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Short communication

Pregnancy and COVID-19, focus on vaccine and pharmacological treatment

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ARTICLE INFO

Keywords:
Pregnancy
COVID-19
Vaccine
Drugs

ABSTRACT

The global pandemic of COVID-19 is currently ongoing. Clinical evidence shows that specific population groups such as the elderly, individuals with comorbidities, and pregnant women may be at increased risk for infection and serious complications. In particular, physiologic changes during pregnancy may be significant on the immune and respiratory systems and progression of COVID-19 disease. Pregnant women are routinely excluded from pre-registration clinical trials, this potentially limits their access to therapies through off-label or compassionate use. Vaccination remains an important pillar of the response to COVID-19, particularly as variants of the virus continue to spread across countries. Growing evidence indicates that COVID-19 mRNA vaccines do not cause pregnancy complications for expectant mothers and their infants. In this brief review, we explore current knowledge about COVID-19 in pregnancy by highlighting current recommendations for vaccination and drug treatments.

1. Introduction

1.1. COVID-19

The COVID-19 global pandemic is currently ongoing. Coronavirus disease 2019 (COVID-19) is caused by the SARS-CoV-2 virus. The pathogenesis of SARS-CoV-2 infection can manifest totally asymptotically, with mild symptoms, or with severe respiratory failure and multi-organ dysfunction that can also cause death of the individual (Wang et al., 2020; Huang, 2020; Vitiello et al., 2021). SARS-CoV-2 virus uses the ACE-2 receptor for endocellular penetration (Vitiello and Ferrara, 2021, 2020). ACE-2 is an important regulatory factor of the renin-angiotensin system (RAS) (Vitiello et al., 2021). When it binds to respiratory tract epithelial cells, SARS-CoV-2 begins to replicate and migrate to alveolar epithelial cells in the lungs. In the most severe stages of infection, an unregulated inflammatory/immune system and a cytokine storm are responsible for acute respiratory distress syndrome, which is considered to be the leading cause of severe tissue injury and death in patients with COVID-19 (Vitiello et al., 2020, 2021; Vitiello and Ferrara, 2021). Pharmacological treatments used are aimed at avoiding severe complications (Ferrara and Vitiello, 2021; Vitiello and Ferrara, 2021; Vitiello et al., 2021; Ferrara et al., 2020). Some antivirals (e.g, Remdesivir) indicated for other diseases have been authorised for use in SARS-CoV-2 infection (Ferrara et al., 2020; Vitiello and Ferrara, 2020). New antiviral agents against SARS-CoV-2 such as Molnupiravir and Paxlovid have recently been authorised. Some specific population groups such as the elderly, individuals with comorbidities, and pregnant women may be at increased risk for infection and serious COVID-19 complications.

2. Pregnancy and COVID-19

Physiologic, hormonal, and immunologic changes in pregnancy have the potential to influence the susceptibility and severity of COVID-19.
Pregnant women have an increased risk of developing severe respiratory injury from COVID-19 (Poon et al., 2020; Schwartz and Graham, 2020) compared with non-pregnant women. Emerging data also demonstrate vertical transmission from mother to fetus (Qiao, 2020; Schwartz, 2020). Pregnant women are at increased risk of developing severe COVID-19 because of their weakened immune systems, increased concentration of circulating proinflammatory mediators, and increased thromboembolic risk (Fig. 1). Data support pregnancy as a risk factor for severe COVID-19-associated disease; some of the best evidence comes from the U.S. Centers for Disease Control and Prevention(CDC), which reported that pregnant people were more likely to be admitted to an intensive care unit, require invasive ventilation, require extracorporeal membrane oxygenation, and die than non-pregnant women of reproductive age. In addition, evidence is accumulating that SARS-CoV-2 infection during pregnancy is associated with a range of adverse pregnancy outcomes, including preeclampsia, preterm delivery, and stillbirth, especially among pregnant persons with severe COVID-19 disease. The placenta has been shown to possess ACE2 receptors on the villous cytotrophoblast and syncytiotrophoblast, this suggests that SARS-CoV-2 can make endocellular penetration through these receptors as well. In addition, the presence of ACE2 receptors in the placenta may increase the risk of vertical transmission. COVID-19 infection in pregnant women makes clinical management and drug treatments more difficult to use with the risk of possible teratogenic drug effects (Chen et al., 2020). Vaccination can prevent COVID-19 disease and may be important for both mother and fetus. Clinical data supporting the efficacy and safety of COVID-19 vaccines in pregnant and lactating women are continually increasing. According to the U.S. CDC recommendation, COVID-19 vaccination is recommended for people who are pregnant, breast feeding, trying to become pregnant now, or who may become pregnant in the future. People who are pregnant should receive a COVID-19 vaccine booster when the time comes. Although data on pregnancy safety are rapidly accumulating, more information is needed on birth outcomes, particularly among people vaccinated early in pregnancy.

