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REVIEW ARTICLE

Pharmacological consideration of COVID-19 infection and vaccines in pregnancy

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Abstract: COVID-19 is a pandemic of the 21st century that recorded 234 809 103 confirmed cases and more than 4 800 375 deaths. Many studies report the effect of COVID-19 in the overall population; nevertheless, there is information scarceness related to pharmacological management and pregnancy and fetal outcomes during the epidemic. Pregnancy is a state of change in immune physiology and anatomy modulation in preference to immune suppression. Additionally, manifold interactions with the health care system during pregnancy increases the chance of infection, and managing, pregnant population poses a more significant challenge. This review will summarize the available data on pharmacological considerations and vaccines in pregnancy and their adverse effects on fetal outcomes. Several drug choices include but are not limited to antivirals and antimalarial and combinations, corticosteroids, nonsteroidal anti-inflammatory drugs, and antipyretics. Approved vaccines for pregnancy include Pfizer/BioNTech and mRNA-1273 Moderna/National Institutes of Health. COVID-19 treatment approaches vary across different countries; the WHO and the Centers for Disease Control and Prevention guidelines and country regulators advise managing adverse effects on pregnancy and fetal outcome. But the efficacy of these drugs is questionable. There is no adequate literature to demonstrate the safety of these drugs in pregnant and lactating women. Hence, well-conducted studies that assess the safety of anti-COVID-19 medications and vaccines in pregnancy and lactating women are needed.

Keywords: COVID-19; Drugs and vaccines; Pregnancy; Pregnant and lactating women; SARS-CoV-2

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) or corona virus 2019 (COVID-19) is a pandemic of the 21st Century that recorded 234 809 103 confirmed cases, including 4 800 375 deaths and 6 188 903 420 vaccine doses administered worldwide as per October 2021 globally.[1]

Initially, COVID-19 was considered a respirational virus; later, research suggested that other organs like the brain, heart, intestine, and vascular system are also attacked by the virus.[2,3] Studies pointed out that all populations are generally vulnerable for COVID-19. Age, sex, and underlying diseases like diabetes, cardiovascular diseases, are the three significant aspects playing a substantial role in the severity of the disease. Pregnant women are more susceptible to infections like SARS-CoV-2 or COVID-19 due to cardiovascular and immune physiology changes during pregnancy.

The COVID-19 contagion has sparked arguments surrounding the use of specific pharmacologic involvements and exclusion of pregnant women from the vaccine studies and trials. This review article summarizes the available data and pharmacological considerations of COVID-19 infection in pregnancy.

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2. COVID-19 IN PREGNANCY

2.1. Pathophysiology and immunology

The study on the pathological roles of the COVID-19 virus has attained remarkable heights; still, the life cycle of SARS-CoV-2 remains a mystery. COVID-19 virus, like other beta coronaviruses, is a positive, enveloped, single-stranded RNA virus with large genomes (29 903 nucleotides) and has a conserved 5′ leader sequence with 12 open reading frames which infects via angiotensin-converting enzyme 2 (ACE2).[4,5]

The genome of coronaviruses can be divided into two parts: (1) genes encoding- pp1a and pp1b polyproteins (nonstructural). (2) Genes encoding structural genes—Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) proteins. The translation of nonstructural proteins from the single-stranded RNA (5, capped, 3′polyadenylated ssRNA+) starts the replication in COVID-19.[2]

Pregnancy is a state of change in the modulation of immune physiology in preference to immune suppression. The immune response from the placenta and its tropism for particular pathogens disturb the outcome of the pregnant woman's vulnerability and severity of certain infectious diseases like SARS-CoV.[6] Previous research has provided evidence that pregnancy-associated complications are associated with MERS-CoV and SARS-CoV infections.[7,8]

Current studies have shown that the stringency of the disease was associated with pregnant women with COVID-19 infection, and pregnancy-related complications were increased.[9,10] An increased risk of pregnancy complications, fetal distress, and premature

membrane ruptures are the problems associated with COVID-19 disease in pregnancy. In Akhtar et al review of 22 studies identified 156 pregnant women with COVID-19 and 108 neonatal outcomes; COVID-19 infection leads to shortness of breath, gastrointestinal symptoms, and fever (6%, 4%, and 3%, respectively) in neonates.[11]

