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# Pregnancy, peripartum, and COVID-19: An updated literature review

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**ABSTRACT**

Due to the physiological changes of the pregnancy and considering the susceptibility of the fetus, pregnant women are among the vulnerable health groups. The current COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has multiplied the health burden on vulnerable and susceptible groups. With over 500,000 new cases daily, the vulnerable groups are in danger more than ever. Therefore, early diagnosis, effective treatment, and efficient prevention strategies are significant among these groups. Since the clinical knowledge about the diagnosis, management, prevention, and many other aspects of pregnancy and lactation during COVID-19 has significantly changed and improved from the pandemic's beginning, most of the previous knowledge has changed, and the previous publications might not be helpful anymore. This review aims to provide an updated and comprehensive review of the mutual impact of pregnancy and COVID-19 infection, discuss the current controversies based on the most recent findings, and highlight the existing knowledge gaps. Due to the increased susceptibility, undesired outcomes are more expected among pregnant women with COVID-19 infection. Still, prevention measures are the best way of managing COVID-19 in this population. Moreover, further clinical studies should address the long-term complications, outcomes, safety of vaccination, and the impact of the pandemic on mental health.

**Keywords:** breast feeding, critical care, COVID-19, pregnancy, severe acute respiratory syndrome coronavirus 2

## INTRODUCTION

Coronaviruses are a family of zoonotic viruses, causing illnesses varying from a common cold to acute infectious pneumonia [1]. On January 7th, 2020, a new coronavirus was identified, which was further called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by World Health Organization (WHO) [2]. The virus's rapid spread makes COVID-19 a global concern [3]. It has led to one of the deadliest pandemics observed by human beings, with over 219,000,000 confirmed cases and over 4,500,000 deaths worldwide until September 2021.

The most important thing about communicable diseases is protecting the vulnerable population [4]. As pregnant women face a decreased functional residual capacity and increased oxygen consumption, COVID-19 infection may pose more significant risks [5]. Also, pregnancy is a critical condition in which the body's immune system is suppressed [6]. In addition to the concerns about the pregnant women's health condition, the health status of the fetus and the mechanisms of mother-to-fetus transmission, known as vertical transmission, are also important [7,8].

Despite the global thrive on obtaining a better knowledge of COVID-19, limited evidence are available about the impact of COVID-19 on pregnancy [9]. Therefore, this review aims to provide practical and evidence-based information on this issue.

## PREGNANCY & INCREASED SUSCEPTIBILITY

Pregnancy modulates the immune system instead of suppressing it. Recent studies have shown that the immune response of the placenta and its tropism in infectious diseases affects the susceptibility and severity of the disease in pregnant women [6]. It is undeniable that pregnant women are more prone to infections due to the impacts of pregnancy. The immune system of pregnant women undergoes many changes, mainly in order not to reject the placenta [10]. Although this

