

Impact of COVID-19 on pathophysiological changes on fetomaternal health and treatment strategies: A literature review

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- Received Date: 17 Feb 2022
- Accepted Date: 23 Feb 2022
- Publication Date: 26 Feb 2022

Keywords

COVID-19, coronavirus, pregnancy, and maternal health

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Abstract

Aim: During the coronavirus disease 2019 (COVID-19) pandemic, physiological changes in pregnancy have placed both the mother and the fetus at potential risk of infection. Particularly, changes in cardiovascular function, the coagulation cascade, the immune system, and the respiratory system may be instrumental in the COVID-19 disease progression. Since this is a novel virus, the management, treatment, and prevention of COVID-19 is still evolving in general and obstetric patients as well. Therefore, it has become very crucial to study its effect on pregnancy and how providers adapted new practices pragmatically without prior scientific data. Our goal is to focus on addressing these issues systematically.

Methods: We selected all the peer-reviewed articles on pregnancy-related to COVID-19 infection. Search terms were COVID-19, coronavirus, pregnancy, and maternal health using google scholar, Centers for Disease Control and Prevention (CDC), and PubMed.

Results: We demonstrated the direct and indirect impact of COVID-19 on maternal health, including physical, mental, and social effects. We primarily highlighted case series and cohort studies discussing the clinical course, management, pathophysiological (immunological) changes, and the outcomes of COVID-19 infection in pregnant women.

Conclusion: We discussed the physiological, pathological, and mental health changes in pregnant women with COVID-19 infection and the current evolving management plans, treatment approaches, and preventive measures to combat the disease. A global effort in further research is essential to determine and minimize the impact of COVID-19 on pregnant women and their outcomes.

Introduction

The rapid coronavirus disease 2019 (COVID-19) outbreak across the world has tremendously affected our health and lives with uncertainty. As this is a novel virus, the management, treatment, and prevention of COVID-19 is still evolving. While this global crisis generally affects various susceptible individuals and groups, obstetric patients are particularly vulnerable.

Pregnancy with its significant physiological changes during this pandemic is of serious concern owing to the potential risk of infection to both the mother and the fetus [1]. Changes in the cardiovascular

function, the coagulation cascade, immune system, respiratory system may play a primary role in the progression of COVID-19 disease. It has become critical to study its effect on pregnancy and how providers adapted new practices pragmatically without prior scientific data [2]. Global effort in further research is essential to determine and minimize the impact of COVID-19 on pregnant women and their outcomes. It is imperative to discuss the physiological, pathological, and mental health changes in pregnant women with COVID-19 infection and the current evolving management plans, treatment approaches, and preventive measures to combat the disease.

Citation: Hussain H, Tabassum T, Tasmin R, et al. Impact of COVID-19 on pathophysiological changes on fetomaternal health and treatment strategies: A literature review. 2022;2(1):1-8.

Moreover, due to the shift of social and healthcare practice to a new norm, mental stress has increased during the prenatal period, which passively affects maternal health [2,3]. A limited number of studies highlight these areas, which eventually led us to explore the impact of COVID-19 on pregnancy.

Physiological changes during pregnancy and its implication in the occurrence of COVID

Immunological changes during pregnancy

Many physiological and immunological changes during pregnancy help nurture and accommodate the developing fetus inside the body [4]. Among the immunological responses, T cells play a significant role in modulating immune responses. T helper cells can be classified as helper T cells and cytotoxic T cells. Helper T cells are further classified into Th1 and Th2 cells, Cytokine producing cells. Th1 cells produce IL-2, IFN- γ , which are pro-inflammatory cytokines and are involved in cellular immunity. Th2 cells generate IL-4,5 & 13, which are anti-inflammatory, counteract the effects of Th1 cytokines, and are involved in humoral immunity, as shown in Figure 1.