Studies showed 2.5% to 5% of babies born to COVID-19 infected mothers were tested positive for SARS-CoV-2 infection, and SARS-CoV-2 IgG was also identified in such infected infants.[12–15] Increased synthesis of immunoglobulin (Ig) and reduced cell-mediated response to disease is observed in the second trimester of pregnancy which turns to pro-inflammatory in the third-trimester pregnancy. This might be the reason for the need for intensive care admission invasive ventilation or death among the COVID-19 infected pregnant women.[16]

2.2. Pharmacological considerations and safety view

2.2. 1. Nonsteroidal anti-inflammatory drugs

SARS CoV-2 binds the host through ACE2. Assumed potential to increase the ACE2 expression in patients taking ibuprofen, raised concern initially concerning the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in COVID-19 patients.[17] Many studies suggest no association between the low-dose aspirin and pregnancy outcomes, but no data are available on analgesic doses, neurodevelopmental outcomes, and utero aspirin exposure.[18]

There are no specific contraindications to the use of indomethacin as a tocolytic and NSAIDs for postpartum analgesia in COVID-19 infection. Consequently, the International Federation of Gynaecology and Obstetrics and the American College of Obstetricians and Gynaecologists (ACOG) have detailed inadequate data regarding low-dose aspirin usage for prophylaxis against placenta-mediated pregnancy hitches.[2]

All hospitalized pregnant women with confirmed COVID-19 infection, or those up to 6 weeks postpartum, should be presented with thromboprophylaxis for ten days subsequent hospital discharge. A more extended period of thromboprophylaxis should be measured for women with insistent morbidity.[19]

2.2. 2. Corticosteroids

Administration of dexamethasone has demonstrated a reduced mortality rate in COVID-19 individuals requiring oxygen ($p < 0.001$, odds ratio = 0.83, confidence interval = 0.73–0.93) in the RECOVERY clinical trial.[20]

Evidence supports the usage of a single course of antenatal corticosteroids like betamethasone or dexamethasone) at risk of preterm birth in women between 24 and 34 weeks of gestation and no solid evidence for the use of corticosteroids after 34 weeks of gestation. Dexamethasone is a pregnancy category C drug and, on chronic use, causes defects in osteogenesis and malformation of the fetus.[21,22]

Corticosteroids for fetal lung maturity are not without adverse fetal effects. Exposure to repetitive courses of antenatal glucocorticoids has been associated with adverse neurologic outcomes, small head circumferences, fetal growth restriction, and increased risk of neonatal hypoglycemia.[23]

Instead of dexamethasone, the RECOVERY trial recommends oral (once daily) prednisolone 40 mg, hydrocortisone (80 mg) intravenously (twice daily for those who cannot take the oral drug).[20] The placenta metabolizes prednisolone and hydrocortisone but, dexamethasone cross over the placenta. Thus, replacing dexamethasone with prednisolone and hydrocortisone, equally effective in treating COVID-19 infection, reduces fetal risks.

Recent guidelines from the ACOG recommend that when steroids are essential for fetal lung maturity and COVID-19, dexamethasone of a four-dose course should be used over 2 days. For instance, the clinicians should discuss the hyperglycemia risk and blood sugar monitoring. After the treatment course, dexamethasone must be substituted with methylprednisolone to complete a 10-day course.[23]

2.2. 3. Antivirals

2.2. 3.1. Remdesivir

A broad-spectrum antiviral nucleoside analog, regarded as a potential breakthrough to COVID-19, has shown clinical effectiveness and admissibility. Studies conducted by Grein et al and Beigel et al showed shortened recovery time using Remdesivir (11 days compared to 15 days).[24,25]

In a case series study of Mulangu et al, pregnant women treated with Remdesivir for Ebola did not refer to any unfavorable outcomes.[26] No adverse effects were observed in other studies[27–29] but, in all the studies, Remdesivir was given inside of the second- and third-trimester pregnant women only. Among 67 pregnant and 19 immediate postpartum women with severe COVID-19 who received compassionate use remdesivir, had high preterm delivery but demonstrated a high recovery rate with a low rate of significant unfavorable events.[30]

