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Review

Adverse Pregnancy Outcomes (Maternal, Fetal, and Neonatal) in COVID-19: A Review

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Abstract

Pregnant women represent a vulnerable population due to their altered immune response, potentially leading to increased susceptibility and severity of infections. The COVID-19 infection might increase the risk of adverse pregnancy outcomes in this population, however, to date, it has not been established whether SARS-CoV-2 infection leads to these outcomes as differing conclusions have been made by the published studies and reviews. This comprehensive review explores the impact of COVID-19 on pregnancy outcomes, encompassing maternal, fetal, and neonatal health. The current literature reports higher rates of adverse maternal outcomes among pregnant women with COVID-19, this includes increased rates of cesarean section, preeclampsia, and elevated risk of intensive care unit (ICU) admission and maternal death. Fetal and neonatal outcomes are also influenced by COVID-19 infection during pregnancy. Findings suggest an elevated risk of preterm birth, low birth weight, stillbirth, and Neonatal ICU admissions among newborns of mothers with COVID-19. The emergence of SARS-CoV-2 variants, such as the Delta variant, raises concerns about their potential impact on more adverse outcomes compared to the wild type. Vaccination has demonstrated safety and efficacy in pregnant women, providing a potential preventive measure against COVID-19. However, the potential impact of vaccination on adverse pregnancy outcomes requires further investigation. To address current knowledge gaps, future research should also focus on long-term effects, fertility considerations, child development, and the impact of emerging variants.

1. Introduction

The Coronavirus disease-19 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had significant implications for global health, with millions of people affected worldwide [1]. The virus responsible is a member of the Coronaviridae family, characterized by the presence of spike-like structures resembling crowns on their external surfaces [2].

The majority of individuals suffering from COVID-19 may experience either no symptoms or mild ones, such as a slight fever and dry cough [3,4]. However, in severe instances, particularly among older individuals, those with high blood pressure, or diabetes, the SARS-CoV-2 virus can lead to the development of acute respiratory distress syndrome (ARDS) [5]. While COVID-19 is commonly described as a respiratory infection, aggregated data indicates that it is a systemic disease affecting multiple parts of the body, such as the nervous, digestive, immune, and circulatory systems. The diverse array of symptoms observed could be attributed to the abundant and widespread occurrence of angiotensin-converting enzyme 2 (ACE2) in different organs [6].

Pregnant women represent a particularly vulnerable population, as their immune response to infections may be altered, potentially leading to increased susceptibility and severity of infectious diseases [7]. Research on past outbreaks of human coronaviruses, specifically SARS-CoV and the Middle East respiratory syndrome coronavirus, suggests that both pregnant women and their unborn children are prone to these viral infections [8]. Furthermore, COVID-19 during pregnancy might also increase the risk of adverse pregnancy outcomes, such as preterm birth and stillbirth. Therefore, understanding the impact of COVID-19 on pregnancy is of paramount importance as knowledge of these effects will guide the management of COVID-19 in pregnant women, ultimately improving the outcomes. The data to date, however, do not conclusively establish whether SARS-CoV-2 infection leads to these outcomes as differing conclusions have been made by the published studies and reviews [9].

This review aims to summarize the current literature on adverse maternal, fetal, and neonatal outcomes associated with COVID-19. While selecting the articles for this review, Kscien's list has been considered to avoid the inclusion of papers that have been published in predatory journals [10].

2. Clinical Characteristics of Pregnant COVID-19 Patients

The symptomatic findings of pregnant women with COVID-19 seem to closely resemble those seen in women who are not pregnant [11]. According to a recent meta-analysis, one-third of pregnant women with COVID-19 were asymptomatic, and when symptoms were present, they most frequently included high fever, chills or shivers, fatigue or tiredness or muscle pain, cough, difficulty breathing or shortness of breath, chest pain or tightness, mucus production, nasal congestion or runny nose, diarrhea, headache, and sore throat [12]. Their findings were in agreement with results reported in earlier systematic reviews focused on pregnant women [13-16].