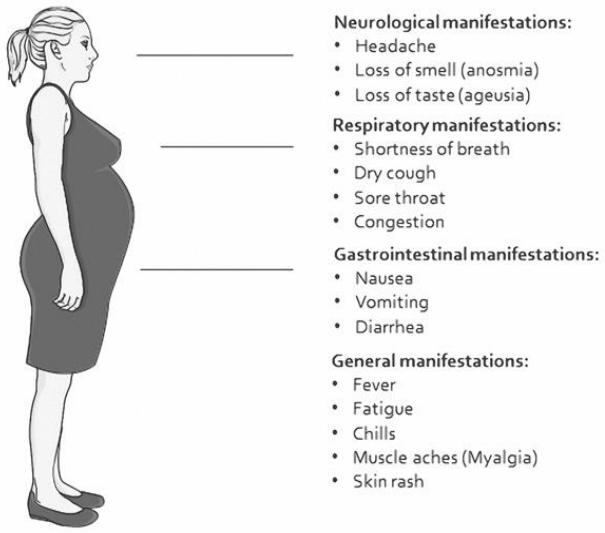


**Figure 1.** Pregnancy & increased susceptibility to COVID-19. *Parts of the figure were created using pictures from Servier Medical Art (https://smart.servier.com/).*
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safety modification is essential for fetal preservation and health, it could harm the mother. Evidence suggests that immunomodulation changes the balance of maternal T cells in the direction of T-helper type 2 (Th2) instead of T-helper type 1 (Th1) [6]. Therefore, pregnant women are more prone to severe flu complications and other infections [11,12]. As the pregnancy progresses, the immunological changes might impair pathogen clearance, which–along with other physiological changes in pregnancy, such as the decrease in lung capacity and the changes in urinary and blood flow–may increase the severity of the acquired infections [10]. In addition, the tropism of the placenta to certain viruses and pathogens increases a pregnant woman's susceptibility to certain infections [6]. Some studies have shown an increase in the incidence of infection among the pregnant populations compared with the non-pregnant women of childbearing age [13-15]. Controversial viewpoints are available regarding mortality risk, but most studies have pointed to an increase [16-18]. Infection among pregnant women results in higher hospitalization rates or intensive care unit (ICU) administration, preterm delivery, and cesarean delivery [19-21]. Despite this increased risk of infection, most pregnant women present with a mild or asymptomatic illness [22,23].

Hormonal changes are an important characteristic of pregnancy. Steroid hormones in the first trimester of pregnancy cause the ligaments to relax, including those attached to the thoracic ribs, which causes the diaphragm to move upward and reduce the lungs' functional residual capacity anatomically [24,25]. Hormonal changes during pregnancy are also associated with increased Th1 and Th2 responses, so more secretion of interferon (IFN)-α, interleukin (IL)-1, IL-4, IL-6, and IL-10 are associated with more severe complications of the disease [26]. It also shifts the Th1-to-Th2 ratio towards Th2, which is associated with more complications than non-pregnant people [27]. Suppression of natural killer (NK) and T cells in late pregnancy also slows down the process of cell clearance [28,29]. On the other hand, there appears to be a link between angiotensin-converting enzyme 2 (ACE2) and viral S protein in how the virus enters the cell, and this protein tends to bind to ACE2 receptors. [30-32]. As a result, increased ACE2 expression–which occurs in various organs of pregnant women, including the kidneys, placenta, and uterus–can increase the risk and severity of the disease (**Figure 1**) [33].

## Clinical Manifestations, Diagnosis, & Complications during Pregnancy

According to the current evidence, no significant difference has been observed between the clinical manifestation of COVID-19 in pregnant women and other patients [34]. Women with symptoms of COVID-19 infection and a history of contact with confirmed or suspected COVID-19 cases should be monitored [35,36]. Evaluating every pregnant woman is not obligatory, but it is preferred [37]. Fever is the most common symptom among pregnant COVID-19 patients [34]. Fever and hyperthermia can affect fetus organogenesis during the first trimester of pregnancy [38,39]. It also could lead to defects of the neural tube and miscarriage [40]. Maternal fever could also affect cranial development and heart and teeth health [41]. Studies found that even a mild fever exposure through the pre-implantation phase could lead to abortion [42]. Acetaminophen can be safely used to prevent complications, but the current evidence suggests that using Ibuprofen might exacerbate the condition and should not be used for COVID-19 patients [43-45].

Other common signs and symptoms include shortness of breath, fatigue, dry cough, sore throat, headache, weakness, myalgia, nasal congestion, and gastrointestinal manifestations, such as nausea and vomiting [46-49]. In contrast, many patients experience no evident symptoms [50]. Although the asymptomatic patients usually show no manifestations of the disease, the more critical issue facing these patients is that they are still carriers and can transmit the virus to the surrounding healthy individuals [51].

The most common symptoms in pregnant patients are not much different from the other patients, some of which are also seen in normal pregnancies, including fatigue, dyspnea, nausea, and vomiting. Imaging and laboratory findings are similar to those of non-pregnant women; therefore, the diagnosis of COVID-19 among the pregnant patients is not different from the others–except for the fact that other differential diagnoses, such as preeclampsia, HELLP-like syndrome, and deep vein thrombosis (DVT) should be considered and appropriately addressed [23,52,53]. **Figure 2** presents the most common symptoms of COVID-19 among pregnant women.