2.2. 3.2. Favipiravir

Favipiravir is an oral antiviral drug used to treat influenza and re-purposed as a possible candidate for COVID-19 infection. It inhibits RNA-dependent RNA polymerase enzyme activity, thereby inhibiting replication of the virus inside the host. Cai et al observed improvement in the radiological aspects of COVID-19 subjects treated with favipiravir and superiority over lopinavir/ritonavir (LPV/r).[31]

Favipiravir is an emergency drug in India, China, Russia, and Japan to treat COVID-19 infection.[2] The drug has shown delay in embryo development in animal studies and death of embryo in peri- and pre-implantation period. The available data and clinical trials show that favipiravir cannot be recommended in pregnant and lactating women.[32]

2.2. 3.3. Lopinavir/ritonavir

Lopinavir and ritonavir are antiviral drugs used for the treatment of HIV patients. These viral proteinase inhibitors inhibit viral replication and cytochrome P450-3A4 enzymes.[2]

Previous studies have not shown any adverse effects on pregnancy but, a small dose of the drug crossed the placenta. Thus, LPV/r is a remedial option against COVID-19 infection in pregnant women. Existing guidelines advise HIV-infected mothers not to breastfeed their newborns. Hence, there is restricted use of LPV/r during breastfeeding.[33]

In a randomized clinical trial of hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir-ritonavir treatment outside standard care.[34]

Beyls et al showed the risk of bradycardia in elderly COVID-19 patients. Cardiological or neurological impairment could be a critical sign of bradycardia since it is related to lymphopenia that appears to imitate the COVID-19 infection severity.[35]

2.2. 3.4. Umifenovir

Umifenovir is an antiviral and anti-inflammatory drug used in the prophylaxis treatment and influenza A or B, oseltamivir-resistant viruses, and flu symptoms caused by viruses. It has been shown to inhibit the virus-cell membrane and virus-endosome bonds, which act directly and prevent entry to the target cell by the virus, thereby defending the target cell from infection.[36]

Studies on Umifenovir in COVID-19 patients show conflicting results. Lian et al study showed patients in the umifenovir group (n = 45) had a more extended hospital stay (13 days [interquartile range {IQR} 9–17] vs 11 days [IQR 9–14], $p = 0.04$) than patients in the control group (n = 36) and did not improve the prognosis of COVID-19 clearance.[37]

In a retrospective cohort study by Deng et al, the isolated use of LPV/r was compared with umifenovir use and observed better viral clearance and pulmonary tomographic aspects in the LPV/r plus umifenovir group.[38] In difference, Zhu et al concluded that arbidol (Brand name) monotherapy showed better results than LPV/r monotherapy when evaluating the viral load in patients with COVID-19 (patients in the LPV/r group had a higher viral load after 14 days of treatment [44.1%], $p < 0.01$).[39]

There are no well-controlled studies on the use of umifenovir during pregnancy. The use of umifenovir during pregnancy is contraindicated. It is unknown whether the metabolites generated can enter breast milk. If it is necessary to use umifenovir during this period, it is recommended to stop breastfeeding

2.2. 4.Antiparasitic

2.2. 4.1. Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial and immune-modulatory drug mainly used for malaria and immune-related conditions. HCQ has shown antiviral properties by inhibiting viral replication by binding to the ACE2 receptors and dampening the cytokine storm *in vitro* studies.[40]

Initial studies showed beneficial effects but, in the WHO SOLIDARITY study, HCQ failed to show any beneficial effect in severe infection. Administration of HCQ showed prolonged QTc interval in cardiovascular patients and cardio-pulmonary impaired severe COVID-19 infection. Hence, HCQ is not recommended for COVID-19 treatment in pregnancy.[41]

2.2. 4.2. Ivermectin

Ivermectin, a broad-spectrum anti-parasitic and pregnancy C category (US FDA) drug, has shown potential as antiviral activity against DNA/RNA viruses. It acts on viruses by inhibiting the activity of importin alpha/beta and blocking the viral protein entry into the host cell.[42]

