REVIEW

Bali Medical Journal (*Bali MedJ*) 2022, Volume 11, Number 3: 1967-1975
P-ISSN.2089-1180, E-ISSN: 2302-2914

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

David Tjahyadi[1*]

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.

[1]Department of Histology, Faculty of Medicine, Universitas Trisakti, Indonesia;

*Corresponding author:
David Tjahyadi;
Department of Histology, Faculty of Medicine, Universitas Trisakti, Indonesia;
davesaboch@trisakti.ac.id

Received: 2022-09-26
Accepted: 2022-11-16
Published: 2022-12-20

Keywords: Pregnant women, SARS-CoV-2, COVID-19, vertical transmission of SARS-CoV-2.
Cite This Article: Tjahyadi, D. 2022. Controversial of SARS-CoV-2 transmission in pregnant mothers: a review. *Bali Medical Journal* 11(3): 1967-1975. DOI: 10.15562/bmj.v11i3.3759

INTRODUCTION

Coronavirus disease-19 (COVID-19) is caused by the 2019 novel coronavirus (2019-nCoV),[1] then, by WHO the virus was given the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] This statement is important for the public to understand.[3] In addition, many cases of COVID-19 have been reported during the pandemic, including cases in patients with diabetic ketoacidosis and hypertension.[4] 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.[5] In addition, people with heart disease are also reminded to be careful to avoid COVID-19.[6] 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.[7] In addition, it was also reported that SARS-CoV-2 infection induces acute aortic occlusion.[8] Moreover, an acute aortic dissection surgery has also been performed on patients with COVID-19.[9]

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%.[10] However, women are often faced with social and economic problems due to the COVID-19 pandemic compared to men.[11] 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.[12] A previous study demonstrated that in Canada, there are 8,786 cumulative pregnancies affected by SARS-CoV-2 (as of October 31, 2021).[13]

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.[14] 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".[15,16] 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.[17,18] 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.[19] 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 budge new viruses.[20,21] 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.[22] 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,

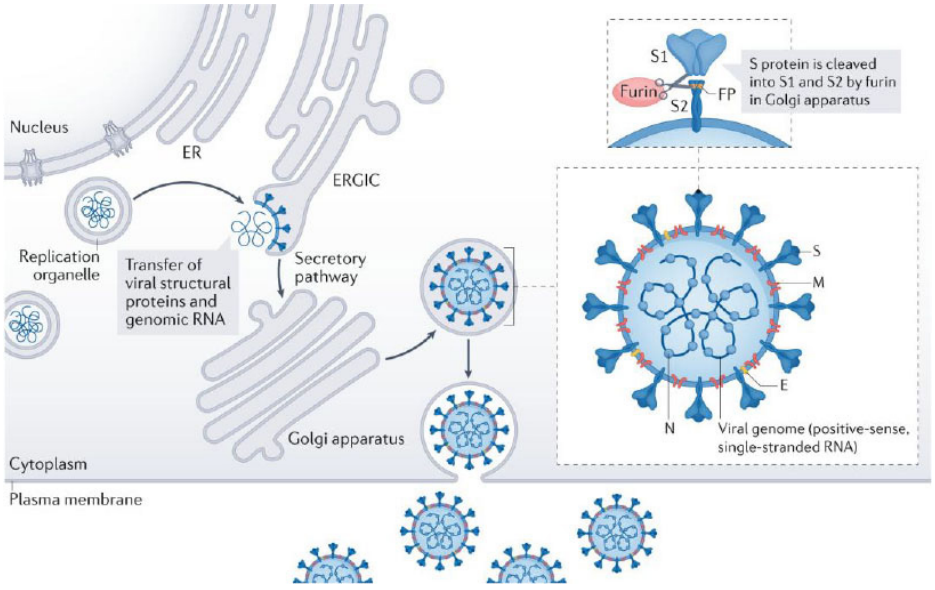


Figure 1. Mechanisms of SARS-CoV-2 entry into cells.[22]