3. COVID-19 vaccines and pregnancy

Evidence shows that pregnant women may be more vulnerable to infectious pathogens (Dashraath et al., 2020). To date, COVID-19 vaccines with different mechanisms of action, mRNA, viral vector, inactivated vaccin, protein subunit, and DNA are available. Clinical data supporting the efficacy and safety of COVID-19 vaccines and drug treatments in pregnant and lactating women are growing, and some recommendations regarding COVID-19 vaccination in pregnancy and lactation have already been issued (Adhikari and Spong, 2021; Vora et al., 2020). The Food and Drug Administration (FDA) leaves open the option for pregnant and lactating women to receive the vaccine. The World Health Organization (WHO) suggests considering vaccination for pregnant women who are at high risk for infection (e.g., health care workers) or who have comorbidities. Although thrombosis-associated cases of thrombocytopenia, albeit very rare, have occurred after the administration of viral vector vaccines, and considering that pregnant women have a higher rate of developing thrombosis than the general population, risk factors could add up. However, to date the evidence does not show any particular safety warning signals, and the benefits are still considered to far outweigh the risks (Oldenburg et al., 2021). A rapid systematic review was recently conducted to assess the safety of COVID-19 vaccines in pregnant women, including their components, and their technology platforms (Ciapponi et al., 2021). This rapid review found no evidence of safety concerns associated with pregnancy with COVID-19 vaccines. The findings support current WHO guidelines recommending that pregnant women may consider receiving COVID-19 vaccines, particularly if they are at high risk for exposure or have comorbidities that increase the risk of serious illness. Another study showed that pregnant women had significantly lower levels of SARS CoV-2 IgG in maternal serum, regardless of the trimester in which they were vaccinated compared with non-pregnant women (Bookstein Perez et al., 2021). Another study showed that the IgG transfer ratio at birth was significantly lower for third trimester than for second trimester infection (Beharier et al., 2021). Overall, it can be assumed that COVID-19 mRNA vaccination applied to pregnant women in the second trimester or earlier may be a better choice than that given in the third trimester (Adhikari and Spong, 2021). An interesting study showed that the incidence of systemic adverse reactions increased after the second dose of vaccination in Modern and Pfizer mRNA vaccinations (Shimabukuro et al., 2021). In addition, evidence shows that there are no demonstrable significant differences in the frequency of gestational hypertension or thrombosis between vaccinated and unvaccinated pregnant women (Cavalcante et al., 2020). Vaccination during pregnancy builds antibodies that could protect the baby. Antibodies produced after a pregnant person receives a COVID-19 mRNA vaccine have been found in umbilical cord blood. This means that COVID-19 vaccination during pregnancy could help protect babies against COVID-19 (Gray et al., 2021).

