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Maternal and Fetal Health in the Context of the COVID-19 Vaccination; A Depth Review Study for Guidelines, Risks and Benefits of COVID-19 in Pregnancy

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Abstracts

The COVID-19 pandemic has raised significant concerns regarding maternal and fetal health, particularly in the context of vaccination during pregnancy. Research indicates that COVID-19 vaccination during pregnancy is generally safe and beneficial for both maternal and fetal health. However, uptake remains suboptimal due to various factors, including misinformation and mistrust. This answer synthesizes findings from multiple studies to provide a comprehensive overview of the impact of COVID-19 vaccination on maternal and fetal health. The impact of COVID-19 on fetal health has emerged as a significant concern, particularly as the pandemic has highlighted various risks associated with maternal infection. The overall decline in healthcare access during the pandemic has further complicated the situation, as many women are unable to obtain necessary prenatal and postnatal care. The impact of COVID-19 on fetal immunity is a critical area of research, particularly given the unique immunological challenges

faced by pregnant women.

Keywords: Maternal health, Fetal Health, Covid-19, Guidelines, Recommendations, Vaccination and Pregnancy

Introduction

The COVID-19 pandemic has had a profound impact on maternal health globally, exacerbating existing challenges and creating new barriers to care. A significant increase in maternal mortality rates has been observed, with estimates suggesting an 8.3–38.6% rise in maternal deaths per month across 118 countries due to the pandemic's indirect effects on health care access and delivery. (1, 2) This alarming trend is largely attributed to a reduction in essential maternal health services, which has been estimated to decrease by around 45% over a six-month period, potentially leading to an additional 56,700 maternal deaths. (1) Maternal age of ≥ 40 and BMI ≥ 40kg/m2 are among identifiable risk factors for severe COVID-19 infection in pregnancy. Barriers to accessing maternal health care have intensified during the pandemic, with pregnant women facing numerous challenges such as movement restrictions, transport difficulties, and heightened anxiety about exposure to the virus. These barriers have made it increasingly difficult for women to receive timely antenatal, delivery, and postnatal care, which are crucial for preventing maternal morbidity and mortality. (1, 2) The disruption of maternity care services not only affects immediate health outcomes but also poses long-term risks for both mothers and infants, as the psychological stress associated with the pandemic can lead to increased rates of anxiety and depression among pregnant women. (3)

The impact of COVID-19 on fetal health has emerged as a significant concern, particularly as the pandemic has highlighted various risks associated with maternal infection. Research indicates that SARS-CoV-2 can adversely affect fetal growth and development during pregnancy, necessitating a comprehensive understanding of these effects to mitigate potential harm to both mothers and their children. (4) One of the primary concerns is the increased risk of adverse maternal and perinatal outcomes, especially in resource-constrained settings. Studies have reported heightened risks of complications such as prematurity and low birth weight, which are critical indicators of fetal health. The exacerbation of clinical symptoms in pregnant women infected with COVID-19 has been linked to a higher likelihood of preterm births, further complicating neonatal health. (5, 6) Although evidence of vertical transmission of the virus from mother to fetus remains limited, there have been documented cases of neonatal infections, raising alarms about the potential for direct impacts on newborns.(5, 7) The maternal-fetal interface may be affected by the infection, leading to adverse fetal outcomes, including placental abnormalities that can compromise fetal health. Moreover, the pandemic has indirectly influenced maternal health through reduced access to reproductive health services and increased mental health challenges, which can further exacerbate risks for both mothers and their babies. (8) The lack of comprehensive data on COVID-19 prevalence among pregnant women complicates the strategic planning of obstetric and neonatal care, particularly in regions already facing healthcare challenges.(5)