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.[23] 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.[24]

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.[25] 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.[26] In addition, it has also been reported that SARS-CoV-2 infection can cause neurodevelopmental disorders.[27]

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.[28] 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.[29] 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.[30]

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.[31] Another study showed that 85% of pregnant women with Covid-19 had mild symptoms.[32] 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.[33]

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.[34] 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%).[35] Several reports of pregnant women with COVID-19 showing similar symptoms.[31,36,37] There are also reports of atypical clinical presentations in pregnant COVID-19 patients, including normal temperature and leukocytosis,[38,39] and other symptoms, including nasal congestion, rash, phlegm production, headache, malaise and loss of appetite.[40] 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.[41] 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.[42] Recent research results show that pregnant women infected with SARS-CoV-2 include cesarean delivery and premature birth.[13]

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.[31]

During the current COVID-19 pandemic, it is necessary to educate about preventing the transmission of COVID-19 from mother to fetus during pregnancy.[43] 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.[44] In addition, in the context of preventing and controlling COVID-19, efforts have also been made to increase public knowledge about COVID-19.[45,46] 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.[47]

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%,[48] 3.2%,[49,50], and 6.3%.[51] 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.[49,50] 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.[52] 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.[53] 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.[54]

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.[52] 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.[55] The detection of SARS-CoV-2 RNA in placental was reported as proof of vertical transmission in pregnant women.[52,56] 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.[57,58]

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.[59,60] 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.[61]

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).[62,63] 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.[64]

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.[28,65] 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.[66]

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.[67] Good measures to prevent the transmission of SARS-CoV-2 to the fetus and the medical personnel who help need to be taken.[68] Childbirth in mothers with COVID-19 infection is more severe than normal childbirth.[47] 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.[69] 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.[70] 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.[25,47]

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 retroplasental clots (retroplacental cloth). 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.[55] 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.[42] Other researchers reported detection of SARS-CoV-2 RNA in placental tissue by immunohistochemistry to express the SARS-CoV-2 Spike protein.[52] 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.[52,56]

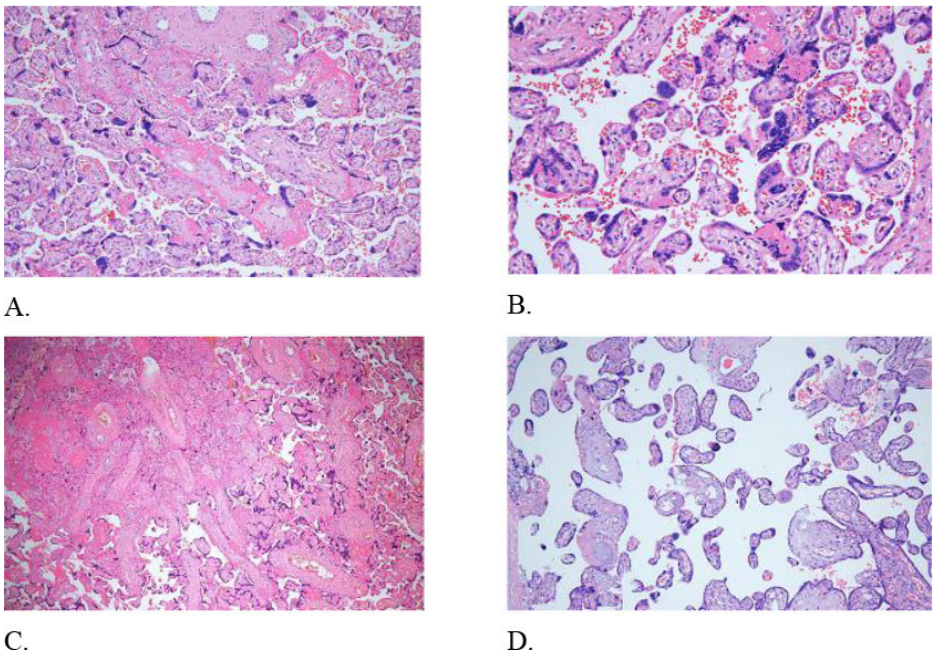
Placental examination

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 syncytiotrophoblast in 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.