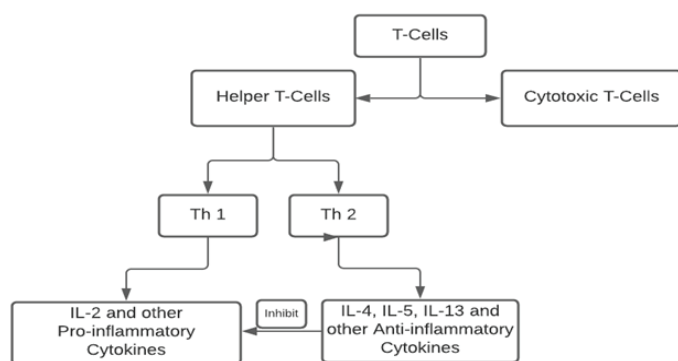


Figure 1. T-cells immunomodulatory function in pregnancy.

During pregnancy, the effects of Th1 are downregulated and there is a shift towards Th2, which allows for immune tolerance for developing fetuses and contributes to increased susceptibility towards viral infection, especially respiratory pathogens. However, an overt Th1 response towards SARS-CoV-2 has been implicated in the development of the severity of COVID-19 [5]. A Th1 mediated immune response plays a key role in the lung damage of COVID-19 patients, and the release of Th1 mediated cytokines such as IL-6 has been associated with adverse outcomes. Therefore, shifting of immunological response towards Th2 and downregulation of Th1 helps pregnant women to have reduced effects of COVID-19 severe complications [5,6].

Additionally, the Natural Killer cells decrease in amount during pregnancy which also reduces viral clearing capacity. Despite that, whether this diminution in the amount of Natural Killer cells has any effect on the occurrence of COVID-19 infection, has not been clarified. Moreover, progesterone level increases during pregnancy, which has some immunomodulatory effects. Progesterone increases the repair of lung damage induced by the influenza virus. Therefore, it can be inferred that high levels of progesterone have beneficial effects over pregnancy to protect the mother and fetus from the severity of COVID-19 [6].

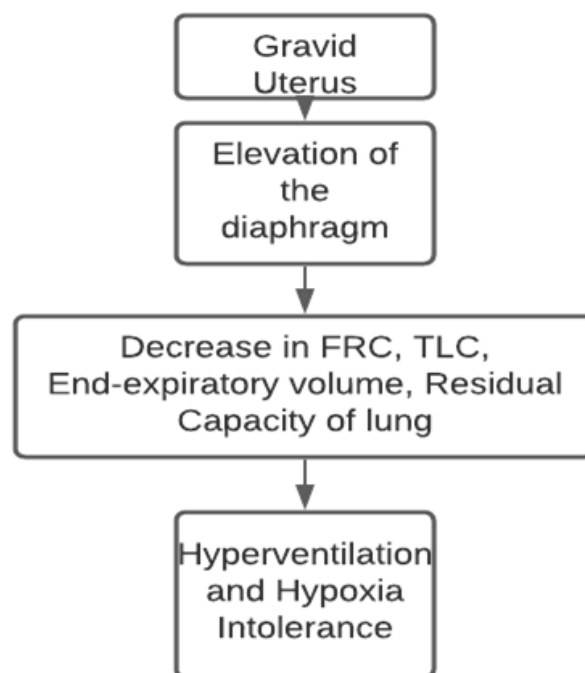


Figure 2. Respiratory changes during pregnancy.

However, during pregnancy, every organ system undergoes some changes to adapt to the new change. Among those changes, some have beneficial effects for both mother and fetus, and some can cause deleterious effects if pregnant women are infected with infectious diseases. For example, during pregnancy, cardio-pulmonary and hematologic changes can cause some detrimental effects if pregnant women become infected with COVID-19.

Cardiopulmonary changes during pregnancy

During pregnancy, the diaphragm elevation by the gravid uterus causes a decrease in total lung capacity, functional residual capacity, end-expiratory volume, and residual volumes [5,6]. Besides this, pregnancy causes respiratory mucosal edema and increased oxygen consumption, which in turn causes hypoxia intolerance, as shown in Figure 2. It has been proposed that hyperemia and edema of the upper respiratory tract, in addition to the restricted lung expansion and subsequent reduction of the clearance of respiratory secretions, contribute to increased susceptibility of pregnant women to respiratory pathogens [6,7]. Therefore, if a pregnant patient is infected with SARS-CoV-2, there is a risk of development of severe pneumonia and hypoxemic respiratory failure (demonstrated in Figure 3) [6,7].