Previous studies have not found that, compared to the general population, pregnant women are more likely to contract COVID-19 [17-19]. However, a particular study reported that the rate of SARS-CoV-2 infection in pregnant women was 3.02 times higher than in the broader population [20]. The progression of the illness appears to be more severe in pregnant women. Despite the fact that over 90% of pregnant women with COVID-19 recover without major health complications, the disease makes pregnant women actually more susceptible to requiring ventilator support and intensive care unit (ICU) admission, and face a higher risk of maternal mortality [12,21,22].

Furthermore, some studies suggest that pregnant women infected with new strains of SARS-CoV-2 experience a more severe disease progression [23,24]. A study conducted in Turkey that compared pregnant groups before and after the emergence of these new variants reported a significant escalation in serious and critical cases, pregnancy complications, respiratory support requirements, and ICU admissions within the group exposed to the newer variant [25].

3. Pathophysiology of COVID-19 in Pregnancy

SARS-CoV-2 infection in pregnant women may involve several mechanisms that could contribute to adverse pregnancy outcomes. The virus primarily targets the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in various tissues, including the placenta [26]. This receptor mediates the entry of the virus into host cells, enabling viral replication and dissemination [6].

The immune response to SARS-CoV-2 infection in pregnancy is complex and may play a critical role in determining the course of the disease and the risk of adverse outcomes. Pregnancy is characterized by a shift in the maternal immune system to accommodate the developing fetus, with a fine balance between pro-inflammatory (Th1-type cytokines, including IFN-c, IL-1a, IL-1b, IL-6, and IL-12) and anti-inflammatory (Th2-type cytokines, such as IL-4, IL-10, IL-13, and TGF-b) responses. Inflammation-induced by COVID-19 may disrupt this balance, leading to a heightened immune response and potentially contributing to complications such as preterm labor and preeclampsia [27].

During pregnancy, a woman's body experiences significant immunosuppression along with several anatomical, physiological, and biochemical changes like increased oxygen consumption, elevated heart rate, and an upward shift of the diaphragm due to the expanding uterus [22,28,29]. When a pregnant woman is infected with a virus, particularly respiratory viruses, these immune alterations could hinder the body's ability to clear pathogens. Other changes might also exacerbate the clinical consequences and intensify the severity of the infection, especially during the third trimester [29-31]. Pregnancy-induced changes in the respiratory tract, brought about by increased levels of estrogen, progesterone, and other hormonal

fluctuations, coupled with limited lung expansion, could make expectant mothers more vulnerable to respiratory infections. If these infections occur, they may take a severe path. As a result, a severe maternal illness may compromise oxygen delivery to the fetus, resulting in intrauterine growth restriction or stillbirth [32]. Pregnancy also features a pro-inflammatory state, notably during early and late gestation, potentially escalating the risk of SARS-CoV-2-induced cytokine storms, which can trigger excessive inflammation [22]. This could have harmful effects on both the mother and the fetus.

In previous SARS patients, there was a sustained activation of the Th1 response, leading to an elevation in the pro-inflammatory cytokines for more than 14 days from disease onset, resulting in extensive lung damage [33]. Moreover, research on animal models indicates that elevated circulating pro-inflammatory cytokines in the mother's blood stream can potentially induce preterm labor or cause miscarriage [34], which aligns with studies on adverse maternal and perinatal outcomes during SARS in pregnancy.

Interestingly, in COVID-19, comparable levels and durations of both Th1 and Th2 responses are observed. This includes the presence of both IFN-c, IL-1b (pro-inflammatory), and IL-4, IL-10 (anti-inflammatory), with IL-6 being a critical pro-inflammatory cytokine. A rise in its blood levels is linked to a higher mortality risk in COVID-19 patients [33]. Given the substantial impact of the inflammatory reaction in causing harm during a coronavirus infection, the cytokine pattern seen in COVID-19 could indicate a lower level of severity compared to SARS-CoV infection.

4. Possibility of Vertical Transmission

It has been estimated that a minimum of 40% of premature births are linked to infection or inflammation occurring inside the uterus. Prior investigations into different coronavirus infections, such as SARS and Middle East respiratory syndrome coronaviruses, have revealed the absence of vertical transmission in pregnant women [35]. However, the situation is a bit more controversial in SARS-CoV-2 infection.