Effects of COVID-19 on Maternal and Fetal Immunity

The impact of COVID-19 on fetal immunity is a critical area of research, particularly given the unique immunological challenges faced by pregnant women. Maternal infection with SARS-CoV-2 can significantly alter immune responses at the maternal-fetal interface, which is crucial for fetal immunity and overall well-being of both mother and child. (9, 10) One of the primary concerns is the disruption of maternal-fetal immune tolerance, which is essential for the fetus's development. SARS-CoV-2 infection may compromise this tolerance, leading to potential immunological damage to embryos and affecting fetal immunity. This disruption can result in immune system defects in newborns, making them more vulnerable to infections and other health complications. (11) Moreover, studies have indicated an increased prevalence of preterm deliveries among pregnant women infected with COVID-19, suggesting that the virus may adversely affect fetal development. Although there is currently no evidence of vertical transmission of the virus, the implications of preterm birth on fetal health are significant, as it can lead to various developmental challenges and increased susceptibility to infections. (9) The immune responses observed in the placenta of SARS-CoV-2-infected women reveal markers associated with pregnancy complications, such as heightened activation of placental natural killer (NK) and T cells, alongside increased expression of interferon-related genes.(10) These immune alterations may contribute to an inflammatory environment that could further compromise fetal immunity. Additionally, maternal SARS-CoV-2 infection has been shown to inhibit the transfer of neutralizing antibodies to the fetus, which is vital for providing passive immunity.(12) This inhibition could diminish the fetus's ability to respond effectively to infections, thereby increasing the risk of adverse health outcomes postnatally. In summary, the effects of COVID-19 on fetal immunity are multifaceted, involving disruptions in immune tolerance, increased risks of preterm delivery, and potential impairments in antibody transfer. These factors collectively underscore the need for heightened protective measures for fetuses and newborns of SARS-CoV-2-infected mothers to mitigate adverse health events. (11) Understanding these dynamics is essential for developing effective treatment and preventive strategies for pregnant women and their infants during the pandemic.

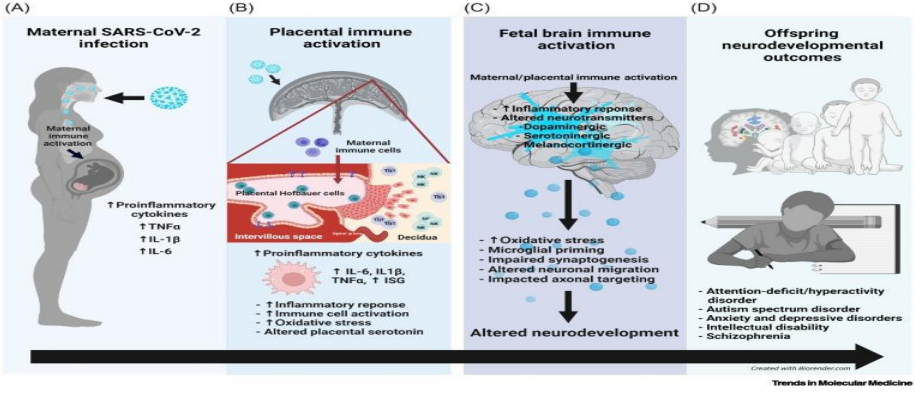

Figure 1: Coronavirus disease 2019 (COVID-19) in pregnancy and implications for offspring neurodevelopment (13).

(A) Maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection results in maternal immune activation (MIA) and increased proinflammatory cytokines in the maternal periphery.

(B) Maternal SARS-CoV-2 infection can impact the placenta via two mechanisms:

I. Placental immune activation and inflammation resulting from MIA (likely most common)

II. Direct placental infection with SARS-CoV-2 (rare per the current literature).

Placental immune activation and inflammation are associated with placental Hofbauer cell activation or priming, increased natural killer (NK) and T-helper 1 (Th1) cells at the maternal–fetal interface, increased proinflammatory cytokine production, upregulation of interferon-stimulated genes (ISGs), placental serotonin dysregulation, and increased oxidative stress. When direct placental infection with SARS-CoV-2 occurs (which is rare with the ancestral and other pre-Delta strains), the syncytiotrophoblast and cytotrophoblast layers are most infected, and once the virus gains access to the intervillous space, it can theoretically gain access to the fetal circulation.

