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Worse Impact of COVID-19 in Pregnant Women

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Abstract

The COVID-19 pandemic has raised concerns about the impact of the virus on pregnant women and their unborn babies. This review aims to provide a comprehensive summary of the outcome of COVID-19 in pregnancy

Studies have shown that the possibility of developing severe illness increased in pregnant women compared with non-pregnant women infected with COVID-19. They have higher rates of ICU admission, mechanical ventilation, and mortality. Additionally, the risk of preterm birth has been increased in pregnant women infected with COVID-19, with several research reporting higher rates of preterm delivery among infected pregnant women.

Cesarean section delivery rates are also higher among pregnant women with COVID-19, possibly due to the need for expedited delivery in cases of severe illness or fetal distress. However, the transmission of the virus from mother to fetus is rare during pregnancy or delivery. The virus is transmitted vertically from mother to fetus, with most infants born to mothers with COVID-19 testing negative for the virus.

While vertical transmission is rare, there is evidence suggesting a potential impact of COVID-19 on fetal development. Some studies have reported cases of fetal growth restriction and abnormal placental findings in pregnant women with COVID-19. However, further research is needed to fully understand the long-term consequences.

Abbreviations: WHO: World Health Organization, SARS: Severe Acute Respiratory Syndrome, MERS: Middle Eastern Respiratory Syndrome, FIGO: International Federation of Gynecology and Obstetrics, ACE2: angiotensin-converting enzyme 2, TMPRSS2: primes the S protein using transmembrane serine protease 2, NK: natural killer, PDCs: plasmacytoid dendritic cells, TLRs: Toll-like receptors, DIC: disseminated vascular coagulopathy, CMV: Cytomegalovirus, HSV: herpes simplex virus, VZV: varicella-zoster virus, ZIKV: zika virus.

Conflict of Interest

The author declared that they have no conflict of interest.

تأثير فيروس كوفيد-١٩ على النساء الحوامل

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الملخص

أثارت جائحة كوفيد-١٩ مخاوف حول تأثير الفيروس على النساء الحوامل واجنتهم الذين لم يولدوا بعد. يهدف هذا المراجعة إلى تقديم ملخص شامل لنتائج كوفيد-١٩ في الحمل.

أظهرت الدراسات أن النساء الحوامل المصابات بكوفيد-١٩ يتعرضن لمخاطر أكبر للإصابة بالمرض مقارنةً بالنساء غير الحوامل. لديهن معدلات أعلى للإدخال إلى وحدة العناية المركزة واستخدام اجهزة التنفس ومعدلات الوفيات. بالإضافة إلى ذلك، ارتبطت إصابة كوفيد-١٩ أثناء الحمل بزيادة خطر الولادة المبكرة، حيث أبلغت العديد من الدراسات عن معدلات أعلى للولادة المبكرة بين النساء الحوامل المصابات.

تعد معدلات الولادة القيصرية أيضًا أعلى بين النساء الحوامل المصابات بكوفيد-١٩، ربما بسبب الحاجة إلى إجراء ولادة سريعة في حالات المرض الشديد أو الضيق الجنيني. ومع ذلك، فإن انتقال الفيروس عموديًا من الأم إلى الجنين خلال الحمل أو الولادة نادر، حيث يظهر معظم الأطفال الذين يولدون من أمهات مصابات بكوفيد-١٩ سلبية الاختبار للفيروس.

على الرغم من ندرة انتقال الفيروس عموديًا، هناك أدلة تشير إلى وجود تأثير محتمل لكوفيد-١٩ على تطور الجنين. أفادت بعض الدراسات بحالات تقزم الجنين واضطرابات غير طبيعية في المشيمة لدى النساء الحوامل المصابات بكوفيد-١٩. ومع ذلك، يتطلب الأمر إجراء المزيد من البحوث لفهم العواقب على المدى الطويل بشكل كامل.

في الختام، تشكل إصابة كوفيد-١٩ أثناء الحمل مخاطر كبيرة، بما في ذلك المرض الشديد والولادة المبكرة وزيادة معدلات الولادة القيصرية. على الرغم من ندرة انتقال الفيروس عموديًا، هناك أدلة على وجود تأثير محتمل على تطور الجنين. يتطلب استمرار البحث والمراقبة لفهم تأثير الفيروس.