A B

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.[71]



A. B.

C. D.

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).[73]

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.[71] 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.[72]

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 intervillositis. 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.[73] 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.[74] 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.[75,76] 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.[77,78] 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.[79] 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 ecstasy. 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.[71] 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.[42]

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.[66] 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.[80] Furthermore, there have been no reports of infection with SARS-CoV-2 against breastfeeding babies, although ACE-2 receptors are expressed in breast tissue.[81,82] 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 SARSCoV-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.

FUNDING

The author did not get funding from anywhere in the writing of this manuscript.

AUTHOR'S CONTRIBUTION

DV: drafted and wrote this review script.

REFERENCES

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020, 579:270-273. Available from: https://www.nature.com/articles/s41586-020-2012-7
2. WHO (World Health Organization). Naming the coronavirus disease (COVID-19) and the virus that causes it. 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technicalguidance/naming-the-coronavirus-disease-(covid2019)-and-the-virus-that-causes-it
3. Parwanto MLE. Virus Corona (2019-nCoV) Penyebab COVID-19. J Biomed Kes. 2020, 3:1-2. Available from: https://www.jbiomedkes.org/index.php/jbk/article/view/117/62
4. Parwanto MLE, Digambiro RA, Nusantara DU, Rarasati T. Coronavirus disease 2019 (COVID-19): A case report in a patient with diabetic ketoacidosis and hypertension. Bali Med J. 2020, 9(3):520-526. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/viewFile/1939/1558
5. Parwanto MLE, Guyansyah A. Hello Indonesia, Be Careful with COVID-19 in the Elderly with Hypertension and Diabetes Mellitus. Clin Mother Child Health. 2020, 17:370. Available from: https://www.longdom.org/open-access/hello-indonesia-be-careful-with-covid19-in-the-elderly-with-hypertensionand-diabetes-mellitus.pdf
6. Parwanto MLE. People with Heart Disease have to be more Vigilant so as to Avoid COVID-19. Health Sci J. 2020, Sp. Iss 2(007):1-2. Available from: https://www.hsj.gr/inpress.php. https://www.hsj.gr/medicine/people-with-heart-disease-have-to-bemore-vigilant-so-as-to-avoid-covid19.pdf.
7. Parwanto MLE, Mediana D, Samara D, Wartono M, Pakpahan A, Widyatama HG. Aortic enlargement: A case report of cadaveric heart and geat vessels dimensions. Bali Med J. 2020, 9: 416-418. Available from: https://www.balimedicaljournal.org/index.php/bmj.
8. Minalyan A, Thelmo FL, Chan V, Tzarnas S, Ahmed F. Severe acute respiratory syndrome coronavirus 2-induced acute aortic occlusion: a case report. J Med Case Rep. 2021, 15(112):1-6. Available from: https://jmedicalcasereports.biomedcentral.com/articles/10.1186/s13256-021-02692-x
9. Ahmet A, Saygin T, Gulsum T, Hasan T. Acute Aortic Dissection Surgery in a Patient With COVID-19. Ann Thorac Surg. 2021, 111(1):e1-e3. Available from: https://www.annalsthoracicsurgery.org/action/showPdf?pii=S0003-4975%2820%2930941-3
10. Satuan Tugas Penanganan COVID-19, Republik Indonesia. Peta Sebaran COVID-19. 2021, (as of January 10, 2021 at 10.23 Western Indonesian Time). Available from: https://covid19.go.id/peta-sebaran
11. Burki T. The indirect impact of COVID-19 on women. Lancet Infect. 2020, 20(8):904-905. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30568-5fulltext.
12. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020, 369(m1985):1-12. Available from: https://www.medrxiv.org/content/10.1101/2020.04.23.20076042v1
13. McClymont E, Albert AY, Alton GD, Boucoiran I, Castillo E, Fell DB, et al. Association of SARS-CoV-2 Infection During Pregnancy With Maternal and Perinatal Outcomes. JAMA. 2022, 327(20):1983-1991. Available from: https://jamanetwork.com/journals/jama/fullarticle/2792031
14. Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. Gene Rep. 2020, 19(100682):1-6. https://doi.org/10.1016/j.genrep.2020.100682
15. Snijder EJ, Limpens RWAL, de Wilde AH, de Jong AWN, Zevenhoven-Dobbe JC, Maier HJ, et al. A unifying structural and functional model of the coronavirus replication organelle: tracking down RNA synthesis. PLoS Biol. 2020, 18 (e3000715):1-25. Available from: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000715
16. Wolff G, Limpens RWAL, Laugks JCZD, Zheng S, De Jong AWM, Koning RI, et al. A molecular pore spans the double membrane of the coronavirus replication organelle. Science. 2020, 369:1395-1398. Available from: https://www.science.org/doi/10.1126/science.abd3629
17. Goldsmith CS, Tatti KM, Ksiazek TG, Rollin PE, Comer JA, Lee WW, et al. Ultrastructural characterization of SARS coronavirus. Emerg Infect Dis. 2004, 10 (2):320-326. Available from: https://stacks.cdc.gov/view/cdc/7769
18. Stertz S, Reichelt M, Spiegel M, Kuri T, Martínez-Sobrido L, García-Sastre A, et al. The intracellular sites of early replication and budding of SARS-coronavirus. Virology. 2007, 361:304-315. Available from: https://www.sciencedirect.com/science/article/pii/S0042682206008762
19. Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell. 2020, 78:779-784 https://doi.org/10.1016/j.molcel.2020.04.022. Available from: https://www.sciencedirect.com/science/article/pii/S1097276520302641
20. Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S, et al. A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol. 2011, 174:11-22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4486061/
21. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J. 2019, 16(69):1-22. Available from: https://virologyj.biomedcentral.com/articles/10.1186/s12985-019-1182-0
22. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol. 2022, 23:3-20. Available from: https://www.nature.com/articles/s41580-021-00418-x
23. Jiao, J. Under the epidemic situation of COVID-19, should special attention to pregnant women be given?. J Med Virol. 2020, 92:1371-1372. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25771
24. Nurdianto AR, Aryati, Suryokusumo MG, Mufasirin, Suwanti LT, Sunarjo, et al. Effect of Hyperbaric Oxygen Therapy on ICAM-1 Expression in artery spiralis of pregnant Rattus norvegicus infected by tachyzoite from Toxoplasma gondii. Eurasia J Biosci. 2020, 14(1):1757-1762. Available from: http://www.ejobios.org/download/effect-of-hyperbaric-oxygen-therapy-on-icam-1-expression-in-artery-spiralis-of-pregnant-rattus-7696.pdf
25. Martins-Filho PR, Tanajura DM, Santos HP, Santos VS. COVID-19 during pregnancy: Potential risk for neurodevelopmental disorders in neonates?. Eur J Obstet Gynecol Reprod Biol. 2020, 250:255-256. Available from: https://www.ejog.org/article/S0301-2115(20)30264-5/pdf
26. Khan MDSI, Nabeka H, Akbar SMF, Mahtab MA, Shimokawa T, Islam F, et al. Risk of congenital birth defects during COVID-19 pandemic: Draw attention to the physicians and policymakers. J Glob Health. 2020, 10(2):020378. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7690649/pdf/jogh-10-020378.pdf
27. Nonweiler J, Rattray F, Baulcomb J, Happé F, Absoud M. Prevalence and associated factors of emotional and behavioural dificulties during COVID-19 pandemic in children with neurodevelopmental disorders. Children. 2020,