## Critical Care in Pregnant COVID-19 Patients

Pregnant women are among the group of patients who are more in need of intensive care and respiratory support with mechanical ventilation due to the anatomic and physiologic changes during pregnancy, including the rise in levels of estrogen and progesterone, peripheral vasodilatation, increased cardiac output, higher blood pressure, and changes in lung mechanics [54,55]. About 7-15% of COVID-19 pregnant patients will develop moderate to severe disease [56].

The WHO recommends maintaining maternal peripheral oxygen saturation ($SpO_2$) over 92% to 95%. If this number drops, arterial blood gas (ABG) can be used to measure the partial pressure of oxygen ($PaO_2$), which should be maintained above 70 to ensure that the fetus receives enough oxygen [57]. In the ICU, critical patients with COVID-19 are frequently

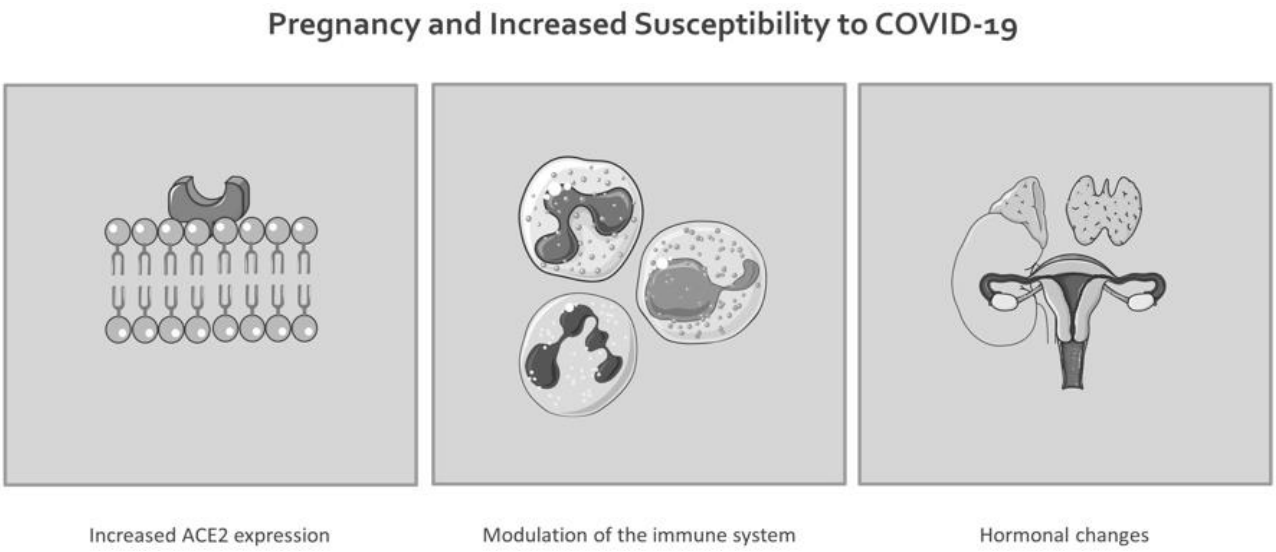


**Figure 2.** Common symptoms of COVID-19 infection in pregnant women.

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controlled withinside the prone position, and some ICUs have prolonged this technique for pregnant patients [58]. Padding above and underneath the gravid uterus>24 weeks is ideal for offloading the uterus and keeping away from aortocaval compression [59].

Fever management is another primary objective for pregnant patients under intensive care [60,61]. Permissive hypercapnia ($PCO_2$<60 mmHg) and extracorporeal membrane oxygenation (ECMO) appear to be safe in the management of acute respiratory distress syndrome (ARDS), although not many studies have been performed [62, 63]. However, high positive end-expiratory pressure strategies (>10 mmHg) require constant monitoring of the mother and fetus because of the reduction in the cardiac preload and output [59].