The potential for SARS-CoV-2 to be vertically transmitted from a mother to her child comes through three multiple routes: 1) "In-utero" via the placenta during pregnancy, infecting the amniotic fluid, which then enters the fetus's airways, digestive tract, or ear canal, 2) "Intrapartum" during labor via contact with the mother's genital lining and its secretory products or other biological fluids (such as blood), and 3) "Ascending" where the virus ascends from the vagina to the uterus. The former two methods have been documented for SARS-CoV-2; however, the third, ascending infection, has not been documented to date [36].

Transmission of SARS-CoV-2 through breastfeeding has been largely ruled out, as the virus is rarely been observed in milk, and even when detected, the viral load is very low, and its ability to replicate has not been confirmed [37].

Previous research and some newer ones reported that there was no vertical transmission (mother-to-child transmission) of COVID-19 observed in their study and emphasized that precautionary measures should be implemented after childbirth [38,39]. However, this contrasts with some other studies that reported babies born with COVID-19 to mothers infected with the SARS-CoV-2 virus [36,40]. In a 2023 study of pregnant COVID-19 women by Alcover, about 88% of placentas were tested positive for SARS-CoV-2, and 60% of fetuses were tested positive for the virus [41].

Despite the possible occurrence of vertical transmission, it seems to happen only rarely. Even though recent studies have found the virus present in maternal milk and the placenta, the question of how this virus can be vertically transmitted during pregnancy remains a topic of ongoing research [42].

5. Current Evidence on COVID-19 and Adverse Pregnancy Outcomes

5.1. Maternal outcomes

5.1.1. Maternal morbidity and mortality in COVID-19

Several studies have reported higher rates of maternal morbidity and mortality among pregnant women with COVID-19 compared to non-infected pregnant women [21,43-45]. According to multiple studies [46-48], pregnant COVID-19 patients were nearly two times more likely to deliver via Caesarean section (50.8 to 57% of cases). This is significantly greater than the overall occurrence of Caesarean section (21%), as per data from the World Health Organization [47].

A systematic review and meta-analysis by Wang et al. noted a higher mortality rate among COVID-19 pregnant patients compared to their non-pregnant counterparts (0.90% vs 0.55%) [22]. According to Allotey et al., in comparison to expectant mothers not infected with COVID-19, those who had contracted the disease had a higher likelihood of maternal death (odds ratio = 6.09) and being admitted to the ICU (odds ratio = 5.41) [21]. A meta-analysis encompassing 20 studies of confirmed COVID-19 pregnant women indicated a maternal ICU admission rate of 7.0% and a death rate of 0.9% [49]. The worldwide maternal death ratio in 2015 was recorded at 216 deaths/100,000 live births, this is lower than the death rate found for COVID-19 pregnant women, suggesting that the higher death ratio could be tied to the COVID-19 disease [50].

Pregnancy, as a natural condition, has various impacts on the cardiovascular system. When pregnant women contract COVID-19, it can lead to additional disturbances in the cardiovascular system. Elevated levels of cardiac enzymes like pro-brain natriuretic peptide and cardiac troponin indicate the presence of myocardial inflammation and damage. Several studies have established a connection between myocardial inflammation, injury, severe disease progression, and increased mortality rates among infected individuals [22].

5.1.2. Other pregnancy-related maternal complications

Emerging evidence suggests that COVID-19 may be associated with an increased risk of preeclampsia that involves high blood pressure and damage to other organs, often the kidneys and liver, and usually occurs after 20 weeks of gestation. longitudinal

study involving 2184 pregnant women found that COVID-19 infection was strongly associated with an increased risk of preeclampsia, even after adjusting for potential confounders [51]. In a study by Wei et al., a strong association between SARS-CoV-2 infection during pregnancy and increased likelihood of preeclampsia was identified (with an odds ratio of 1.33) [52]. Another comprehensive meta-analysis evaluated raw or unadjusted odds ratios and found that the likelihood of experiencing preeclampsia was notably greater in pregnant women who had contracted the SARS-CoV-2 virus compared to those who had not. Specifically, 7.0% of pregnant women with SARS-CoV-2 infection developed preeclampsia, as opposed to only 4.8% in the non-infected group. This translates to a pooled odds ratio of 1.62, signifying that the odds of developing preeclampsia increase by 62% when a pregnant woman is infected with SARS-CoV-2 [53]. This underscores the critical importance of implementing preventative measures against COVID-19, particularly among expectant mothers.