Furthermore, pregnant women undergo some cardiovascular changes, which can cause some adverse outcomes if they are infected with COVID-19 [5-7]. During pregnancy, stroke volume and cardiac output increase, and resistance to blood flow through peripheral vessels reduces. The effect of heightened vasodilation on lung endothelial cell function is yet to be established [6,8]. However, pregnancies complicated with preeclampsia, which is caused by disruption of spiral artery remodeling in the placenta, prevents blood flow

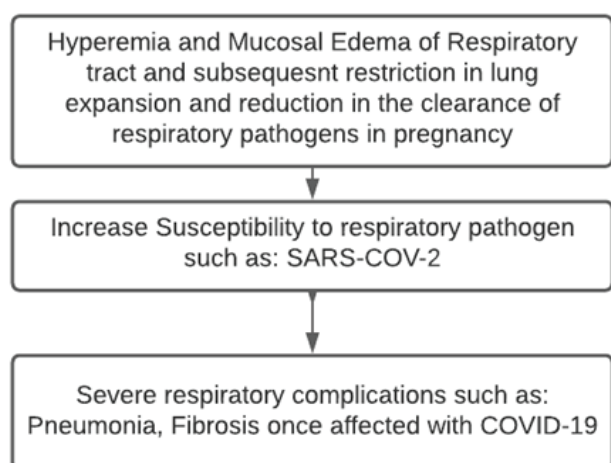


Figure 3. Effect of COVID-19 on pregnant women.

to the placenta. This culminates in reduced perfusion in the uteroplacental circulation.

The secretion of pro-inflammatory cytokines by the placenta could be attributed to the decreased blood flow in the placental circulation, which spread to maternal circulation and cause an insufficient decrease in vascular resistance and associated endothelial cell dysfunction and maternal hemodynamic instability. Therefore, pregnant women with preeclampsia who are infected with COVID-19 may develop severe complications [6,8].

Coagulation changes

Pregnancy is a hypercoagulable state [4-6,9]. During pregnancy certain coagulation factors such as Factor VIII, IX, and X increase, and certain anticoagulants such as antithrombin and protein S decrease in amount [4,5,9]. The overall anticoagulant activity is reduced throughout the pregnancy and returns rapidly to baseline following delivery. Moreover, any infection stimulates the coagulation cascade and the inflammatory response. This event further stimulates the release of pro-inflammatory cytokines, which causes activation of the coagulation cascade. Therefore, pregnant patients infected with COVID-19 have an increased risk of pulmonary embolism and other severe complications related to COVID-19 [5,10].

Signs and Symptoms of pregnant women infected with COVID -19

The clinical course of pregnant and non-pregnant individuals has been reported as quite similar despite the physiologic and immune function changes in pregnant women. Yet, there is no evidence of whether the virus transfers or not during childbirth or pregnancy. Hence, a systematic review should be done to know more about the outcomes of pregnancy infected with covid-19 [11].

Some reviews have shown that the vertical transmission could be possible. The third trimester can be most critical, but there are variations in the rates of adverse outcomes. More research should be done on pregnant women (before and after delivery) and their infants [12]. Data shows that the sign symptoms of covid-19 infected pregnant women are similar to

that of the non-pregnant covid-19 infected female of the same age. Pneumonia is the most common outcome in both cases. Surveillance programs should be activated at the end of the second trimester [13].

The sign symptoms of COVID infected pregnant patients are similar to that of the non-pregnant young females. Anatomical and respiratory structures change in pregnancy [14]. Mindfulness, meditation, and biofeedback have shown effectiveness in improving one's mental health through countering dejection. Freehand physical exercise such as yoga could ameliorate dispiritedness, anxiety and may even influence birth outcomes in a positive manner. We should focus on methods to increase ease of uptake and ensure each option is available at home [13,14].