1. Introduction

The World Health Organization reported that coronavirus was responsible for the coronavirus illness 2019 (COVID-19) in December 2019, which has spread rapidly around the world, and causes severe acute respiratory syndrome coronaviruse2 (SARS-Cov-2). The WHO proclaimed the outbreak to be a pandemic on March 12, 2020. As the COVID-19 pandemic spread, pregnant women were identified as a vulnerable group and advised to take extra precautions. (Lai *et al.*, 2020) Pregnant women are more likely to experience complications and serious illness when infected with other coronaviruses, such as SARS and MERS. The (FIGO) advised eliminating much regular antenatal care and whenever possible, substituting video or phone consultations to reduce the risk of transmission to both pregnant patients and medical workers. (Chen *et al.*, 2020)

1. Pregnancy-Related Physiological Changes and Their Impact on COVID-19

1.1 Biochemical Mechanism

COVID-19 is caused by an RNA virus with a capsule–like capsule–like structure. Like other viral infections, the immune system's ability to fight COVID-19 is reliant on resilience.

A COVID-19 infection can cause a major sickness with a high risk of mortality or a minor illness that is successfully cured by the immune system. Unknown is where exactly pregnant women fall on this spectrum. (Wu and McGoogan, 2020) Pregnancy-related immune responses to infections shift as a result of the immune system's adaptation to the growing fetus. Understanding COVID-19 pathophysiology and molecular mechanisms and researching them in the context of the altered maternal immune response is crucial to understanding the COVID-19 phenotype throughout pregnancy. SARS-CoV-2 enters the body through the nasal cavity, infects pulmonary cells utilizing the angiotensin-converting enzyme 2 (ACE2) and the SARS-CoV receptor, and primes the S protein with transmembrane serine protease 2 (TMPRSS2). It spreads via close human contact, direct contact with insects, and respiratory droplets, and may be produced aerosols. (Hoffmann *et al.*, 2020)

Pregnancy-related changes to the immune system may influence how the body reacts to infections, particularly viruses. According to the alternative idea, a shift in the thCD+4 T cell population toward the Th2 phenotype rather than the Th1 phenotype – a response that prioritizes humoral over cellular immunological responses is responsible for at least some of the inflammatory response to viruses during pregnancy. (Piccinni and Romagnani, 1996) The body's natural killer (NK) cell count declines during pregnancy. Given that viruses are necessary for this process, it may make it more difficult for the innate immune system to get rid of viruses. (Brandstadter and Yang, 2011) A decline in the quantity of plasmacytoid dendritic cells (pDCs), which are essential for producing type 1 interferon, a virus-fighting protein, in the blood. The steroid hormone progesterone has the power to affect the immune system. ((Reizis, 2019), (Druckmann and Druckmann, 2005)) High progesterone levels during pregnancy may help with recovering from viral lung infections because they can enhance lung health. The pattern-recognition Toll-like receptors (TLRs), in particular, are altered by pregnancy in the innate immune system. (Amirchaghmaghi *et al.*, 2013)

1.2. A breathing Reaction

In addition to the systemic immunological changes brought on by pregnancy, the respiratory system exhibits structural changes that may impair lung function. The gravid uterus causes physiological alterations in the diaphragmatic splinting curvature, which affects respiratory function. Despite an increase in the tidal volume of 30-40%, end–expiratory volumes, early pregnancy residual volumes, and functional residual capacity are all decreased by the chest volume reduction. Because their ability to expel secretion is more difficult and their lung capacity is decreased overall, pregnant women may be more vulnerable to severe respiratory infections (Rajewska *et al.*, 2020)

1.3 Inflammation and Thrombosis

According to research including 184 critically sick patients (24% female), COVID-19 is linked to greater risks of thromboembolic events in the general population. 31 percent of them experienced thrombotic events. This is a result of active coagulation pathways, which can eventually lead to diffused vascular coagulopathy (DIC) and fibrinolysis, both of which result in dynamic hypercoagulation and thrombocytopenia. (Rajewska *et al.*, 2020) Excessive bleeding occurs during pregnancy. A deadly thromboembolic event is more likely to occur in pregnant women. Therefore, thrombosis risk factors for pregnant women who carry the COVID-19 virus may be combined or synergistic. A case report of a woman with COVID-19 dying at 29 weeks gestation as a result of a major basilar artery embolism and pulmonary embolism lends support to this theory. (Di Renzo and Giardina, 2020)

