab, maternal blood, vaginal secretions (vaginal secretions) and breast milk.<sup>57,58</sup>

### Transplacental transmission

There is no agreement on whether SARS-CoV-2 can be transmitted from mother to fetus transplacental. A previous study

found no evidence of vertical transmission of SARS-CoV-2 from mother to fetus.<sup>59,60</sup> These results are supported by the fact that there is a significant shortage of canonical cells in the trophoblast to prevent vertical transmission of SARS-CoV-2, consequently, SARS-CoV-2 cannot cross the placental villi due to caveolin deficiency.<sup>61</sup>

On the other hand, it was suggested that is possible that SARS-CoV-2 can infect the human placenta via alternative receptors (DPP4 and CD147) and proteases (Furin).<sup>62,63</sup> Previous research demonstrated that SARS-CoV-2 could cross the placenta and migrate from mother to fetus. This conclusion was proven by studies using real-time PCR with samples of amniotic fluid, fetal placenta, umbilical cord blood, nasopharyngeal swabs, and vaginal secretions, and other specimens from pregnant women and newborns with COVID-19.<sup>64</sup>

### Delivery of pregnant mothers infected with covid-19

Clinical diagnosis of pregnant women with COVID-19 is done through anamnesis, physical examination, and supporting examinations. Careful anamnesis is carried out to determine the main complaints of pregnant women and assist health workers in determining the clinical degree of pregnant women. Therefore, the physical examination includes general condition, vital signs, cardiac examination, pulmonary examination and other examinations that must be adjusted according to indications. Furthermore, supporting examinations such as routine blood, pulmonary imaging, and real-time reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 with samples taken through a throat swab. Supporting examinations in the form of serological are not recommended by WHO except for research purposes.<sup>28,65</sup> It has been stated that there is no SARS-CoV-2 in the vaginal fluids of pregnant women with COVID-19, so vaginal delivery may be a safe option.<sup>66</sup>

With the prolonged COVID-19 pandemic, new protocols or guidelines are applied to pregnantwomen and pregnant women about to give birth. To minimize the transmission of SARS-CoV-2, the

CDC recommends that pregnant women continue to do antenatal care, for example, consultations through providers. In addition, if pregnant women want to give birth, first screening using real-time PCR against SARS-CoV-2.<sup>67</sup> Good measures to prevent the transmission of SARS-CoV-2 to the fetus and the medical personnel who help need to be taken.<sup>68</sup> Childbirth in mothers with COVID-19 infection is more severe than normal childbirth.<sup>47</sup> When the labor process makes the mother's condition worse or more critical, cesarean section is the most appropriate choice. Indications that include an emergency due to COVID-19 or suspected COVID-19 are deterioration, respiratory difficulties even with the help of mechanics or ventilation, and fetal compromise. Cesarean delivery should be carried out with infection prevention measures, personal protective equipment (PPE), and in rooms with negative ventilation pressures.<sup>69</sup> Treatment of pregnant women with COVID-19 using a combination of Lopinavir/Ritonavir and Ribavirin. This combination is lower in side effects compared to single Ribavirin.<sup>70</sup> Drug administration of pregnant women with mild symptoms is better than giving non-teratogenic drugs. If you need oxygen, it is necessary to monitor the hypoxemia. Maternal safety is number one when severe symptoms of infection are found. The decision to terminate pregnancy needs to consider several things, including viral load, generation of transmission, range of pulmonary lesions, maternal age, and comorbid diseases of the mother.<sup>25,47</sup>

The following is an example of handling cases of pregnant women with COVID-19. In mid-March 2020 (mid-March 2020), a 35-year-old (non-Hispanic Asian Amercian) woman, gravida 3, para 1011 (G3P1011), presented at 22 weeks gestation with symptoms of COVID-19. Observations made are vital signs and physical examinations. In these cases, vaginal bleeding and abdominal pain were obtained on physical examination. SARS-CoV-2 RNA is detected with reverse transcription PCR (RT-PCR) from a nasopharyngeal swab. Medical history, pregnancy comorbidities, chest x-ray, transabdominal ultrasound and Laboratory studies were carried out. Multidisciplinary consultations