In Vero-hSLAM *in vitro* cell culture (48 hours post-infection) study, ivermectin showed reduced SARS-CoV-2 load by 5000-fold. Even the oral dose of about 120 mg *in vitro* (to reach Cmax) was a less effective concentration for *in vitro* activity, raises efficacy and safety concerns, and is practically impossible to administer a higher concentration of ivermectin in human beings.[43]

System review and meta-analysis of 17.3% of pregnant women at first trimester by Nicolas et al study demonstrated inconclusive evidence regarding the efficacy and safety concerns in pregnant and lactating women.[44]

2.2. 5.Antimicrobials

2.2. 5.1. Azithromycin

Azithromycin is a broad-spectrum antibiotic and pregnancy Category B (US FDA) with proven antiviral activity against Ebola, Zika, and Influenza A (H1N1). Few studies demonstrated that the combination therapy of HCQ and Azithromycin was significant in treating COVID-19 patients.[45] Brazilian clinical trial I and II COALITION study did not improve the clinical outcomes of the 447 enrolled COVID-19 patients (OR 1.36 [95% confidence interval 0.94–1.97], $p = 0.11$).[46]

Azithromycin expels into human milk, but there are inadequate *in vivo* and *in vitro* data about the harmful effects on the fetus or infant. However, Azithromycin can be used during pregnancy and breastfeeding in emergency use.[47]

2.2. 5.2. Doxycycline

Doxycycline, a tetracycline group of antimicrobial, and pregnancy category D (US FDA) drugs, have shown antiviral activities against HIV.[48]

It increases the pH and upregulates the intracellular zinger finger proteins thereby, inhibiting viral replication. Malek et al study in COVID -19 patients demonstrated doxycycline and HCQ or other putative agents showed anti-inflammatory and antiviral activities by reducing the cytokine storm.[49]

Tetracyclines are known to show bone formation defects and staining of tooth enamel and enamel damage. Hence, doxycycline in pregnancy, lactating women, and children below eight years is not recommended.[50]

2.2. 6.Interleukin-6 inhibitors

Tocilizumab (TCZ) is a recombinant humanized monoclonal IgG1 antibody that disrupts signaling of both soluble and membrane-bound interleukin-6 inhibitor receptors, reducing effects on inflammation downstream and the innate immune response.[51] TCZ is licensed in over 75 countries for rheumatoid arthritis and related rheumatological diseases and chimeric antigen receptor T-cell therapy-associated cytokine release syndrome.[52]

In a German case series, among 16 prospectively registered cases with maternal TCZ, 4 had spontaneous abortions (SAB).[53] In Hoeltzenbein et al review of pregnancy-related TCZ safety database review, among 108 reported pregnancies, 50.9% of live births, 28.7% spontaneous abortions, 20.4% of elective terminations, and three infants with congenital anomalies were reported.[54]

The use of TCZ appears to be safe in using COVID-19 infection in pregnancy. But limitations of available findings are relatively small sample size. Therefore, controlled studies are vital for investigating the adverse effects of TCZ on pregnancy and pregnancy outcomes.

2.2.7.Monoclonal antibodies

Currently, three anti-SARS-CoV-2 monoclonal antibodies (mAbs) products have received Emergency Use Authorizations from the FDA to treat mild to moderate COVID-19 in non hospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization. *Bamlanivimab plus etesevimab*; Casirivimab plus imdevimab: Sotrovimab: These aims an epitope in the receptor-binding domain of the spike protein of COVID-19 virus that is preserved between SARS-CoV and SARS-CoV-2.