2. Placental Responses to SARS-CoV-2

The placenta typically serves as a robust barrier to stop the vertical transmission of maternal diseases to the fetus. It is common knowledge that some diseases can pass through this barrier and cause serious harm to the growing embryo. Each of the syndrome-causing congenital viruses (ZIKV), (VZV), (HSV), and (CMV)—has a distinct rate of transmission and degree of severity that changes depending on when an infection first appears during pregnancy. (Burton and Jauniaux, 2015)

The chorionic villi in the human placenta is in direct contact with the mother's blood because the human placenta is hemochorial. Specifically designed cells called trophoblasts, which are formed from fetal tissue, make up the majority of the placenta. Terminally developed, multinuclear syncytiotrophoblast cells. Syncytiotrophoblasts are produced by progenitor villous cytotrophoblast cells. Extravillous trophoblast cells that enter the uterus and alter its vasculature link the chorionic villi to it. (Brett *et al.*, 2014)

Several case reports have looked into the placentas of women infected with the COVID-19 virus. SARS-CoV-2 expression has been found in mid-trimester placenta samples, but it is unclear whether this was due to a primary infection or because placental damage from other illnesses made the virus more contagious. SARS-CoV-2, which was identified on RT-PCR of swabs and biopsies following spontaneous fetal mortality at 19 weeks of gestation. In samples of the placenta and umbilical cord obtained after a pregnancy that was aborted at 22 weeks gestation, SARS-CoV-2 was also shown to be strongly expressed. (Whittaker *et al.*, 2020)

Severe maternal hypertension, thrombocytopenia, Placental abruption, and coagulopathy all contributed to the pregnancy's termination. Virus-like particles appeared to be present in the cytoplasm of the placental cells. Placental histology revealed macrophage infiltrates and fibrin deposits, which the authors believed were most likely related to a viral infection. ((Vivanti *et al.*, 2020), (Baud *et al.*, 2020))

3. SARS-CoV-2 Vertical Transmission

It's not always the case that diseases or injury to the fetus result from viral infections of the placental cells. The findings of infant SARSCoV2 tests have been reported in 15 studies thus far, with positive results being infrequent. Even in the presence of SARS-CoV2, severe newborn respiratory infections seem to be uncommon. Based on PCR results from SARSCOV-2 testing it is unclear if the infection occur in utero, during labor or delivery, or whether transmission occur from the infected mother or asymptomatic hospital staff in the first days following birth. (Ferrazzi *et al.*, 2020), (Khan *et al.*, 2020)).

However, additional proof that vertical transmission might be a possibility has been presented through antibody testing. Some infants delivered to moms who have COVID-19 have greater IgM and IgG levels for SARS-CoV-2. IgM, which has a higher molecular weight, cannot passively transmit from mother to fetus during pregnancy. Even though at birth, all of the infants in reports so far have been asymptomatic and tested negative for SARS-CoV-2 viral RNA. The finding of circulating SARS-CoV-2 IgM in the newborn indicates vertical transmission of the virus. We still don't know how viruses get into the placenta. (Zeng *et al.*, 2020)

When SARS-CoV-2 enters lung cells via the ACE2 receptor, the serine protease TMPRSS2 is thought to be responsible for cleaving the spike glycoprotein to allow fusion. To ascertain whether ACE2 +/TMPRSS2 expression is found in placental cells, single-cell RNA sequencing data analysis was incorporated into three experiments. (Choudhary *et al.*, 2021) Combined data from an earlier investigation employing samples of two-term placentas with secondary analysis of single-cell transcriptase profiles from decidua and placenta samples at 6–12 weeks of gestation that were openly accessible. The ACE2 gene was discovered to be expressed in decidua stromal, perivascular, cell of syncytiotrophoblast and villous cytotrophoblast types were seen in samples taken during the first trimester and term however the expression of ACE2 was commonly shown to be very low in placental and decide cell types in a 2nd investigation that used the same first trimester date set. ((M. Li *et al.*, 2020), (Pique-Regi *et al.*, 2020))

SARS-CoV-2 most likely accesses the tissues of the placenta through a separate pathway because ACE2 and TMPRSS2 are not expressed in the placenta. Other proteases have been linked to this as well. The placenta's high levels of DPP4 and CD147 expression during gestation may have a role in cell entrance. (Jaimes, Millet and Whittaker, 2020). To stop cell invasion, tranexamic acid is a possible therapeutic target for plasmin, which may also leave this site. RNA from the severe acute respiratory syndrome coronavirus2 was found in a sample of amniotic fluid in circumstances where there have been reports of significant maternal infections, even though neonatal positive following birth has been infrequent. (Zamaniyan *et al.*, 2020)