Vertical transmission of COVID-19 from mother to fetus

UWHO has declared COVID-19 as a global pandemic. Ever since the pandemic hit, millions of people across the globe have lost their lives within a few days after contracting the virus. Nevertheless, it has been predominantly non-pregnant adults, who have been the subject of the research regarding the impact of COVID-19 for the most part [15]. Therefore, the severity among pregnant patients is not fully known except for the few recorded cases. Though there is a hypothesis based on the point that COVID-19 can transmit vertically from mother to fetus, there is not sufficient data to bolster this hypothesis. In this review article, we will try to write down some of the cases to support the doubt on the hypothesis.

A study by Huang and Colleagues published in the lancet did a retrospective review of the records of nine pregnant patients who were admitted at the beginning of the pandemic with COVID-19 symptoms such as fever, cough, and shortness of breath within 37 to 41 weeks of gestation in Wuhan, China. Although all the patients had Cesarean section within three days of admission, none of them were intubated. The outcomes of the mother and neonates were good except one neonate who tested positive for SARS-CoV-2 at 36th hour after delivery. He was kept in the neonatal unit but later discharged in good health. All the pregnant women received oxygen therapy via nasal cannula, antiviral treatment, antibiotics, interferons, and some Chinese medicines. Five patients were also treated with methylprednisolone after cesarean section. They were discharged after their symptoms subsided, and two consecutive tests for SARS-CoV-2 came out negative. In the beginning, all of the patients had B/L pneumonia, and later the findings were normal. However, this study mentioned some limitations. For instance, all nine pregnant patients were in their third trimester, so the effect of COVID-19 on the fetus in the first and second trimester still needs further study [15]. Furthermore, there was not any evidence on whether it is vertically transmissible. Long-term outcomes and mother to fetus transmissibility needs further investigation, as we discussed earlier.

Though SARS and MERS had deleterious effects on pregnancy outcomes and caused maternal death, on the other side COVID-19 has similar effects and complications both in pregnant and non-pregnant populations. Another review article described the impact of COVID-19 on 38 pregnant women and neonates. In this review article, 38 pregnant women and their neonates have been tested for SARS-CoV-2 in China and the effects of COVID-19 on pregnancy, neonates, and transmissibility. Unlike SARS and MERS, SARS-CoV-2

had no adverse effects on pregnancy as well as on neonates. In addition to that, there was no evidence of COVID-19 on the placenta, which casts doubt on whether COVID-19 can transmit vertically [16].

However, another article reviewed sixty articles to determine the transmissibility of COVID-19 to fetuses, and they found that a total of 1287 SARS-CoV-2 positive pregnant cases were reported. In these studies, severe COVID-19 and critical COVID-19 illnesses were approximated to those of the non-pregnant population. Among them, nineteen neonates were SARS-CoV-2 positive. Possible vertical transmissions were assessed by RT-PCR testing of the nasopharyngeal swab, placenta, cord blood, and breast milk. Four placenta and one cord blood sample came out to be positive irrespective of having negative RT-PCR in these neonates. Forty-five breast milk samples were assessed and were found to be SARS-CoV-2 negative [17]. Therefore, we cannot entirely exclude the possibility of COVID-19 transmission from mother to fetus.

Moreover, another review article has mentioned the effects of COVID-19 on neonates and the outcome of pregnancy by reviewing the records of 108 pregnant women infected with COVID-19. Although perinatal outcomes were found to be satisfactory, there was one neonatal death, and six neonates were transferred to NICU and then discharged in good health. No maternal to neonatal transmission has been recorded except one neonate who tested positive for SARS-CoV-2 at 36 hours after the delivery, even though no mother and neonate contact took place, and isolation was placed immediately after delivery. Besides, another neonate had high levels of IgG and IgM even though he was tested negative for RT-PCR. Both of these neonates' mothers were COVID-19 positive [18].

Although there are few cases with the possibility of COVID-19 transmission from mother to fetus, we need to gather more data by including more pregnant women with COVID-19 infection and by excluding all the other factors which can cause the transmission from mother to neonate.

High risk mother infected with COVID-19

Special care should be taken for the high-risk pregnant individual infected with COVID-19 infection. This includes patients with hypertensive disorders like preeclampsia, gestational hypertension, pregestational and gestational diabetes mellitus, maternal cardiovascular disease or neurologic conditions. Patients with history of preterm birth, prior stillbirth, intrauterine growth restriction, congenital anomalies, and multiple gestations including monochorionic placentation are also considered high-risk mothers, when these patients are screened as positive for COVID-19; close monitoring and frequent prenatal follow-ups are mandatory [7].