3.1. COVID-19 vaccine and miscarriage

Miscarriage, or pregnancy loss occurring at less than 20 weeks gestation, is an outcome that affects between 11% and 22% of pregnancies. Pregnant women with severe COVID-19 have increased rates of preterm delivery (<37 gestational weeks), cesarean delivery, and neonatal admissions to intensive care units. Data showing estimates of the risk of miscarriage after receipt of a COVID-19 mRNA vaccine, either before conception (30 days before the first day of the last menstrual period) or during pregnancy are limited. An interesting study by the CDC, conducted as part of the v-safe COVID-19 vaccine pregnancy registry project, determined the cumulative risk of miscarriage from 6 to less than 20 weeks’ gestation. Pregnant women who had received at least one dose of a Covid-19 mRNA vaccine before conception or before 20 weeks’ gestation and who did not experience a pregnancy loss before 6 weeks’ gestation were included in this analysis. The results of the study showed that the risk of miscarriage after vaccination with Covid-19 mRNA before conception or during pregnancy was consistent with the expected risk of miscarriage (Zauche et al., 2021). A case-control study using data from Norwegian registries on first-trimester pregnancies, Covid-19 vaccination identified all women who were registered between February 15 and August 15, 2021, as those who had a miscarriage before 14 weeks’ gestation (case patients) and those with primary care-based confirmation of ongoing pregnancy in the first trimester (controls). The study found no evidence of an increased risk of early pregnancy loss after administration of Covid-19 vaccines (Magnus et al., 2021). In addition, another case-control study on the correlation between COVID-19 vaccination during pregnancy and miscarriage showed that miscarriages were no more likely to have been exposed to COVID-19 vaccination in the preceding 28 days than ongoing pregnancies (Kharbanda et al., 2021).

Fig. 1. Pregnant women have an increased risk of developing severe COVID-19 respiratory injury (Vitiello and Ferrara, 2020), due to the physiological, immune, and hormonal changes that occur during pregnancy.
3.2. COVID-19 vaccine and Comorbidity during pregnancy

It is known that certain populations such as diabetic or obese patients are more susceptible to developing severe COVID-19 forms. SARS-CoV-2 infection in diabetic patients has been shown to correlate with a poor course and worse prognosis than in non-diabetic individuals (Apicella et al., 2020). Several meta-analyses have shown that COVID-19 patients with diabetes are at a higher risk of severe disease with a higher rate of Intensive Care Unit (ICU) admissions and death (Shi et al., 2020). Similarly, obese and COVID-19 patients may present with more severe disease than non-obese individuals with an increased risk of ICU admission, proportional to body mass index (BMI) levels (Lighter et al., 2020). In the case of pregnant women, in the presence of other risk factors such as diabetes (pre-gestational and gestational), cardiovascular disease and obesity, and COVID-19 infection, the risk of severe forms may be higher. In support of this a case series study, showed that in critically ill pregnant women with COVID-19, 60% of patients had gestational diabetes and BMI ≥ 25 kg/m2 (Pelcer et al., 2021). In addition, evidence shows that in pregnant women hospitalized for severe COVID-19, the most common conditions were pre-pregnancy BMI ≥ 30 kg/m2 and type 2 diabetes (Lokken et al., 2021). Available clinical data on the effects of COVID-19 in pregnant women with comorbid conditions such as gestational diabetes/obesity suggest that this population group is particularly recommended to receive COVID-19 vaccines (Sculli et al., 2021).

3.3. Safety profile

Emerging evidence shows that COVID-19 vaccines have a good safety profile when administered in pregnant women and that the benefits largely outweigh the risks. A prospective cohort study of pregnant women immunized with COVID-19 mRNA vaccines demonstrated that the incidence of COVID-19 vaccine side effects was relatively similar between pregnant and nonpregnant women and no serious complications occurred in either group; therefore, the study data support the continued use of the vaccine for pregnant patients (Nakahara et al., 2022). Another cohort study showed that the rates of adverse pregnancy outcomes of 133 women who received at least 1 dose of the COVID-19 vaccine during pregnancy were similar to those of unvaccinated pregnant women (P > .05 for all); and specifically stillbirths (0.0% vs 0.2%), fetal abnormalities (2.2% vs 2.5%), postpartum hemorrhage (9.8% vs 9.0%), cesarean delivery (30.8% vs 34.1%), small for gestational age (12.0% vs 12.8%), maternal high dependency unit or intensive care unit admission (6.0% vs 4.0%), or neonatal intensive care unit admission (5.3% vs 5.0%). This study contributed to the body of evidence that COVID-19 vaccination in pregnancy does not alter perinatal outcomes (Blakeway et al., 2022). In addition, a retrospective cohort study was performed, including all women who gave birth between January and June 2021 at Soroka University Medical Center, the largest birth center in Israel. A total of 4,399 women participated in this study, 913 (20.8%) of whom were vaccinated during pregnancy. The study showed that COVID-19 vaccines had no adverse effects on the course and outcomes of pregnancy (Wainstock et al., 2021). Finally, a recent meta-analysis that included a total of 6 studies showed that vaccination prevented pregnant women from SARS-CoV-2 infection (OR = 0.50, 95% CI, 0.35–0.79) and COVID-19-related hospitalization (OR = 0.50, 95% CI, 0.31–0.82), and that no adverse events of COVID-19 vaccination were found on pregnancy, fetal, or neonatal outcomes. This study highlighted and confirmed the efficacy and safety of COVID-19 vaccines for pregnant women (Ma et al., 2022).