(C) Both MIA and placental immune activation can lead to fetal brain immune activation, inflammation, and altered neurotransmitter signaling, including the serotonergic, dopaminergic, melanocortinergic, GABAergic, and glutamatergic systems. Fetal brain immune responses are associated with microglial priming, altered neural progenitor cell proliferation, impaired neuronal migration, synaptogenesis, and axonal targeting, all of which can result in altered offspring neurodevelopment.

(D) Offspring affected by MIA are at increased risk for attention hyperactivity deficit disorder, autism spectrum disorder, anxiety, depression, impaired cognition, learning disabilities, and schizophrenia.

COVID-19 Vaccination and Pregnancy

COVID-19 vaccination during pregnancy has become a critical topic as health organizations, including the Centers for Disease Control and Prevention (CDC) and American College of Obstetricians and Gynecologists (ACOG), recommend vaccination for all pregnant individuals at any stage of pregnancy. This recommendation is based on the understanding that pregnant women are at a higher risk for severe illness from COVID-19, including hospitalization and complications such as preterm birth and stillbirth. Despite initial hesitance due to concerns about safety and fertility, emerging data has shown that mRNA COVID-19 vaccines, such as those developed by Pfizer-BioNTech and Moderna, are safe for pregnant individuals and do not increase the risk of complications. (14) In fact, reassuring data from accidental pregnancies during clinical trials indicate that these vaccines do not harm fertility or increase miscarriage rates. (15) Moreover, vaccination during pregnancy can lead to the transfer of protective antibodies to the fetus, potentially safeguarding newborns from COVID-19. (16) This transplacental transfer of antibodies is crucial as it provides short-term passive protection to infants while their immune systems are still developing. Additionally, vaccinated breastfeeding mothers can pass these antibodies through breast milk, further enhancing the infant's immunity.

The limited data available on the safety of COVID-19 vaccines in pregnancy has been a concern, especially since pregnant individuals were initially excluded from clinical trials. However, real-world data now supports the safety and efficacy of these vaccines in this population, reinforcing the importance of vaccination to mitigate the risks associated with COVID-19 during pregnancy. (15, 17)

Safety and Efficacy of COVID-19 Vaccines in pregnancy

The safety and efficacy of COVID-19 vaccines during pregnancy have become critical areas of research, particularly given the heightened risk of severe illness from COVID-19 in pregnant individuals. Pregnant women are at an increased risk for severe COVID-19, especially those with comorbidities, which can lead to adverse pregnancy outcomes such as preterm birth and maternal morbidity. (18) Therefore, vaccination is essential for protecting both maternal and fetal health. A systematic review evaluating the safety of COVID-19 vaccines in pregnant women found no evidence of pregnancy-associated safety concerns related to the vaccines or their components. (19) This review is particularly significant as it addresses the urgent need for reliable data, given that pregnant individuals were often excluded from initial clinical trials. However, reassuring data from accidental pregnancies during these trials indicate that vaccination does not harm fertility or increase the rate of miscarriage. (15) This information is crucial for alleviating concerns among young women who may hesitate to receive the vaccine due to fears about fertility. Emerging observational data from vaccine registries further support the safety profile of COVID-19 vaccines in pregnancy, showing no increased risk of pregnancy complications compared to unvaccinated individuals. (18) Additionally, vaccination during pregnancy can lead to maternal antibody transfer to the fetus, potentially providing newborns with some level of immunity against COVID-19 [4]. This aspect underscores the dual benefit of vaccination for both the mother and the child. Public health recommendations strongly advocate for COVID-19 vaccination in pregnant individuals to mitigate the risks associated with severe illness and complications. Health organizations emphasize the importance of shared decision-making, allowing pregnant women to weigh the risks and benefits of vaccination in consultation with their healthcare providers.(18)