Numerous studies have shown that the death rate in pregnant women is higher than in non-pregnant ones [20, 64-66]. Hospitalization, ICU administration, the need for mechanical ventilation, and ECMO reception were also increased [16,67]. The over-activation of the inflammatory pathways in some patients could contribute to a higher need for mechanical ventilation and relying on high-dose corticosteroids and intravenous immunoglobulin (IVIg) for recovery [68]. Studies also have shown an association between the severity of COVID-19 and the incidence of preeclampsia and preeclampsia-like syndrome in pregnant women [69].

Older age (more specifically, over 35), increased body mass index (BMI), and underlying medical illnesses (such as high blood pressure, diabetes, and asthma) are risk factors for severe disease and increased risk of mortality [15,47,70-72]. Also, some studies have observed the effect of African-American and Asian races on increasing the severity of the disease, which still requires further studies to clarify the reliability of the previous findings and subtract the socio-economic confounding factors [73,74].

Recent studies have found that COVID-19-positive mothers are at higher risk for miscarriage, preterm delivery, preeclampsia, and cesarean delivery than the general population. Moreover, their newborns are at greater risk for premature death and hospitalization in the neonatal intensive care unit (NICU) [75-77]. Moreover, since COVID-19 infection is frequently seen with different symptoms among infants–including the multisystem inflammatory syndrome in children (MIS-C)–the infants require more careful monitoring to detect the atypical symptoms [78,79]. Pregnant hospitalized patients with critical infection, patients with comorbidities who require oxygen therapy, and patients with severe infection require a multispecialty crew and intensive care settings [16,80].

### Home Care and Follow-up

Outpatient management of the confirmed or suspected cases of COVID-19 in pregnant women is similar to non-pregnant ones [81]. In addition to the self-assessment tools, initial telephone triage also can determine the appropriate patients for self-care [82,83]. For women recovering from COVID-19, assessing the fetal growth using ultrasound is suggested, especially in patients who have experienced a severe illness [84]. Also, for suspected patients, pregnancy management must be based on clinical and ultrasound findings [85].

### Routine Perinatal Care

As mentioned earlier, pregnant women are at higher risk for complications and mortality from respiratory infections than the general population. As a vulnerable population, they must be more preserved from exposure to potential carriers. Several practical algorithms and clinical protocols have been published for managing pregnant patients [86]. Several changes have been suggested, which are based on risk levels (such as multiple pregnancies, high blood pressure, and diabetes) and include a reduction in the number of in-person visits, remote care, and duration of visits in order to minimize maternal contact with others, limit clients during visits and tests, determine the time of ultrasound examinations, and frequency and duration of using stress tests and biophysical profiles. It is recommended for all visits to be performed remotely unless the patient has a severe problem, which accounts for an emergency [59]. In these cases, the general principles of ultrasound diagnosis are to maximize prenatal diagnosis and minimize the risk of exposure [87]. Probable and

definite cases should be treated separately in a solitary room with negative pressure [88].

### Labor and Delivery

Pregnant women should be screened for COVID-19 before the scheduled induction or cesarean section [89]. This depends on balancing the risks and benefits of continuing pregnancy due to a positive or negative COVID-19 test result. Delivery time for each person should be determined based on the severity of the disease and complications such as preeclampsia, history of childbirth, gestational age, and fetal status [90].

Symptomatic patients should be followed up to prevent unexpected exacerbation in the clinical status. In other words, if the test results for COVID-19 are positive, the course of the disease may become more severe over time. In critical cases, continued pregnancy may jeopardize the safety of the mother and the fetus. In such cases, labor may begin even if the fetus is premature, and termination of pregnancy before the fetus reaches viability may be an option to save the mother's life after careful consultation with the patient and her family [91]. In mild cases and sustainable response to treatment, pregnancy can continue under strict supervision [91].

In general, delivery management does not change in suspected or confirmed patients during the pandemic. Contact between people and the length of labor should be limited to reduce the risk of spread (such as inpatient cervical ripening to decrease the time from induction to delivery) [92]. Before entering the delivery room, all healthcare workers should implement personal protective equipment (PPE), including a gown, gloves, surgical mask, and face shield [93]. Interventions that might increase the risk of infection and have not been proven beneficial should be limited as much as possible.