4. Drugs in pregnant women with COVID-19

Management of COVID-19 drug therapy in pregnant women should minimize fetal risks. To date, there are limited data on the management of drug therapy of COVID-19 infection during pregnancy. Therefore, the safety of anti-COVID-19 therapies should be carefully evaluated before conception, during pregnancy, and during lactation. The classes of drugs used are anti-inflammatory/immunomodulatory drugs, anticoagulants, and off-label antivirals. Many of these drugs lack reliable data to support their safety in treating disease during pregnancy. Many antiviral drugs are contraindicated during pregnancy because of their proven teratogenicity. To treat COVID-19 infection during pregnancy most quickly and effectively, there are pharmacologic agents that show less risk of teratogenicity than others. Remdesivir is an intravenously administered antiviral with good efficacy against SARS-CoV-2 because of its activity in reducing viral replication by inhibiting RNA-dependent RNA polymerase. This drug has been used without fetal toxicity in pregnant women receiving supplemental oxygen, intubated or not, and in non-severe disease. Results from the compassionate use program provide strong support that remdesivir is safe in pregnant women with high rates of clinical recovery (Birwick et al., 2020). Several studies have revealed its safety during pregnancy (Favilli et al., 2020). However, Data regarding the use of remdesivir in pregnant women do not exist or are limited in number. Animal studies are insufficient to demonstrate reproductive toxicity. Remdesivir should not be used during pregnancy unless the woman’s clinical condition requires its use, but we believe it is necessary and important to remember that the literature on the efficacy of remdesivir is continually evolving. Low-molecular-weight heparin (LMWH) is the most commonly recommended anticoagulant in pregnancy, having demonstrated efficacy and safety in multiple prospective clinical trials (Lu et al., 2017). All pregnant women hospitalized because of COVID-19 infection should receive prophylactic treatment with heparin. If the woman is close to delivery, it is generally preferable to use unfractionated heparin rather than LMWH (Schnettler et al., 2020). However, even in the postnatal phase and in COVID-19 disease, LMWH should be administered. To date, dexamethasone is the only proven and recommended experimental treatment for pregnant women with COVID-19 who are mechanically ventilated or require supplemental oxygen. In addition, it is important to avoid fetal exposure to a prolonged course of dexamethasone, which may have some adverse effects by crossing the placenta with increased risk of preterm delivery (Bergella et al., 2020). In addition, it is important to consider whether gestational diabetes is present, as dexamethasone may worsen the situation. Antibacterials are not indicated for viral infections and COVID-19, but if bacterial pneumonia is present, some protocols recommend it. Azithromycin is a macrolide antibiotic with antimicrobial and immunomodulatory properties commonly used in infectious pneumonia and inflammatory lung disease (Zimmermann et al., 2018). Azithromycin at a dosage of 500 or 250 mg every 24 h for up to 5 days, either orally or intravenously, appears to be safe for a pregnant woman (López et al., 2020; Jacobson et al., 2021). At this time, there is very limited published experience with the use of tocilizumab in pregnancy. No indication of a substantially increased risk of malformation has been observed (Hoelzelben et al., 2016). The use of colchicine in pregnancy is controversial. Some evidence shows that colchicine therapy did not significantly increase the incidence of fetal malformation or miscarriage during pregnancy (Table 1) (Ferrara, 2020; Indraratna et al., 2018; Di Domenico et al., 2021). Some oral analgesic drugs used for self-medication can be used in pregnancy, such as ibuprofen, which has been shown to be safe for pregnant patients with covid-19 (Ceulemans et al., 2022). Tocilizumab is an anti-inflammatory monoclonal antibody with IL-6 inhibitory effects used for rheumatic diseases. Currently, it is recommended for the treatment of COVID-19 because of its properties to decrease elevated levels of pro-inflammatory cytokines associated with severe COVID-19 disease. Currently, more studies are needed on the use of tocilizumab for the treatment of COVID-19 in pregnant and lactating women (Favilli et al., 2020). Molnupiravir is an antiviral pro-drug taken orally that inhibits viral replication through incorporation of the active metabolite into viral RNA (Imran et al., 2021; Vitiello et al., 2021; Ferrara and Vitiello, 2021), is licensed for the treatment of COVID-19 in adults, who have at least one risk factor for
developing severe disease. Preclinical data on reproductive toxicity in animals are conflicting. There are currently no human data regarding the safety of molnupiravir in pregnancy. Molnupiravir is not recommended in pregnancy until further studies have established its efficacy and safety (Vitiello and Ferrara, 2021; Vitiello et al., 2021; Kharbanda et al., 2021). There are no data regarding the use of Paxlovid in pregnant women, a second antiviral oral medication available to treat adults at high risk of progression to COVID-19 severe. In embryo-fetal developmental toxicity studies in the rat or rabbit, no PF-07321332-related effect on fetal morphology or embryo-fetal viability was demonstrated at any dose tested, although a reduction in fetal body weight was observed in the rabbit. Its use in pregnancy is not currently recommended (Paxlovid, 2022).