The association between COVID-19 and preeclampsia may be mediated by several factors, including infection-induced inflammation, endothelial dysfunction, and activation of the renin-angiotensin system [52]. Further research is needed to confirm the association between COVID-19 and preeclampsia and to explore the underlying mechanisms.

In addition to the outcome discussed above, some studies have reported an increased risk of other complications, such as gestational diabetes, pregnancy-related cholestasis, postpartum hemorrhage, and placental abruption, among pregnant women with COVID-19 [46,54,55]. However, according to Wei et al., no significant connection was found between SARS-CoV-2 infection during pregnancy and the onset of gestational diabetes or the occurrence of postpartum hemorrhage [52]. Moreover, according to Ozbasli et al., COVID-19 during pregnancy did not affect any adverse pregnancy outcome [56].

Hence, as the evidence is limited and controversial, more research is needed to determine the exact association between COVID-19 and these outcomes and to identify the potential mechanisms involved.

5.2. Neonatal and fetal outcomes

Adverse Neonatal and fetal outcomes refer to a broad range of unfavorable events. The literature associates COVID-19 with several of these outcomes, such as; preterm birth (birth before 37 weeks of gestation), low birth weight (when the newborn is less than 2500 grams) and small for gestational age (a newborn with a weight that is less than the 10th percentile for their gestational age), miscarriage (death of a fetus before 20 weeks of gestation) and stillbirth (death of a fetus at or after 20 weeks of gestation), neonatal ICU admission (NICU), and neonatal death (death of a baby within the first 28 days of life) [57,58].

5.2.1. Preterm birth

Several studies have reported an increased risk of preterm birth among pregnant women with COVID-19 compared to those without the infection [21,59]. A meta-analysis of 42 studies, including over 400,000 pregnant women, found that COVID-19 infection was associated with a nearly three-fold increased risk of preterm birth [52]. The findings of another recent meta-analysis by Karaçam et al. showed that 18% of expectant mothers with COVID-19 experienced preterm labor [12]. This proportion is very similar to a study by Novoa et al., which reported 18.9% [46], and it is relatively higher compared to the studies done by Della Gatta et al. [13] and Elshafeey et al. [18], which recorded preterm labor rates of 12% and 15% respectively. On the other hand, the studies by De Rose et al. [17], Smith et al. [15], and Yang et al. [16] present even higher figures, reporting 34%, 64%, and 21% respectively. These percentages also exceed the rate observed in the broader population, which stands at 11% [12]. Given that preterm birth is closely linked to the risk of infant mortality, such data should be thoughtfully factored into the medical management and continuous monitoring of newborns exposed to COVID-19.

Potential mechanisms linking COVID-19 to preterm birth may include infection-induced inflammation, placental dysfunction, and direct damage to the fetal membranes. Furthermore, medical interventions, such as the decision to induce labor or perform a cesarean section due to maternal or fetal distress, may also contribute to the increased rate of preterm births among COVID-19-positive pregnant women [27,60,61].

5.2.2. Low birth weight and small for gestational age

Similar to preterm birth, low birth weight has been reported to be more common among COVID-19-infected patients. A meta-analysis by Karaçam et al. highlighted that approximately 19% of babies born to women diagnosed with COVID-19 had low birth weight [12]. This figure aligns well with a past study [17]. In contrast, other studies, like those by Elshafeey et al. [18] and Yang et al. [16], show less frequent occurrences of low birth weight, reporting rates of 8% and 5.3% respectively. Meanwhile, a higher rate of 43% was reported by Smith et al. [15]. Such variations may be linked to the prevalence of preterm labor in pregnant women affected by COVID-19.

Possible mechanisms linking COVID-19 to low birth weight include placental dysfunction, impaired oxygen and nutrient transport to the fetus, and infection-induced maternal or fetal stress [62]. Moreover, preterm birth, which is more common among COVID-19-positive women, is also a major risk factor for low birth weight [63].