Guidelines and Recommendations for Vaccination

Guidelines and recommendations for COVID-19 vaccination during pregnancy have been established by several authoritative organizations, including ACOG, CDC and the Society for Maternal-Fetal Medicine. These guidelines collectively support the vaccination of pregnant individuals to mitigate the risks associated with COVID-19, particularly severe illness and complications during pregnancy. (20) ACOG strongly recommends that pregnant individuals receive COVID-19 vaccines, emphasizing the importance of vaccination in reducing the risk of severe illness. The CDC echoes this recommendation, advocating for the administration of vaccines to pregnant persons as a critical public health measure. (20) Given that pregnant individuals were excluded from initial vaccine trials, there is a need for ongoing evaluation of vaccine safety and efficacy in this population. However, emerging data indicate that COVID-19 vaccines, particularly mRNA vaccines like Pfizer-BioNTech and Moderna, are safe and effective for pregnant individuals. (21) Timing of vaccination is also a crucial consideration. Vaccination can occur at any trimester, but early vaccination is encouraged to maximize health benefits for

both the mother and the baby. (20) Additionally, pregnant individuals who are immunocompromised are advised to receive additional vaccine doses to ensure adequate protection against severe illness. Booster doses are recommended for pregnant individuals after completing their primary vaccination series, particularly with bivalent mRNA vaccines, to enhance protection against COVID-19 variants.

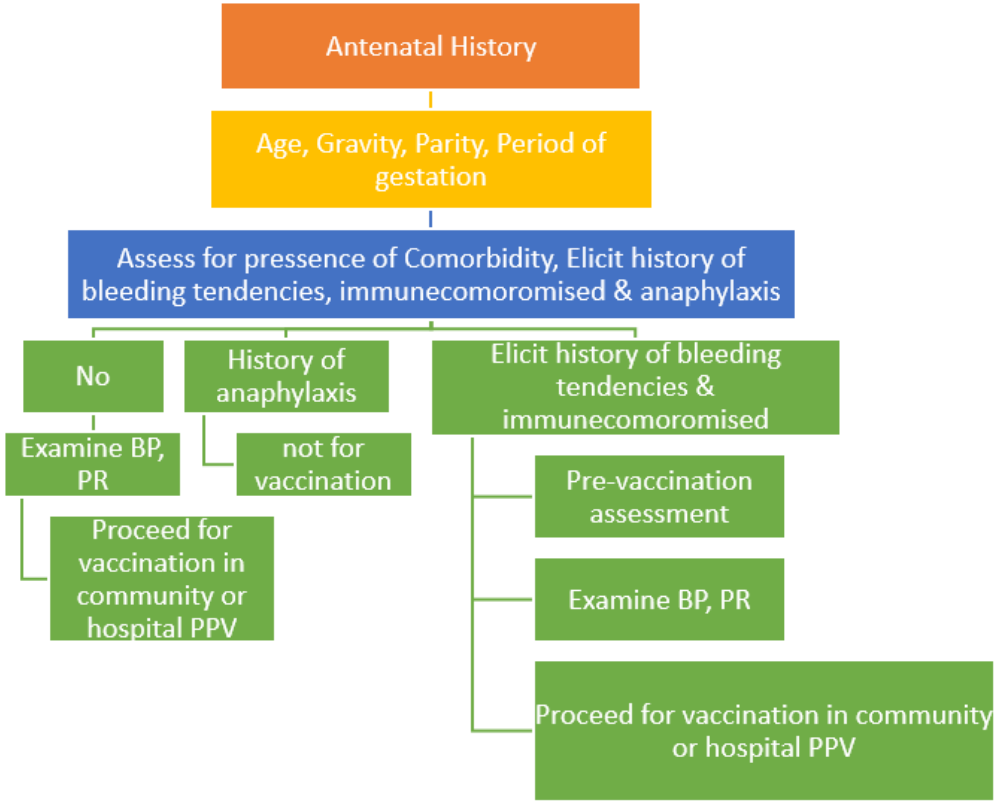

Figure 2: Flow chart on Pre-vaccination assessment for antenatal mothers on presentation to clinic or hospital (1st dose).