7(128):1-4. Available from: https://www.mdpi.com/2227-9067/7/9/128
28. Yuliana LW. Clinical Characteristic of Pregnancy with Coronavirus Disease (COVID-19). J Ilm Kesehat Sandi Husada. 2020, 12(2):726-734. Available from: https://akper-sandikarsa.e-journal.id/JIKSH/article/view/397
29. Rohmah MK, Nurdianto AR. Corona Virus Disease 2019 (COVID-19) pada wanita hamil dan bayi: Sebuah Tinjauan Literatur. Medica Hospitalia: J Clin Med. 2019, *7*(1A):329-336. Available from: http://medicahospitalia.rskariadi.co.id/medicahospitalia/index.php/mh/article/view/476
30. Brandt JS, Hill J, Reddy A, Schuster M, Patrick HS, Rosen T, et al. Epidemiology of coronavirus disease 2019 in pregnancy: risk factors and associations with adverse maternal and neonatal outcomes. Am J Obstet Gynecol. 2020, XX:1.e1-1.e9. Available from: https://www.em-consulte.com/article/1397112/epidemiology-of-coronavirus-disease-2019-in-pregna
31. Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, et al. Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. N Engl J Med. 2020, 382 (25):E100(1)-E100(3). Available from: https://www.nejm.org/doi/full/10.1056/nejmc2009226
32. Ryan GA, Purandare NC, McAuliffe FM, Hod M, Purandare CN. Clinical update on COVID-19 in pregnancy: A review article. J Obstet Gynaecol Res. 2020, 46 (8):1235-1245. Available from: https://obgyn.onlinelibrary.wiley.com/toc/14470756/2020/46/8
33. Wu X, Sun R, Chen J, Xie Y, Zhang S, Wang X. Radiological findings and clinical characteristics of pregnant women with COVID-19 pneumonia. Int J Gynecol Obstet. 2020, 150:58-63. Available from: https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.13165
34. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020, S0002-9378(20):30343-30344. Available from: https://www.binasss.sa.cr/gine/2.pdf
35. 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, 20:559-564. Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30176-6/fulltext
36. Ferrazzi E, Frigerio L, Savasi V, Vergani P, Prefumo F, Barresi S., et al. Vaginal delivery in SARS-CoV-2 infected pregnant women in Northern Italy: a retrospective analysis. BJOG. 2020, 127(9):1116-1121. Available from: https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.16278
37. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records. Lancet. 2020, 395 (10226):809-815. Available from: https://pubmed.ncbi.nlm.nih.gov/32151335/
38. Ashokka B, Loh M-H, Tan CH, Su LL, Young BE, Lye DC., et al. Care of the pregnant woman with COVID-19 in labor and delivery: anesthesia, emergency cesarean delivery, differential diagnosis in the acutely ill parturient, care of the newborn, and protection of the healthcare personnel. Am J Obstet Gynecol. 2020, 223(1):66-74.e3. Available from: https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/es/covidwho-380384
39. Liu H, Liu F, Li J, Zhang T, Wang D, Lan W. Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children. J Infect. 2020, 80 (5):e7-e13. Available from: https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/en/covidwho-7063
40. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynaecol Obstet. 2020. 150(1):47-52. Available from: https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.13182
41. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020,38:1504-1507. Available from: https://www.sciencedirect.com/science/article/pii/S0735675720302771?ref=cra_js_challenge&fr=RR-1
42. Mercedes BR, Serwat A, Naffaa L, Ramirez N, Khalid F, Steward SB, et al. New-onset myocardial injury in pregnant patients with coronavirus disease 2019: a case series of 15 patients. Am J Obstet Gynecol. 2020, XX:1.e1-1.e9. Available from: https://www.ajog.org/action/showPdf?pii=S0002-9378%2820%2931206-0