Telehealth during the antenatal period is beneficial since it lessens the risk of exposure to coronavirus when a pregnant mother receives prenatal care. Thereupon, it is of great importance that telehealth should be advised and geared for high-risk prenatal patients. Limited care of barriers was seen with commercial insurance. Additional patient levels and operational support are required to optimize the access of patients for Medicaid [19].

In high-risk populations, a severe disease often leads to intubation, intensive care admission (ICU) admission, and in many cases, death. The implications for pregnancy remain largely unknown. Early data suggest that COVID-19 may not pose an increased risk in the pregnant population. Vertical

transmission has not yet been confirmed. Since no definite treatment, and no herd immunity exist, social distancing is the best mechanism available to safeguard against coronavirus [20].

High-risk pregnant mothers are more susceptible to covid-19 infection and are more susceptible to respiratory failure. It is critical to deliver timely and administer steroids in critically ill patients. A high-risk pregnancy can severely affect maternal and fetal outcomes. Sometimes mechanical ventilation and premature termination of pregnancy are required, as explained in the schematic model in Figure 4 [21].

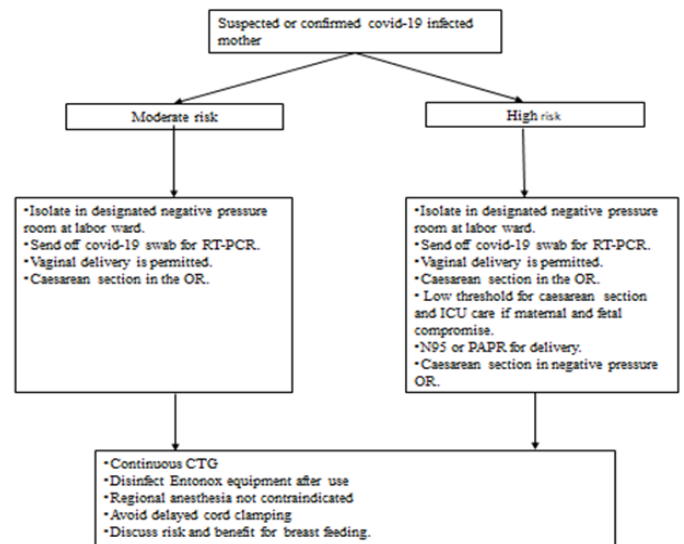


Figure 3. Schematic representation demonstrating a model for stratifying risk in obstetric patients presenting to the labor floor [21].

Diagnostic testing for COVID in pregnancy

General labs and imaging

The diagnostic performance for different upper and lower respiratory tract specimens and the role of blood and fecal specimens. Laboratory testing techniques constitute nucleic acid amplification tests, antigen detection tests, antibody detection tests, and point-of-care tests [22].

Imaging modalities are essential for the management of suspected Covid-19 patients. Before reverse transcription polymerase chain reaction (RT-PCR) test results turned out to be affirmative; the chest computed tomographic (CT) findings were conclusive of COVID-19 for a high percentage (60-93%) of patients. The point-of-care lung-ultrasound examination could play an important role in the triage of women with suspected COVID-19 [23].

Histopathology of placenta of mother infected with COVID-19

The presence of SARS-CoV-2 RNA in the vaginal swab suggests perinatal transmission could be possible. The possible relationship between placental fibrin deposition and chronic and acute intervillitis, non-reassuring fetal heart rate, and coagulopathy in pregnant women with COVID-19 [24].

Impact of COVID -19 on maternal mental health

Maternal mental health and well-being are imperative to address during pregnancy but have become more challenging

during this pandemic. Currently, no FDA-approved pharmaceutical interventions indicated for use in pregnant women are commercially available, thus leading to increased fear or concern about getting infected. It led pregnant women to rely on behavior change and non-pharmaceutical interventions such as self-isolation, physical distancing, working from home. As we are gradually getting accustomed to maintaining social distancing, the higher-risk groups are also being asked to 'cocoon', thus contributing to more factual reports of increasing levels of anxiety and depression among pregnant women. Besides, accounts of domestic violence are on the rise, the reasons for which are multifactorial and include increased economic stress, disaster-related instability, increased exposure to abusive relationships, and reduced external support, especially during their antenatal period [25].