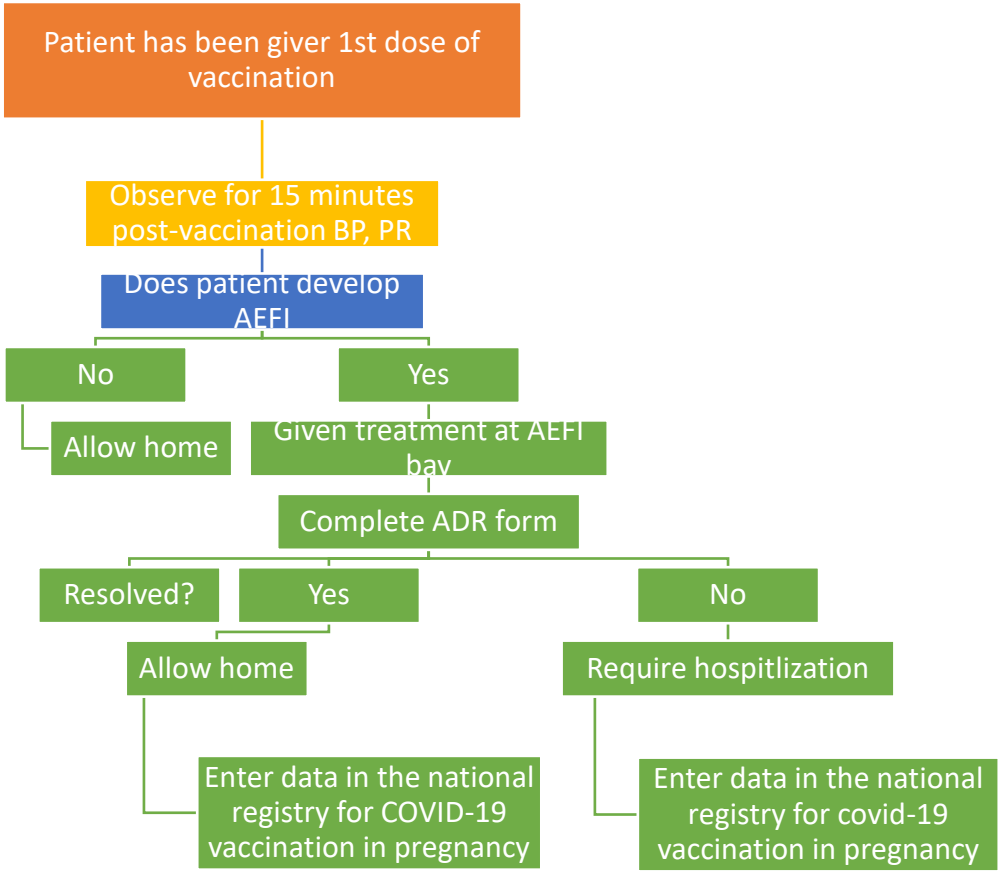

Figure 3: Flow chart on post-vaccination assessment for antenatal mother.