43. Martinelli I, Ferrazzi E, Ciavarella A, Erra R, Iurlaro E, Ossola M, et al. Pulmonary embolism in a young pregnant woman with COVID-19. Thromb Res. 2020, 191:36-37. Available from: https://www.thrombosisresearch.com/article/S0049-3848(20)30138-9/fulltext
44. Siregar RN, Aritonang J, Anita S. Pemahaman Ibu Hamil Tentang Upaya Pencegahan Infeksi Covid-19 Selama Kehamilan. J Healthc Technol Med. 2020, 6(2):798-805. Available from: https://jurnal.uui.ac.id/index.php/JHTM/article/view/986
45. Saputra, D. Fenomena Informasi Palsu (Hoax) Pada Media Sosial di Tengah Pandemi Covid-19 dalam Perspektif Islam Devid Saputra. Jurnal Dakwah dan Ilmu Komunikasi, 2020, *2*(1), 1-10. Available from: http://journal.iaiagussalimmetro.ac.id/index.php/mauidhohhasanah/article/view/69/40
46. Arkeman H, Kartini K, Widyatama HG. Penyuluhan Dengan Metode Ceramah dan Media Digital Untuk Meningkatkan Pengetahuan Tentang Demam Berdarah. JUARA: Jurnal Wahana Abdimas Sejahtera. 2020, 1(2):109-121. Available from: http://dx.doi.org/10.25105/juara.v1i2.5636
47. Guyansyah A. (2020). Penyuluhan Dengan Metode Ceramah Untuk Meningkatkan Pengetahuan Kesehatan Reproduksi Pada Masa Menopause. JUARA: Jurnal Wahana Abdimas Sejahtera. 2020, 1(2):130-136. Available from: https://trijurnal.trisakti.ac.id/index.php/juara/article/view/5680
48. Goh XL, Low YF, Ng CH, Amin Z, Ng YPM. Incidence of SARS-CoV-2 vertical transmission: a meta-analysis. Arch Dis Child-Fetal. 2020, 106(1):112-113. Available from: https://fn.bmj.com/content/106/1/112
49. Fornari, F. Vertical transmission of COVID-19-A systematic review. J Pediatr Perinatol Child Health. 2020, 4(2):7-13. Available from: https://www.fortunejournals.com/articles/vertical-transmission-of-covid19a-systematic-review.pdf
50. 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. AJOG. 2021, 224(1):35-53.e3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7392880/pdf/main.pdf
51. Bwire GM, Njiro BJ, Mwakawanga DL, Sabas D, Sunguya BF. Possible vertical transmission and antibodies against SARS-CoV-2 among infants born to mothers with COVID-19: a living systematic review. J Med Virol. 2021, 93(3):1361-1369. Available from: https://europepmc.org/article/med/33090535
52. Facchetti F, Bugatti M, Drera E, Tripodo C, Sartori E, Cancila V, et al. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of Placenta. Ebio Med. 2020, 59(102951):1-8. Available from: https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/fr/covidwho-716659
53. Pique-Regi R, Romero R, Tarca AL, Luca F, Xu Y, Alazizi A., et al. Does the human placenta express the canonical cell entry mediators for SARS-CoV-2? Elife. 2020, 9(e58716):1-15. Available from: https://elifesciences.org/articles/58716
54. Yang P, Wang X, Liu P, Wei C, He B, Zheng J, et al. Clinical characteristics and risk assessment of newborns born to mothers with Covid-19. J Clin Virol. 2020, 127(104356):1-5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194834/
55. Hosier H, Farhadian SF, Morotti RA, Deshmukh U, Lu-Culligan A, Campbell KH, et al. SARS-CoV-2 infection of the placenta. J Clin Invest. 2020, 130:4947-4953. Available from: https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC7456249&blobtype=pdf
56. Penfield CA, Brubaker SG, Limaye MA, Lighter J, Ratner AJ, Thomas KM, et al. Detection of SARS-COV-2 in placental and fetal membrane samples. Am J Obstet Gynecol MFM. 2020, 2(3),100133:1-2. Available from: https://www.ajogmfm.org/action/showPdf?pii=S2589-9333%2820%2930076-8.
57. Yan Y, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 (COVID-19) in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020, 223(111):e1-e14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177142/pdf/main.pdf