Maternity services vary from elective procedures in that most of the care is time-sensitive and cannot be rescheduled. Regardless of this, many services canceled all routine antenatal appointments and obstetric surgery to allow healthcare systems to redirect care towards large numbers of COVID-19 infected patients requiring respiratory and other support [26]. The International Federation of Gynecology and Obstetrics (FIGO) has recommended that health organizations, fertility experts, and patients avoid pregnancies and temporarily discontinue all fertility treatments at present. Elective gynecological procedures are also being delayed, given the

scale of the current crisis [25].

It is difficult to determine when these patients will be facilitated for future treatment or when the normal antenatal visits will resume. During pregnancy, antenatal visits must be used as an opportunity to assess women who are at risk and ensure the necessary support is put in place to help them, especially during this particularly vulnerable time. This is an area for further review and will likely have a significant impact on society as they return slowly to a state of normalcy [25].

Treatment of COVID-19 during pregnancy

General Treatment of COVID-19

At present, along with standard supportive care, therapeutic approaches to COVID-19 treatment involve using antiviral agents that interfere with the SARS-CoV-2 lifecycle to prevent further viral replication and utilizing immunomodulators to dampen the immune system in order to prevent cytokine storm and tissue damage. While current therapeutic options vary in efficacy, several molecules were either shown to be effective against other viruses such as HIV or show promise in vitro that could add to the growing arsenal of agents used to control COVID-19 severity and spread [27]. Despite being a high-risk population, pregnant women have not been included satisfactorily in clinical trials for COVID-19 treatment, which needs to be addressed [28,29].

Table 1. Pharmacological management of COVID-19 during pregnancy

Name of the drug	Drug Class	Use in COVID-19	Administration	Adevrse Effects	Indication in pregnancy
Remdevisir	RNA polymerase inhibitor	Reduce viral load	IV	Severe liver dysfunction, diarrhea, skin rash and renal dysfunction	Yes
Ritonavir Lopinavir	Protease inhibitor	Reduce viral load	Oral	Headache, GI upset, dizziness, drowsiness, bad taste	Yes
Hydroxychloroquine and Azithromycin combination	Antimalarial and Antibiotic	Reduce viral load (Recent studies failed to show it)	Oral or IV	Headache, dizziness, loss of apetite, GI upset, Rash. BM supression in longterm use.	Yes
Corticosteriods	Analogues of steroid hormones	Anti-Inflammatory	Oral or IV	Fluid retention, Hypotension, Hyperglycemia, stomach upset, secondary infection, osteoporosis, adrenal insufficiency	Yes
Convalescent plasma	Polyclonal human antibodies	IV		Yes	
Tocilizumab	Anti-IL-6 monoclonal antibodies	Effective in COVID-19 with pneumonia	IV		Debatable
Ribavirin				Miscarriage, cranio-facial and limb defect.	Avoid in early pregnancy
Baricitinib				Embryotoxic	Avoid in early pregnancy
Favipiravir	RNA polymerase inhibitor	Reduce viral load	Oral	Teratogenic	No
LMWH		Reduce risk of pulmonary embolism in hospitalized COVID-19 pregnant patient	IM		Contraindicated

Treatment of COVID-19 during pregnancy

The current approach aims at symptomatic treatment and pregnancy-specific management of complications (Sepsis, ARDS). A high Sequential Organ Failure Assessment (SOFA) score and D dimer levels of >1 mg/mL on admission predict increased mortality even though D dimer level needs to be adjusted during pregnancy as the value is physiologically raised in pregnancy. It is not recommended to use systemic corticosteroids as they delay viral clearance with no survival benefit [30].

Despite the use of multiple drugs for treating COVID-19 infection, there is no absolute drug of choice for COVID-19 infection, let alone COVID-19 infection in pregnancy. Although some drugs have shown promising results [31].