Most research does not show a link between COVID-19 and fetal growth restriction or being small for gestational age. The global PANCOVID study found no notable link [64]. Similarly, the COVID-19 GRAVID study showed no meaningful difference in the size of newborns in the bottom 5th or 10th percentiles for gestational age born to COVID-19 infected mothers who caught the disease in their first or second trimester [65]. These findings are further supported by a meta-analysis by Smith and associates that saw no connection between SARS-CoV-2 and fetal growth restriction [66].

5.2.3. Miscarriage and stillbirth

The association between COVID-19 and miscarriage and stillbirth is less clear, as available data are limited and inconsistent. Some studies have calculated the miscarriage rate among pregnant women diagnosed with COVID-19 to align

with that of the general population [67]. However, in a study by Balachandren et al., pregnant women who were self-diagnosed as having COVID-19 in the first trimester had a higher risk of early miscarriage [68].

Some studies have reported an increased risk of stillbirth among pregnant women with COVID-19 [65,69], while some others have found no significant association [56]. A systematic review and meta-analysis of 10 studies reported a pooled stillbirth rate of 1.6% among COVID-19-positive pregnant women, which was higher than the pre-pandemic global rate of 1.4% [70]. In the meta-analysis of Wei et al., a significant connection between SARS-CoV-2 infection and increased likelihood of stillbirth was revealed (with an odds ratio of 2.11) [52]. Additionally, according to Allotey et al., the chance of stillbirth was elevated (odds ratio = 1.81) for infants born to women with COVID-19 compared to those born to women without the disease [21].

Potential mechanisms linking COVID-19 to miscarriage or stillbirth may include direct viral damage to the placenta, infection-induced inflammation, or complications related to severe maternal illness [67]. More research is needed to clarify the association between COVID-19 and miscarriage or stillbirth and to identify the underlying mechanisms involved.

5.2.4. NICU admission

Dileep et al. examined the relationship between the severity of COVID-19 infection during pregnancy and its impact on newborns, given that the virus can affect both the mother and the infant. Patients were categorized based on the intensity of their infection, ranging from mild to moderate. The majority, or 74% of the population studied, were multigravida (women who have been pregnant more than once). Women with severe infections were found to deliver babies with COVID-19, which necessitated admission to the NICU [71]. Additionally, according to Allotey et al., the chances of NICU admission were elevated (odds ratio = 2.18) for infants born to women with COVID-19 [21]. Reports indicate that infants born to vaccinated mothers have a lower frequency of being admitted to the intensive care unit compared to those born to mothers who have not been vaccinated [72].

5.2.5. Neonatal death

In a study by Smith et al. on 37 infants, one neonatal fatality was noted (2.7%) [15]. A similar observation was made by Yang et al. [16] and Zaigham and Andersson [14]. Elshafeey et al. in their systematic review, shared data from 256 newborns, indicating one neonatal death [18]. For COVID-19 women who were pregnant or had recently given birth, in total, there were 127 cases of neonatal deaths from 100 studies involving 23,698 neonates. When compared with women who had recently given birth and did not have the disease, newborns of pregnant women with COVID-19 were at an elevated risk of neonatal death (odds ratio = 2.35) [21]. However, according to a 2023 systematic review, only limited evidence was observed regarding an increased risk of neonatal morbidities and mortalities [73]. Hence, there is currently a scarcity of information on the health complications and death rates among neonates after maternal SARS-CoV-2 infection, especially from lower-income countries and cases involving infections early in pregnancy. There is a need for comprehensive, representative studies to investigate these outcomes.

6. The role of COVID-19 Variants in Adverse Pregnancy Outcomes

Emerging SARS-CoV-2 variants have raised concerns regarding their potential impact on pregnancy outcomes, as they may have mutations that can potentially influence crucial elements of the virus that contribute to its pathogenicity, such as the receptor-binding domain found in the spike protein. Some studies have suggested that specific variants, such as the Delta variant, may be associated with a higher risk of negative outcomes, including a higher rate of hospitalizations and ICU admissions, as well as increased morbidity and adverse outcomes such as preterm birth and pregnancy-related hypertension [74]. A study conducted by the University of Alabama at Birmingham (UAB) monitored rates of admission and neonatal and maternal outcomes of pregnant COVID-19 patients from March 2020 to August 2021, and found that serious morbidity and adverse outcomes were linked to the Delta variant [24]. Moreover, the emergence of the Delta variant has been associated with a surge in vaccine breakthrough infections in different parts of the U.S. There has been a notable increase in the number of pregnant women experiencing severe disease, with over a quarter of these women necessitating hospitalization due to the severity or critical nature of their illness caused by the Delta variant [75]. According to a study by Poisson et al., Stillbirth has a higher association with Alpha and delta variants compared to the wild type and the Omicron variant [76]. Similar findings were observed by Favre et al. [77].