58. Liu W, Wang J, Li W, Zhou Z, Liu S, Rong Z. Clinical characteristics of 19 neonates born to mothers with COVID-19. Front Med. 2020,14:193-198. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7152620/pdf/11684_2020_Article_772.pdf
59. Di Toro F, Gjoka M, Di Lorenzo G, De Santo D, De Seta F, Maso G, et al. Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. Clin Microbiol Infect. 2021, 27(1):36-46. Available from: https://moh-it.pure.elsevier.com/en/publications/impact-of-covid-19-on-maternal-and-neonatal-outcomes-a-systematic
60. Novoa RH, Quintana W, Llancarí P, Urbina-Quispe K, Guevara-Ríos E, Ventura W. Maternal clinical characteristics and perinatal outcomes among pregnant women with coronavirus disease 2019. A systematic review. Travel Med Infect Dis. 2021, 39(101919):1-13. Available from: https://europepmc.org/article/med/33220455
61. Celik O, Saglam A, Baysal B, Derwig IE, Celik N, Mehmet Ak, et al. Factors preventing materno-fetal transmission of SARS-CoV-2. Placenta. 2020, 97:1-5. Available from: https://www.sciencedirect.com/science/article/pii/S0143400420301533?via%3Dihub
62. Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. Stem Cell Rev Rep. 2020, 16(3):434-440. Available from: https://pubmed.ncbi.nlm.nih.gov/32307653/
63. Li Y, Zhang Z, Yang L, Lian X, Xie Y, Li S, et al. The MERS-CoV receptor DPP4 as a candidate binding target of the SARS-CoV-2 spike. iScience. 2020, 23(6)-101160:1-17. Available from: https://www.sciencedirect.com/science/article/pii/S258900422030345X
64. Dong L, Tian J, He S, Zhu C, Wang J, Chen Liu C. et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020, 323(18):1846-1848. Available from: https://jamanetwork.com/journals/jama/fullarticle/2763853
65. Mackenzie JS, Smith DW. COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and what we don't. Microbiol Aust. 2020, 41(1):45-50. Available from: https://www.publish.csiro.au/ma/ma20013
66. Peng Z, Zhang J, Shi Y, Yi M. Research progresses in vertical transmission of SARS-CoV-2 among infants born to mothers with COVID-19. Future Virol. 2022, 17(4):211-214. Available from: https://www.futuremedicine.com/action/showPublications?pubType=journal
67. Yanti E, Irman V, Harmawati. Optimalisasi kesehatan ibu hamil selama pandemi COVID-19. Jurnal Abdimas Saintika. 2020, 2(2):43-46. Available from: https://jurnal.syedzasaintika.ac.id
68. Tantona MD. Anxiety Disorders In Pregnant Women During Covid-19 Pandemic. Jurnal Penelitian Perawat Profesional. 2020, 2(4):381-392. Available from: http://jurnal.globalhealthsciencegroup.com/index.php/JPPP/article/view/181
69. Polónia-Valente R, Moucho M, Tavares M, Vilan A, Montenegro N, Rodrigues, T. Vaginal delivery in a woman infected with SARS-CoV-2–The first case reported in Portugal. Eur J Obstet Gynecol Reprod Biol. 2020, 250:253-254. Available from: https://www.ejog.org/article/S0301-2115(20)30258-X/fulltext
70. Padlilah R, Yulianti I, Purnamasari, A. Komplikasi SARS-COV, MERS, SARS-COV-2 dalam kehamilan: A review. Jurnal Kebidanan Indonesia. 2020, 11(2):55-60. Available from: https://jurnal.stikesmus.ac.id/index.php/JKebIn/article/view/373