Antiviral options:

- Remdesivir - effective against COVID-19 during pregnancy but has serious side effects, including severe liver dysfunction, diarrhea, skin rash, and renal dysfunction [28,31].

- Hydroxychloroquine and Azithromycin combination - In an early nonrandomized controlled trial in France, hydroxychloroquine combined with Azithromycin significantly reduced the viral load, but other studies failed to show this effect. Ironically pregnant women were often missing in these trial populations [29,31].
- Tocilizumab - a humanized anti-human IL-6 receptor monoclonal antibody, effective against COVID-19 with severe pneumonia. Use in pregnancy is debatable [31].
- Ritonavir, Lopinavir - has indications to be used in pregnancy, but pregnant women were often missing in the trial population [29,31].

Contraindicated in pregnancy - Ribavirin (associated with miscarriage, craniofacial and limb defect. Should be avoided in early pregnancy), Baricitinib (embryotoxic), Favipiravir (Teratogenic) [30,31].

Other Therapeutic Options-

- Convalescent Plasma - Can be used safely in pregnancy [31].

Table 2. Vaccination in pregnancy

Name of the Vaccine	Type of vaccine	Placental crossing	Doses	Efficacy	Adverse effects
BioNTech Pfizer	mRNA vaccine (mRNA, encodes stabilized spike lipid nanoparticle)	Low likelihood	2	95%	Fever, fatigue headache, chills, and muscle and joint pains. Neonates born to pregnant individuals with fever in their first trimester have been shown to have an increased risk for certain types of birth defects, although the absolute risk is small.
Moderna mRNA 1273	mRNA vaccine (mRNA, encodes stabilized spike lipid nanoparticle)	Low likelihood	2	94.50%	Fever, fatigue headache, chills, and muscle and joint pains. Neonates born to pregnant individuals with fever in their first trimester have been shown to have an increased risk for certain types of birth defects, although the absolute risk is small.
AstraZeneca and the University of Oxford AZD 1222	Based on viral vectors (Replication incompetent chimpanzee adenovirus vector, wild type spike)	Low likelihood	2	70.40%	Mild to moderate injection site pain. Mild to severe systematic adverse reaction including chills, fatigue, malaise, headache.
Johnson and Johnson Janssen Pharmaceuticals AD26.COV2.S	Based on viral vectors (Replication incompetent human adenovirus 26 vector stabilized spike)	Low likelihood	1	64% overall efficacy; 82% against Beta variant	localized and general side effects like injection site pain, swelling, malaise, muscle ache etc. Blood clots in the brain, abdomen, legs along with low levels of platelet have occurred in some patients.
Novavax	Protein subunit vaccine. Baculovirus (DNA virus that infects insect cells) expressed stabilized spike protein (Recombinant= Substance that are added to vaccines to boost immune response) + Matrix M adjuvant	Low likelihood	2	93% effective against predominantly circulating variants	Mild to moderate localized adverse effects like localized pain, tenderness. Systematic side effects like headache and fatigue are most common. Increased adverse effects with adjuvant.
GSK Sanofi	Protein subunit vaccine. Baculovirus (DNA virus that infects insect cells) expressed stabilized spike protein (Recombinant= Substance that are added to vaccines to boost immune response) + ASO3 adjuvant	Low likelihood	2		#Phase 3 clinical trial has been started in late May, 2021

Anticoagulant - Use of prophylactic low-molecular-weight heparin to reduce the risk of pulmonary embolism in pregnant patients hospitalized with COVID-19 as COVID-19 enhances the risk of intravascular coagulation and pregnancy itself is a hypercoagulable state [31]. All the pharmacological agents are described in Table 1.

Prevention of COVID-19 during pregnancy

General measures

a) Isolation, Quarantine, Community Containment can play an effective role in the prevention of COVID-19.

- Isolation - is the separation of ill individuals from non-infected individuals.
- Quarantine is movement restriction of contacts, often with fever surveillance. Quarantine is implemented when it is not evident whether a contact (who is not yet symptomatic) has been infected or has not been infected.
- Community containment includes measures that range from increasing social distancing to community-wide quarantine [32].

b) Proper disinfection by appropriate choice and method of hand sanitizer, disinfectants, hand gel, hand rub can play pivotal roles in preventing COVID-19. This can play an effective arsenal in our fight against this invisible enemy, especially in the absence of any proven treatment [33].

c) Community-wide mask-wearing may contribute to the control of COVID-19 by reducing the amount of emission of infected saliva and respiratory droplets from individuals with subclinical or mild COVID-19 [34].