The use of anti-COVID-19 mAbs can be considered for pregnant people with COVID-19, particularly those with added risk factors for severe disease. The approved anti-SARS-CoV-2 mAbs, likewise IgG mAbs, would be anticipated to cross the placenta.[55]

2.2.8.Other treatments

2.2.8.1.Convalescent plasma

Use of plasma from recovered COVID-19 infected patients with neutralizing antibodies is under examination for disparagingly ill subjects who are not responding to any other therapies. Mortality rates of 17% vs 32% (OR 0.49) were observed in patients with convalescent plasma (CP) treatment compared with control patient groups, respectively.[56]

In a US national registry-based retrospective study, patients hospitalized with COVID-19 who were not receiving mechanical ventilation, CP lowered the risk of death among COVID-19 infected patients.[57]

Studies on the use of CP in pregnant women in viruses like Ebola and COVID-19 did not show any adverse effects on pregnancy and fetal outcome.[29,58]

In Franchini et al systemic literature review exposed a lack of existing, precisely scientific research designed on the safety of CP for the maternal and fetal outcome. The quality of the

accessible studies is still low as there are only case reports and therefore agonize from applicable reportage bias.[59]

2.2.8.2.Janus kinase inhibitors

Baricitinib (JAK 1 and JAK 2 inhibitor) and Tofacitinib (JAK 1 and JAK 3 inhibitor) are the Janus kinase inhibitors shown to be potential against COVID-19 infection. Preliminary studies show no adverse effects in exposed pregnancies and pregnancy outcomes.[60,61]

Baricitinib in patients with an eGFR <15 mL/min is not recommended. Tofacitinib was associated with additional adverse events, including heart attack, stroke, cancer, blood clots, and death. After 10 to 100 fold exposures, Tofacitinib showed teratogenic effects in preclinical studies on animals, including defects in membranous ventricular septal and malformations or skeletal/cranial variations. In lactating rats, both tofacitinib and baricitinib are defecated into the milk. During pregnancy, JAK inhibitors are contraindicated. During and at least one week after treatment of JAK inhibitors, operative contraception must be used in women of child-bearing age. JAK inhibitors should not be used throughout breastfeeding as it poses risks to newborns or infants.[62]

2.2.8.3.Colchicine

Colchicine induces the arrest of cells at metaphase in mitosis, has an anti-inflammatory effect. Colchicine exposed to 2100 pregnant women did not show any adverse effects on pregnancy outcome and fetal risks.[63,64]

Available data does not show any adverse effects on pregnancy or congenital anomalies. Colchicine belongs to AU TGA pregnancy category: D and US FDA pregnancy category: C. A systemic review by Carnovale et al reported of 1152 pregnancies treated with colchicine in women with familial Mediterranean fever, caused abortions in 31%, miscarriages in 14% of women, fetal anomalies in 16%, eight stillbirths, preterm delivery in 60; nine early gestational age and preeclampsia in three.[65] There are currently limited data for colchicine use in pregnant women with acute COVID-19. The risks of the use of colchicine should be balanced against potential benefits.

Table 1 summarizes the drugs and recommendations to treat COVID-19 in pregnant and breast cancer women.

2.3. COVID vaccines and pregnancy

Pregnant and lactating women were not involved in developing and clinical assessment of COVID-19 vaccines and treatments. The US Food and Drug Administration, the Advisory Committee on Immunization Practices, and other regulatory professional authorities left open the choice for pregnant and lactating women to take the vaccine.

In February 2021, the Pfizer/BioNTech vaccine was the first trial in pregnant women (ClinicalTrials.gov identifier: NCT04754594).[16]

In a study conducted by Gray et al on 131 subjects involving 84 pregnant and 31 lactating women, vaccine-induced antibody titers (Pfizer/BioNTech and mRNA-1273 Moderna/National Institutes of Health) were equal in pregnant and lactating women associated with nonpregnant women (pregnant, median, 5.59; IQR, 4.68–5.89; lactating, median, 5.74; IQR, 5.06–6.22; nonpregnant, median, 5.62; IQR, 4.77–5.98). All titers were suggestively higher than those influenced by severe COVID-19 infection during pregnancy ($p < 0.0001$). The second vaccine dose (boost dose) increased severe COVID-19 infection-specific IgG in maternal blood and breastmilk, but not IgA[58]. Both Pfizer/BioNTech and mRNA-1273 Moderna vaccines use mRNA to carry the SARS-CoV-2 spike antigen to the immune system.[66,67]

The University of Oxford and Astrazeneca's (AZD1222/vaxzevria; ChADOx1 non-replicating chimpanzee adenoviral vector, double dose) is with overall 70.4% efficacy did not involve pregnant women.[68–70]