It is recommended for pregnant COVID-19 patients to have prenatal care and labor in an isolated room with negative pressure on the delivery section [94]. Traffic around this room should be limited [88]. SARS-CoV-2 has not been observed in vaginal and amniotic fluid secretions, so rupture of the fetal membrane could be performed for routine indications. Straining during childbirth often causes defecation. It should be noted that there are reports of live SARS-CoV-2 in feces [95].

In very few cases, the virus has been detected in the vagina or amniotic fluid [96]. On the other side, the mother's stool can be a probable infection source, although the benefits of the cesarean section have not been proven in this case. Thus, the cesarean section does not appear to reduce the infection risk in infants. Even if future studies prove the role of cesarean section in reducing the incidence, this alone is not a sufficient reason or a medical indication for cesarean delivery. Because the cesarean section is associated with risks for the mother, and on the other hand, babies born to infected mothers are often in good condition [97]. There is no increase in anomalies in children born to affected mothers [98, 99]. Also, the rate of stillbirth and intrauterine death is similar to that of the non-infected population [19,100]. However, the stillbirth rate has increased among hospitalized women [101,102]. This issue could be related to the disruption of the pregnancy care process [103-105].

Exposure to any virus in the newborn surroundings should be kept minimum to reduce the risk of infection. Some studies have recommended against the skin-to-skin contact between infants and mothers in these cases, although WHO has not recommended against [106]. One group of researchers has suggested that vernix caseosa remain in place for 24 hours after birth due to its antimicrobial peptides [107]. However, the American Academy of Pediatrics recommends the newborns to be bathed instantly after birth to wear the potential skin-covering microorganisms off [93].

### Miscarriage and Managing the Time of Delivery

Latest studies have found no significant association between the risk of miscarriage and COVID-19 infection [99, 108]. A recent review of six studies reported no cases of miscarriage in the confirmed COVID-19 cases during the first trimester, but two cases of perinatal death were reported out of 41 [109]. About 44% (14 out of 32) of the patients had preterm birth before 37 weeks of pregnancy, and 12.5% (4 out of 32) before 34 weeks. Although mild and moderate COVID-19 have no medical indications for prompt delivery, it seems that increased risk of preterm birth–especially in patients who have developed pneumonia–is one of the complications of COVID-19 among pregnant patients. Clinicians recommend cesarean delivery right after the result of COVID-19 testing has turned negative in order to minimize the risk of postnatal transmission; however, for the hospitalized patients with severe illness, delivery between 32 to 34 weeks of gestational age is advised. The delivery timing is challenging in critically ill patients. Before 32 weeks, continuing maternal support besides the fetal ultrasound monitoring is suggested until the maternal conditions are improved or at least stabled [110]. With current evidence, COVID-19 is not a contraindication for umbilical cord blood banking.

### Vertical Transmission

Although available evidence does not prove in utero transmission of COVID-19 [111,112], the possibility cannot be refused. The SARS-CoV-2 virus is not detected in amniotic fluid, placenta, or cord blood [113]. No definitive criteria for diagnosing COVID-19 vertical infection have been presented yet. Neonate nasopharyngeal swab, elevated immunoglobin M (IgM) level in cord blood, and reverse transcriptase-polymerase chain reaction (RT-PCR) test can be used for infection confirmation in the neonate. Studies have reported an increase in immunoglobin G (IgG) and cytokine levels in nearly all infants with confirmed mother infection [114], although these may have been from the maternal source. Postnatal contact with infected caregivers and parents can lead to a positive result in the IgM tests, which is not always due to the vertical transmission. The infants from mothers with COVID-19 should be considered suspected cases of COVID-19 and be tested within 24 hours following the delivery. Also, they should be isolated from other infants, according to the infection control precautions. Studies have ruled gestational hypertension and diabetes out as risk factors for intrauterine transmission of COVID-19 [115].

Studies have shown that the level of antibodies is elevated in the neonates born to a COVID-19-positive mother two hours after birth. Because of their size, IgM antibodies cannot be transferred to the fetus through the placenta. The infection cannot be ruled out the time of delivery, and IgM antibodies are not typically detectable during the first three to seven days of infection. However, IgM is not generally used to detect congenital infections due to false-positive and false-negative results, cross-reactivity, and testing challenges [93]. IgG antibodies can pass to the fetus via the placenta. Therefore, the elevated IgG levels may reflect maternal or infantile infection.