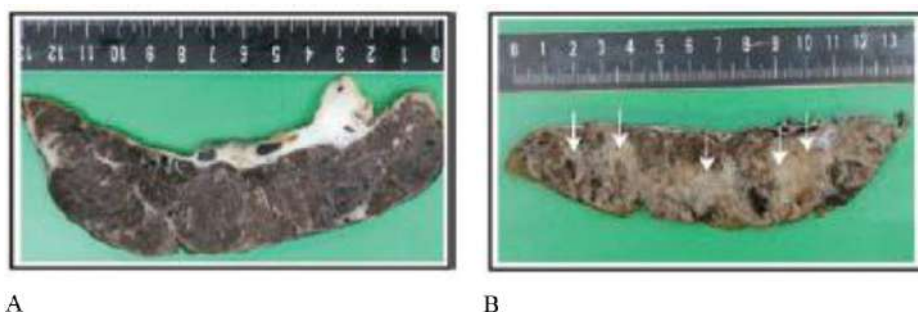


via telemedicine with materno-fetal medicine, neonatology, and infectious disease departments. In these cases, the patient opted for termination of pregnancy to reduce the risk of morbidity or serious maternal death. Termination of pregnancy is carried out by dilation and evacuation (D&E) with general endotracheal anesthesia. Intraoperative findings are retroplacental clots (retroplacental clot). The postoperative finding was that lymphopenia developed, but the coagulation markers improved, then self-isolation was carried out on day 3 postoperatively. An emergency room visit on postoperative day 4 was required to titrate.<sup>55</sup> In addition to the detection of SARS-CoV-2 RNA with reverse transcription PCR (RT-PCR) from nasopharyngeal swab samples, sars-CoV-2 RNA detection was also carried out with COVID enzyme-linked immunosorbent immunoglobulin assay G.<sup>42</sup> Other researchers reported detection of SARS-CoV-2 RNA in placental tissue by immunohistochemistry to express the SARS-CoV-2 Spike protein.<sup>52</sup> Therefore, the successful detection of SARS-CoV-2 RNA in placental can be used as evidence (as a proof) of vertical transmission in pregnant women.<sup>52,56</sup>

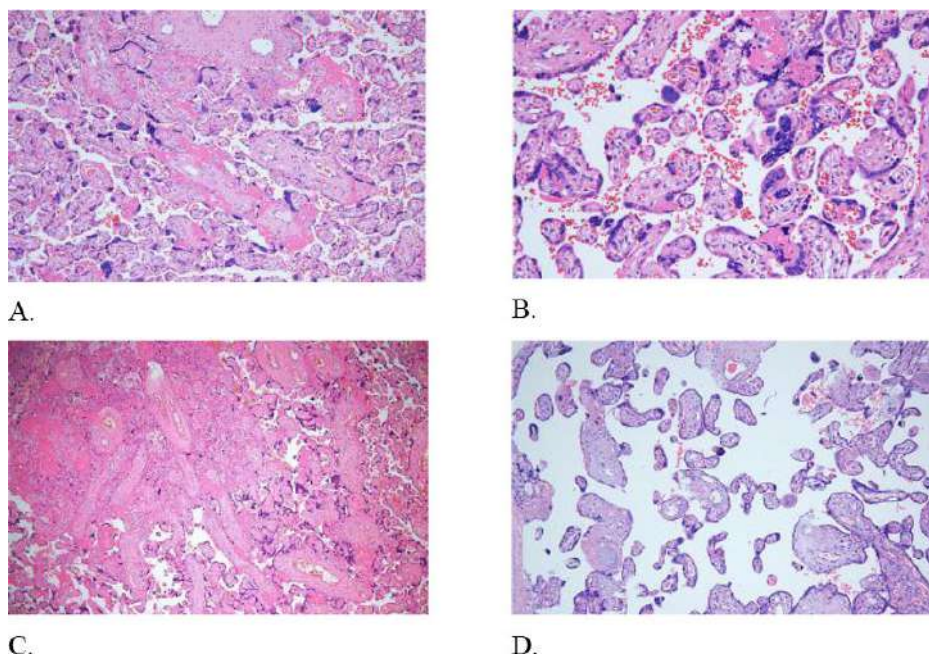
### Placental examination

The observations showed morphological differences between the normal and placenta in people with COVID-19 (Figure 2).