Johnson & Johnson-Janssen Pharmaceutical's Ad26.COV2.S (Ad26 non-replicating human adenoviral vector, single dose) with 65.5% to 66.3% efficacy did not show any adverse effects in pregnant and lactating female rabbits. But in phase III trials, the study reported unintended pregnancies in eight females during vaccination, one miscarriage, and one ectopic pregnancy.[71,72]

The WHO Strategic Advisory Group of Experts on Immunization has issued provisional approval for using the Sinovac-CoronaVac vaccine against COVID-19. The existing data on the Sinovac-CoronaVac vaccine in pregnant women are inadequate to evaluate either efficacy of the vaccine or possible vaccine-associated pregnancy risks. This vaccine is an inactivated vaccine with an adjunct generally used in many other vaccines, including pregnant women, with a well-documented safety profile, such as Hepatitis B and Tetanus vaccines. The benefits of vaccination to pregnant women outweigh the potential risks.[73]

Currently, the Government of India has permitted vaccination of pregnant women against COVID-19 based on the commendations from the National Technical Advisory Group on Immunization. The eligible pregnant woman will be able to get any of the three vaccines currently authorized in India; Covishield (ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), the local version of the AstraZeneca vaccine), Sputnik V (Gam-COVID-Vac, adenovirus vaccine, imported from Russia), or Covaxin (Whole-Virion Inactivated Vero Cell, India's homegrown vaccine). A pregnant woman, who selects to take the vaccination, could be vaccinated at any time of the pregnancy.[74,75]

Table 1

Drugs used to treat pregnant and breastfeeding women in COVID-19 infection

Drug	Crosses the placenta	Safe for use in pregnancy	Compatible with breastfeeding	Present in breast milk
Chloroquine/hydroxychloroquine	✓	✓	✓	✓
Remdesivir	✓	No effects in animals, Under investigation	✓	✓
Lopinavir-ritonavir	✓	✓	✓	✓
Umifenovir	No data available	No data available	No data available	No data available
Favipiravir	No data available	No data available	No data available	No data available
Azithromycin	✓	✓	✓	✓
Corticosteroids	✓	✓	✓	✓
Tocilizumab	✓	X	✓	X
Colchicine	✓	✓	✓	✓
Ivermectin	✓	X	✓	X
JAK inhibitors	✓	X	✓	X

Additionally, the gestational age of de novo production of maternal antibody affects the level of COVID-19 specific antibody in the cord blood, suggesting that there may be an ideal time for vaccination in mothers before delivery to enhance fetus protection. During epidemics, delivery at 32 to 34 weeks is considered. The indication for the Cesarean section should be flexible to minimize the risk of infection during the delivery.[76]

Altogether, it can be supposed that COVID-19 vaccination of mRNA based can be helpful to pregnant women in the second trimester or prior may be a better choice than given in the third-trimester.[77]

In conclusion, COVID-19 causes severe respiratory illness and significant morbidity and mortality, requiring hospitalization of all with SARS-CoV-2–infected pregnant women. Few drugs like doxycycline, favipiravir, HCQ are known to cause adverse effects on pregnancy, and fetal outcomes should be avoided in treating pregnant women with COVID-19 infection. Trials like RECOVERY suggest using prednisolone 40 mg, hydrocortisone (80 mg) intravenously in pregnant women. AICOG indicates that after using dexamethasone, it should be replaced with methylprednisolone to complete a 10-day course. Given what is acknowledged about the COVID-19 drugs and vaccines, the limited data regarding COVID-19 vaccines in pregnant and lactating women from those who have been vaccinated, and the use of other vaccines throughout pregnancy, clinicians can permit to make an informed choice by pregnant or lactating women.

Wearing of masks, hygiene of hands, social distancing should be essential methods for both vaccinated and nonvaccinated pregnant and lactating women due to predilection or exclusion from clinical trial policies. Future investigational data is necessary to assess the safety of the COVID-19 drugs and vaccines in pregnancy-related maternal and neonatal outcomes. Safety archives of suitable value, preferably with an active investigation, would also deliver valid evidence from real-world investigational data.

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