Risks and Benefits of COVID-19 Vaccination for Maternal and Fetal Health

The COVID-19 vaccination presents both risks and benefits for maternal and fetal health, a topic of significant concern as vaccination programs expand. One of the primary benefits of vaccination during pregnancy is the prevention of severe COVID-19 infection, which poses critical risks to both the mother and the fetus. Studies indicate that vaccinated pregnant women experience fewer complications compared to those who contract the virus, which can lead to preterm labor and other adverse outcomes. Moreover, the safety profile of COVID-19 vaccines in pregnant women appears favorable, with few reports of adverse events. (17, 22) This is particularly reassuring given that pregnant individuals were excluded from initial clinical trials. However, data from accidental pregnancies during these trials and ongoing studies suggest that vaccination does not increase miscarriage rates, further supporting the safety of vaccines for maternal health. (15, 17) Reproductive societies have recommended vaccination for women who

are planning to conceive or are already pregnant, emphasizing the importance of vaccination in mitigating the risks associated with COVID-19. The potential for maternal-fetal transmission of the virus raises additional concerns, as COVID-19 can infect the placenta, leading to complications for both mother and child. (17) In terms of fetal health outcomes, research indicates that COVID-19 vaccination does not adversely affect fetal health compared to unvaccinated women. Furthermore, studies have shown that vaccination does not negatively impact neonatal outcomes, such as birth weight and health at delivery. (23) In fact, maternal vaccination can provide passive immunity to the newborn through the transplacental passage of antibodies and the presence of vaccine-induced IgG in breastmilk, offering additional protection to the infant. (22) Despite the overall positive findings, it is essential for healthcare providers to address the concerns of pregnant women regarding vaccination, including fears about infertility and potential adverse effects. (17)

The safety of COVID-19 vaccination during pregnancy has become a critical area of research, particularly concerning maternal and fetal adverse events. Studies indicate that maternal COVID-19 vaccination is associated with a reduced risk of severe illness and adverse outcomes during pregnancy, including complications such as preterm birth and thromboembolic events. Specifically, vaccinated pregnant women demonstrated a lower incidence of COVID-19 infection compared to their unvaccinated counterparts, with only 1.4% of vaccinated women experiencing infection prior to delivery, compared to 10.6% among unvaccinated women. The Adverse Outcome Index, which includes maternal and neonatal complications, revealed no significant differences in adverse outcomes between vaccinated and unvaccinated mothers. For instance, the rates of thromboembolic events and preterm births were similar, with 4.9% of vaccinated mothers experiencing complications compared to 5.0% in unvaccinated mothers. (24) This suggests that the COVID-19 vaccination does not increase the risk of these specific adverse events during pregnancy. Moreover, the vaccination has been endorsed by professional societies such as the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, despite the initial exclusion of pregnant women from clinical trials. The evidence supports that maternal vaccination not only protects the mother but also provides passive immunity to the infant, as maternal antibodies can be transferred to the fetus, potentially reducing the risk of severe outcomes in newborns. (25, 26) Conversely, unvaccinated pregnant women face heightened risks, including increased rates of cesarean deliveries and neonatal admissions to intensive care units due to severe COVID-19 infections. (22) The risk of stillbirth is also notably higher in unvaccinated mothers, emphasizing the importance of vaccination in mitigating these severe outcomes.

Conclusion

The COVID-19 pandemic has profoundly impacted maternal health services, resulting in heightened maternal mortality and underscoring the necessity for adaptive health systems. Policymakers are urged to prioritize the revitalization and improvement of maternal health services to mitigate the pandemic's enduring repercussions, particularly for vulnerable populations. Furthermore, the complex implications of COVID-19 on fetal health necessitate ongoing research and healthcare strategies to ensure the well-being of mothers and infants in this unprecedented health crisis. The guidelines are designed to safeguard maternal and fetal health

amid the pandemic, emphasizing the necessity for healthcare providers to remain updated on the benefits and risks of COVID-19 vaccination for pregnant patients. The evidence robustly indicates that immunization significantly reduces complications and infections for mothers, thus highlighting its vital importance in prenatal care during this health crisis.

Author contributions

Study Design, Investigation, and original Manuscript draft preparation: First Author; Supervision and Methodology implementation: Corresponding author and first author. All authors including co-authors participate and are involved in Data collection, Manuscript text Editing, Review and given final approval of submission to journal for publication.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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Ethical Approval

Not Applicable

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