4. The Effect of COVID-19 on Pregnancy

4.1. Early Pregnancy and SARS-CoV-2

There is little information about COVID-19's potential effects in the early stages of pregnancy (up to 12 weeks gestation). Pregnant women who had previously contracted SARS-CoV-2 did not vary from those who had not in terms of the thickness of the nuchal translucency at the first-trimester scan. Additionally, miscarriage rates among women who received SARS-CoV-2 in the first trimester have not increased. (la Cour Freiesleben *et al.*, 2021)

4.2. SARS-CoV-2 and Late Pregnancy

Based on the impact of other viruses, COVID-19 infection in late pregnancy (more than 24 weeks gestation) is likely to result in the following symptoms. The less favorable pregnancy outcomes include reduced fetal growth, premature birth, and perinatal mortality. (Dorélien, 2019) Pregnant women do not have a larger risk of developing severe COVID-19 than the general population, according to the bulk of studies done so far. The requirement for artificial respiration and the chance of hospitalization were both markedly raised by pregnancy. (Govind *et al.*, 2020) Because hospital and critical care unit admission and breathing requirements are not defined, it is difficult to apply the research's findings to a larger population. Given that there was no rise in mortality, it is also possible that these results are a reflection of the healthcare system rather than the clinical condition of the women. (Blitz *et al.*, 2020) The same risk factors that affect the general population apply to COVID-19 disease, such as being overweight or obese, having concomitant conditions like diabetes, asthma, or hypertension, and belonging to a racial or ethnic minority. (Knight *et al.*, 2021)

4.3. Postpartum and SARS-CoV-2

4.3.1 Newborns' Results

Neonates born to SARS-CoV2-positive women have not shown any substantial negative effects in the great majority of research that reports on neonatal outcomes. There were differences in the frequency of poor neonatal outcomes among pregnant women with established COVID-19 disease and sick pregnant women not infected with SARA-CoV-2 only three investigations found incidences of SARSCoV-2 positivity after 13 research studies screened newborns for the virus. Newborn SARS-CoV-2 carriers frequently had minimal or transitory symptoms. Three studies found evidence of newborn fatalities. Two of them still had no identified cause. (N. Li *et al.*, 2020) However, no study that revealed higher-than-average preterm birth rates included a denominator group for comparison. Various variables contributed to the premature birth, all of which were iatrogenic due to the mother's deteriorating health. Even though the origin of the COVID-19 pandemic is uncertain, Denmark and Ireland's observational results show that level rates of population preterm birth have dramatically decreased over this time. It is not yet known if COVID-19 infection acts as a sole risk factor for preterm birth. ((Ferrazzi *et al.*, 2020), (Marín Gabriel *et al.*, 2020))

4.3.2. Breastfeeding

SARS-CoV-2 was discovered in breast milk four times in one case investigation. Nine mothers' breast milk samples were evaluated in a different trial, but none of the samples tested positive for the SARS-CoV-2 virus. Current recommendations urge moms to nurse their babies during the postpartum period and even if they test positive during childbirth. (Groß *et al.*, 2020)

Women who have COVID-19 should regularly wash their hands and follow basic hygiene precautions, such as using a surgical mask during feeding if one is available. The advantages of nursing may outweigh any potential transmission risk because newborn diseases are frequently mild and asymptomatic. (Vassilopoulou *et al.*, 2021)

5. Conclusion

It is difficult to say for sure whether pregnant women are more prone to have severe COVID-19 effects based on the available evidence. Most women will only experience mild, transient, or asymptomatic sickness. It seems remarkable that most babies appear to be unaffected by vertical transmission. There are still many questions that need to be answered, including whether COVID-19 is a risk factor for preterm birth on its own, whether infection during pregnancy is almost certain to have long-term negative effects on the fetus, and whether these effects vary depending on gestational age at the time of infection.COVID-19 infection during pregnancy poses significant risks, including severe illness, preterm birth, and increased cesarean section rates. Although vertical transmission is rare, there is a need for continued monitoring and research to better understand the impact of the virus on fetal development and long-term outcomes.

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