7. Prevention and Management of COVID-19 During Pregnancy

Vaccination seems to be a highly effective method of safeguarding against the COVID-19 pandemic. Pregnant or breastfeeding women are eligible to receive COVID-19 vaccines that have been authorized by the U.S. Food and Drug Administration [12]. Several COVID-19 vaccines have demonstrated safety and efficacy in pregnant women [78,79]. Moreover, vaccination during pregnancy has been shown to provide some degree of passive immunity to the newborn, potentially reducing the risk of neonatal COVID-19 infection [80]. Despite vaccination being considered a prevention method, recent evidence is also claiming that the vaccine itself may contribute to adverse pregnancy outcomes; hence, controversy has also risen in this area and further studies have to be conducted [81].

An up-to-date meta-analysis recorded that pregnant women suffering from COVID-19 were administered treatments such as intravenous immunoglobulin, antiviral drugs, antibiotics, corticosteroids, a specific Chinese medication, hydroxychloroquine, , anticoagulants, and oxygen assistance [12]. Concurrently, another study confirmed that treatments for COVID-19 pregnant patients commonly comprised antiviral drugs, antibiotics, oxygen, and corticosteroids [14]. Another

study pointed out that a substantial proportion of hospitalized pregnant women, around 28%, required oxygen support [15]. These observations indicate that the treatment approach for pregnant women with COVID-19 closely mirrors that for non-pregnant individuals [12]. However, there is a pressing need for additional data to better understand the implications of these treatments on pregnancy and the newborn baby. For pregnant women diagnosed with COVID-19, antiviral therapies such as remdesivir may be considered, although data on its safety and efficacy in pregnancy are limited [82]. In some cases, monoclonal antibody treatment may also be an option for high-risk pregnant women with mild to moderate COVID-19 [83]. Decisions regarding treatment should be individualized and based on a careful assessment of the potential risks and benefits for both the mother and the fetus.

8. Future Perspectives

Several knowledge gaps remain in our understanding of the impact of COVID-19 on pregnancy outcomes. The long-term effects of COVID-19 on maternal and child health are not yet fully understood, and more research is required to elucidate the potential consequences of infection during pregnancy for both mother and offspring. Additionally, the impact of COVID-19 on fertility and child development remains an area of ongoing investigation.

Future studies addressing these knowledge gaps should consider several methodological aspects, such as study design, sample size, and control for confounding factors and potential biases. Longitudinal cohort studies with appropriate comparison groups and large sample sizes may be particularly well-suited to address these questions and provide more robust evidence on the association between COVID-19 and adverse pregnancy outcomes.

As the virus continues to evolve, new questions and research areas may arise. The impact of maternal vaccination on pregnancy outcomes and the potential influence of emerging SARS-CoV-2 variants on maternal and fetal health warrant further investigation as there seems to be a lot of controversy in that area as well. Additionally4, understanding the long-term effects of COVID-19 on children born to infected mothers, such as neurodevelopmental outcomes and susceptibility to other infections, will be crucial for informing public health policy and clinical practice.

9. Conclusion

In conclusion, this review has provided a comprehensive overview of the current knowledge on adverse pregnancy outcomes in COVID-19. Emerging evidence suggests that COVID-19 infection during pregnancy is associated with an increased risk of preeclampsia, preterm birth, low birth weight, and stillbirth. However, more research is needed to confirm these associations and to identify the underlying mechanisms involved. Prevention and management of COVID-19 in pregnancy, including vaccination and appropriate clinical care, are essential to reduce the risk of adverse outcomes and ensure optimal maternal and fetal health. Continued research and surveillance are necessary to monitor the evolving impact of the pandemic on pregnancy outcomes and to inform public health policy and clinical practice.

Declarations

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