Pregnancy specific prevention measures

Suspected or confirmed COVID-19 pregnant patients should not be allowed to visit medical institutions unless it is an emergency. In this regard, they can consult with their primary care physician by telephone encounter for prescriptions and advice. If a COVID-19 positive patient in labor has been given an inhalation labor analgesic, then the gas delivery apparatus needs to be decontaminated. If a suspected or confirmed COVID-19 pregnant woman requires supplemental oxygen in labor, a surgical mask should be worn over the nasal cannula to prevent aerosolized nosocomial droplet infection. During breastfeeding, COVID-19 positive mother needs to wear a face mask. For health care workers, the use of surgical masks is sufficient except for high-risk encounters such as endotracheal intubation, where the use of an N95 mask/FFP-2 respirator is appropriate (except for pregnant health care workers) [30,31].

Inclusion of pregnant women in phase 3 clinical trial protocol of adenovirus vectored vaccine and particularly a protein-based vaccine is needed as there are fewer safety concerns in protein-based vaccines [35,36].

Antipyretics should be used for treatment after vaccination (if fever, headache, chills, joint pain occurs) rather than for prophylaxis. Vaccination during pregnancy has tripling benefits as it protects mother, fetus, and newborn. Hence, pregnant individuals and their obstetricians will need to use the limited available data to weigh the benefits and risks of the COVID-19 vaccine during pregnancy (Table 2), taking into account the patient's specific risk of SARS-CoV-2 exposure. Both pregnant and lactating mothers who meet the criteria

for vaccination based on ACIP recommended priority groups should be vaccinated against COVID-19. Breastfeeding should be continued even after vaccination [29,36,37].

However, extensive human-based clinical trials need to be undertaken. Further research focusing on COVID-19 vaccine-associated risk during pregnancy and effects of COVID vaccine on milk production/excretion is required.

Conclusion

From our review of the articles, we were able to notice that an array of physiological changes that occur during pregnancy, gives rise to positive effects by making a favorable environment for the fetus. However, this immunomodulation has some deleterious effects when the mother is infected with COVID-19 resulting in an exaggeration of symptoms and severity. We were also able to appreciate the vertical transmission of SARS-CoV-2 from mother to fetus but there needs to be more research on this topic. The changes in the infrastructure of the health care delivery system and the new social norm have increased the levels of anxiety and depression among pregnant women. To ensure proper prenatal care, pregnant mothers should be advised to seek out telehealth services.

We were able to infer that there is no absolute drug of choice or preferred vaccine during pregnancy. Treatment of COVID-19 during pregnancy is mainly symptomatic based on the risk and benefit ratio. Therefore, inclusion of pregnant patients is needed in clinical trials for drugs and vaccines to determine safety, effect on fetus, lactation, passive immunity in the fetus, and several other outcomes.

Conflict of interest statement

The authors declare no conflict of interest.

Authors and contributors

All authors provided critical feedback and helped shape the review, and outcome of the manuscript. HH, Abstract, intro, maternal mental health, collected the published manuscript of the clinical challenge of COVID-19 in pregnant patient, compiled the framework, drafted the initial manuscript, and designed the figures. TT, reorganized the Figures, and tables, and rewrote some sections. RT Physiological changes, and vertical transmission, compiled the data and wrote the prevalence of COVID-19 in pregnancy. KIA has contributed on the management of COVID-19 in pregnancy, prevention, and conclusion. MJJ, signs, symptoms, and diagnostics part. SH edited the manuscript and helped to streamline it and SK conceived the original idea, edited, and mentored the writing the entire article.

Acknowledgements

The author would like to thank Dr. Alfred A. Simental, Chair of the Department of Otolaryngology for his constant help financially. We also thank Dr. MD. Mamoon to make possible to recruit HH, MA, MM, and PM in the BMANA Research fellowship program.

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