Histochemical staining, a specific SARS-CoV-2 RNA probe, and an electron microscope detected placental syncytiotrophoblastin COVID-19 patients. The placenta in people with COVID-19 looks stiff and pale, the trabeculae are also pale, and histologically there is fibrin deposition in the perivillous. Damage to syncytiotrophoblasts is associated with intervillous inflammatory infiltrate, which is shown in immunohistochemistry by examining M2 macrophages (CD163) and CD68+, cytotoxic (CD8), T-cells helpers (CD4), B-lymphocytes (PAX5 and CD38). There are no signs of villous parenchyma invasion, villitis, or decidual vasculopathy. Histochemically shown the dominant localization of SARS-CoV-2 in syncytiotrophoblast cells of the placenta.



**Figure 2.** Morphological differences between normal placenta and placenta in patients with COVID-19. A. Normal placental morphology. B. Placental morphology with COVID-19. Arrows show pale color in placenta with COVID-19.<sup>71</sup>



**Figure 3.** Histological appearance of the placenta in the 3rd trimester of pregnant women. A. Appearance of the chorionic plate of case 3 (39+ 1 weeks gestation). There is increased deposition of fibrin in the focal perivillous and increased syncytial knots (H&E, magnifications 100 times). B. Increased syncytial knots in the terminal villi with the chorionic plate of case 3 (H&E, magnifications 200 times). C. Chorionic plate of case 2 (39+ 5 weeks gestation). Central placental infarct (H&E, magnifications 40 times) is shown. d, Chorionic plate of case 8 (37+ 6 weeks gestation). Demonstrated distal villous hypoplasia (H&E, magnifications 100 times).<sup>73</sup>

The evidence was corroborated using an electron microscope to show SARS-CoV-2 particles in syncytiotrophoblast. However, it should not be ruled out to detect SARS-CoV-2 RNA using PCR on the fetal side of the placenta. Based on the measurement results, the amount of RNA copies of SARS-CoV-2 in the fetal side of the placenta is higher than in the mother's blood. Although the placenta is a barrier to viral infections during pregnancy, the local environment allows the replication of

the virus. The placenta infected by SARS-CoV-2 causes fibrin deposition, thus inhibiting fetal-maternal gas exchange, resulting in a fetal emergency requiring a premature emergency cesarean section.<sup>71</sup> The mechanism of infection of some types of viruses transplacentally mother-fetus may be similar to SARS-CoV-2. The results of other studies also showed that pregnant women infected with the severe acute respiratory syndrome (SARS) had an increase in fibrin in the subchorionic



and intervillous villi of the placenta so that fetal thrombosis occurred.<sup>72</sup>

The following research results are different from the results of previous studies. This study showed the detection of SARS-CoV-2 in 8 placentas from third trimester pregnant women using FISH and IF. FISH detect genes in SARS-CoV-2, while IF is used to detect the SARS-CoV-2 spike protein. All patients on this study recovered. There is no clinical or serological evidence to suggest vertical transmission of SARS-CoV-2 from the mother to the fetus. An increase in syncytial nodes occurs in all cases. Increased deposition of focal perivillous fibrin occurred in 7 cases out of 8 cases. In the entire placenta observed did not show significant chronic histiocytic intervillitis. The observations on the placenta villi showed that the number of macrophages did not increase significantly in all cases. Inflammatory cells (T cells, B cells and plasma cells) in the placenta villi did not increase significantly in all cases. The results of observations using FISH with SARS-CoV-2 RNA probes showed evidence that 8 cases showed negative results and observations using IF with monoclonal antibodies against the SARS-CoV-2 spike protein. Based on these facts, it can be concluded that there is no evidence of vertical transmission of SARS-CoV-2 from mother to fetus in pregnant women of the third trimester of COVID-19.<sup>73</sup> A histological display of the placenta pregnant women of the third trimester is presented in [Figure 3](#).

It should be noted that a placenta biopsy can produce samples of different tissues, some samples come from the mother, and some come from the fetus. The determination of SARS-CoV-2 in both samples was carried out using RT-PCR. Therefore, the positive test results against SARS-CoV-2 in both samples using RT-PCR cannot be used to assess whether SARS-CoV-2 originated in the mother or fetus.<sup>74</sup> The results of previous studies showed Fluorescence in situ hybridization (FISH) to detect viral gene fusion at cell locations in the placenta. The results of the FISH analysis can provide information about the anatomical distribution of the virus in the placenta.<sup>75,76</sup> Based on this fact, FISH is more practical and provides

more information about diagnosing SARS-CoV-2 invasion in the placenta than RT PCR.