5. Discussions

In this literature review, we highlighted the current knowledge regarding the prevention and pharmacological treatment of COVID-19 in pregnant women. To date, growing evidence indicates that COVID-19 vaccines are safe for the mother and fetus. Although pregnant and lactating women have not been included in pre-registration studies of COVID-19 vaccination to date, experts strongly recommend vaccination to prevent SARS-CoV-2 infection in patients during pregnancy and lactation. Pharmacologic management of COVID-19 infection in pregnant women should be evaluated on a case-by-case basis. For some recently licensed drugs such as the new oral antivirals, to date there are insufficient data to recommend their use in pregnancy, Pharmacological agents such as Heparin on the other hand, are safe for the fetus and have no teratogenic effect. Considering the studies and reviews we reviewed on the topic of corticosteroids as a treatment for COVID-19 infection during pregnancy, we can conclude that experts confirm that the decision of corticosteroid therapy must be evaluated individually for each case. In addition, especially for pregnant women adopting prevention recommendations is essential, namely social distancing, wearing a mask in public, hand hygiene.

6. Conclusions

Pregnant women have an increased risk of developing severe symptoms with COVID-19 infection especially if they have comorbidities such as gestational diabetes and hypertension. The COVID-19 pandemic emergence has led to the administration of numerous treatments with no evidence of efficacy and no guarantee of no long-term fetal effects. Evidence strongly recommends vaccination to avoid SARS-CoV-2 infection in patients during pregnancy and lactation. In addition, there are several pharmacological treatments against COVID-19 that are safe for pregnant women. To date, there are no clear management recommendations for the treatment of COVID-19 infection in pregnant women; clinicians should consider all patient-specific risks and benefits.

Ethical Approval

Not applicable.

Funding

None.

CRediT authorship contribution statement

Antonio Vitiello: Conceptualization. Francesco Ferrara: Writing – original draft, Methodology, Validation, Conceptualization. Andrea Zovi: Writing – review & editing. Ugo Trama: Validation. Mariarosaria Boccellino: Methodology. Francesco Ferrara, the guaranteeing author is - one of the authors needs to guarantee the manuscript’s accuracy and the contributor-ship.

Acknowledgement

We would like to thank the corporate health management and the pharmaceutical department for authorising access and use of company data for scientific purposes.

Consent to Participate

Not applicable.

Consent to Publish

The authors consent to the publication of the manuscript.

Conflicts of interest

None of the Authors have conflicts of interest to disclose.

Availability of data and materials

Full availability of data and materials.

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