71. Schoenmakers S, Snijder P, Verdijk RM, Kuiken T, Kamphuis SSM, Koopman LP, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Placental Infection and Inflammation Leading to Fetal Distress and Neonatal Multi-Organ Failure in an Asymptomatic Woman. JPIDS. 2021, 10:556-561. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7798999/pdf/piaa153.pdf.
72. Ng WF, Wong SF, Lam A, Mak YF, Yao H, Lee KC, et al. The placentas of patients with severe acute respiratory syndrome: a pathophysiological evaluation. Pathology. 2006, 38:210-218. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7131423/
73. Gao L, Ren J, Xu L, Ke X, Xiong L, Tian X, et al. Placental pathology of the third trimester pregnant women from COVID-19. Diagn Pathol. 2021, 16(8):1-11. Available from: https://diagnosticpathology.biomedcentral.com/track/pdf/10.1186/s13000-021-01067-6.pdf
74. Schwartz DA, Morotti D, Beigi B, Moshfegh F, Zafaranloo N, Patane L. Confirming vertical fetal infection with coronavirus disease 2019: neonatal and pathology criteria for early onset and transplacental transmission of severe acute respiratory syndrome coronavirus 2 from infected pregnant mothers. Arch Pathol Lab Med. 2020, 144:1451-1456. Available from: https://europepmc.org/article/med/32886737
75. Coyne CB, Lazear HM. Zika virus-reigniting the TORCH. Nat Rev Microbiol. 2016, 14: 707-715. Available from: https://www.nature.com/articles/nrmicro.2016.125.pdf
76. Schwartz DA. Viral infection, proliferation, and hyperplasia of hofbauer cells and absence of inflammation characterize the placental pathology of fetuses with congenital zika virus infection. Arch Gynecol Obstet. 2017;295:1361-1368. Available from: https://pubmed.ncbi.nlm.nih.gov/28396992/
77. Xiong X, Wei H, Zhang Z, Chang J, Ma X, Gao X, et al. Vaginal delivery report of a healthy neonate born to a convalescent mother with COVID-19. J Med Virol. 2020, 92(9):1657-1659. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.25857
78. Aslan MM, Yuvacı HU, Köse O, Toptan H, Akdemir N, Köroğlu M, et al. SARS-CoV-2 is not present in the vaginal fluid of pregnant women with COVID-19. J Matern-Fetal Neo Med. 2020, 16:1-3. Available from: https://www.tandfonline.com/doi/full/10.1080/14767058.2020.1793318
79. Sinaci S, Ocal DF, Seven B, Anuk AT, Besimoglu B, Keven MC, et al. Vertical transmission of SARS-CoV-2: a prospective cross-sectional study from a tertiary center. J Med Virol. 2021, 93(10):5864-5872. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.27128
80. Pawar P, Gavade V, Patil N, Mali V, Girwalkar A, Tarkasband V, et al. Neonatal multisystem inflammatory syndrome (MIS-N) associated with prenatal maternal SARS-CoV-2: a case series. Children. 2021, 8 (7), 572:1-15. Available from: https://www.mdpi.com/2227-9067/8/7/572
81. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020, 12(1), 8:1-5. Available from: https://www.nature.com/articles/s41368-020-0074-x
82. Dumitriu D, Emeruwa UN, Hanft E, Liao GV, Ludwig E, Walzer L, et al. Outcomes of neonates born to mothers with severe acute respiratory syndrome coronavirus 2 infection at a large medical center in New York city. JAMA Pediatr. 2021, 175(2):157-167. Available from: https://jamanetwork.com/journals/jamapediatrics/fullarticle/2771636