Most researchers assume there is no SARS-CoV-2 in the vaginal fluids of pregnant women with COVID-19, so vaginal delivery may be a safe delivery option. Nonetheless, a cesarean section may not prevent vertical transmission.<sup>77,78</sup> Previous studies have demonstrated that SARS-CoV-2 can be detected in the placenta or vaginal secretions of pregnant women who are positive for COVID-19 but does not increase the risk of contracting COVID-19 in vaginal newborns.<sup>79</sup> Based on the research results above, it is recommended that the delivery method is carried out based on obstetric conditions and not due to infection with pregnant women who are positive for COVID-19. In detail, pregnant women who are positive for COVID-19 cannot have a cesarean delivery.

### Neonatal Outcome

Postpartum neonates showed pediatric inflammatory multisystem-like syndrome with coronary artery ectasy. These neonates require treatment in the neonatal intensive care unit (NICU). This is a disadvantage experienced by neonates during the COVID-19 pandemic, although most pregnant women appear asymptomatic.<sup>71</sup> The results of another study showed that 60% of the 154 pregnant women with COVID-19 gave birth prematurely. The babies showed signs of unstable clinics, severe hypoxemia arrhythmia and fetal bradycardia. Five (35.7%) of the 14 premature babies had a birth weight of <2.5 kg), and 1 (7.1%) had a very low birth weight (birth weight <1.5 kg). In addition, 8 babies (57%) had reassuring Apgar scores in minutes 0 and 5. Three out of 14 premature babies (21.5%) had a moderately depressed Apgar score at 0 minutes and a reassuring score at 5 minutes. Three out of 14 premature babies (21.5%) had a moderately depressed score at 0 and 5 minutes. In addition, 5 infants (35.7%) of the 14 premature babies were admitted to the NICU. The premature baby who had a low birth weight and, after being treated in the NICU was discharged later.<sup>42</sup>

It has been stated that newborns born

to pregnant women who are positive for COVID-19 have a higher risk of experiencing fetal distress, premature birth, intrauterine growth restriction, respiratory problems, low birth weight, unstable body temperature, cardiovascular dysfunction, and digestive dysfunction.<sup>66</sup> There is an assumption that SARS-CoV-2 from mother to fetus causes the production of IgG antibodies. The IgG crosses the placenta, enters the newborn's body, and protects against viral spike proteins.<sup>80</sup> Furthermore, there have been no reports of infection with SARS-CoV-2 against breastfeeding babies, although ACE-2 receptors are expressed in breast tissue.<sup>81,82</sup> Mothers exposed to or infected with SARS-CoV-2 must wear a surgical mask when feeding their babies.

### CONCLUSION

Pregnant women with COVID-19 are predominantly in mild symptomatic conditions, found in 85% of cases. Pregnant women with comorbidities followed by COVID-19 infection are at risk of causing abortion and death in the mother or the fetus, especially if the mother gets the infection in the early trimester. Pregnant women with COVID-19 have an increased risk of angiotensin II because ACE2 experiences impaired work due to COVID-19 infection. This results in pregnant women with COVID-19 at risk of metabolic disorders that result in spontaneous abortions.

The potential for vertical infection between the mother and fetus is possible, although there has been no further research. Pregnant women with COVID-19 are recommended to continue to do antenatal care. Pregnant women with COVID-19 at the time of delivery need screening with real-time PCR SARS-CoV-2 for further delivery management to avoid infection between the mother and fetus and medical personnel. The most important thing is the need to monitor the level of hypoxemia in pregnant women with COVID-19 who are about to give birth. There is a possibility of immediate termination action in case of an emergency in labor. It is more important to note that the angiotensin-converting enzyme (ACE)-2, the SARS-CoV-2 receptor, is greatly elevated during pregnancy, contributing to susceptibility

to SARS-CoV-2. The selection of drugs that demonstrate superior maternal and fetal safety is worth considering for pregnant women with COVID-19.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

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## AUTHOR'S CONTRIBUTION

DV: drafted and wrote this review script.

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