The studies have shown no positive RT-PCR test results for infants, so there is no evidence for congenital infection in these cases in favor of the vertical transmission, although these tests are not always positive in the infected [114,116]. A study of primary infant infection with SARS-CoV-2 found that 33 infants with COVID-19, born to mothers with the disease, had mild clinical symptoms and desired prognosis [117].

### Postpartum Issues

Pregnant women with severe or critical COVID-19 are at higher risk for complications, such as postpartum hemorrhage, thromboembolism, hypertensive disorders, and cesarean delivery [118-120]. Also, preterm delivery is more prevalent among the infected pregnant women than the non-infected, especially among those with pneumonia [66,121-123]. The risks of preterm delivery and membrane rupture increase with fever and hypoxemia, so an increased rate of preterm delivery in severe COVID-19 can be expected. Despite coagulation changes in pregnancy and COVID-19, a recent study has shown no increased risk of postpartum hemorrhage (PPH) in patients with COVID-19 infection. However, in this study, oxytocin usage was increased during and after delivery [124].

Differential diagnoses of intrapartum and postpartum fever are challenging. COVID-19 should be considered, especially in presence of respiratory symptoms. Also, as common causes of fever, chorioamnionitis and endometritis should be tested. For mothers with no symptoms of illness, routine maternal monitoring is enough, and for mild illness, checking vital signs and monitoring the intake and output is recommended. Continuous pulse oximetry monitoring should be performed for patients with moderate illness. Very close monitoring and care are indicated for severe conditions.

Mother-baby contact is associated with factors like mothers' and infants' clinical conditions and the mothers' desire to breastfeed [125]. However, isolating the newborn from the infected mother will decrease the risk of mother-child transmission [126]. WHO recommends no limitation of mother-baby contact [111], while the Centers for Disease Control and Prevention (CDC) advises the mother and the caretakers to use shared decision-making [127].

### Breastfeeding

Close contact during breastfeeding might lead to droplet transmission of the virus. Nevertheless, current evidence disagrees with the transmission of COVID-19 [112]. CDC recommends feeding the expressed breast milk by a healthy caregiver to prevent the infants' possible infection [128]. A breast pump could be used, and after each use, all parts in contact with the breast milk should be cleaned. If not possible, the mother can feed the neonate by taking precautions like wearing a mask and maintaining breast hygiene [129]. Breastfeeding offers health and developmental benefits to the neonate and the mother, and it should be encouraged. In addition, it is a source of anti-infective factors which can protect the neonate from getting infected in the first days of life [130].

### Prevention during Pregnancy

As well as the common recommendations regarding COVID-19 prevention, including social distancing, hand and respiratory hygiene, and frequent disinfecting of the common surfaces, pregnant women should be more careful [131]. Plenty of evidence is available on the benefits of using face masks [132,133]. Considering that no confirmed or prophylactic drug is available so far, the right use of personal protective equipment (PPE), maintaining strict hand hygiene, and regular disinfection are the most efficient measures to prevent this disease [132,134]. Although several studies have shown positive impacts of administering supplements, such as vitamin C, vitamin D, zinc, and Omega-3 fatty acids, against COVID-19 infection, no proof is available of the efficacy and safety of administering these supplements for the prevention of COVID-19 infection during pregnancy and for newborns, so far [135-137]. Current evidence suggests that SARS-CoV-2 is not transmittable by breast milk. However, if the mother is a suspected or confirmed case of COVID-19, feeding the expressed breast milk by a healthy caregiver is more favorable than direct breastfeeding. The mother should use a mask and maintain strict hand hygiene to prevent transmission during the breast milk expressing, by using alcohol-based hand rubs or soap and water. Proper disinfection should also be applied to the equipment by a healthy person.

### Vaccination

Pregnant women are more susceptible to a severe COVID-19, so the CDC recommends vaccination for this group. The vaccines do not pass through breast milk, but crossing antibodies provide hope that breastfed infants might have some level of protection against COVID-19 in case of maternal vaccination [138].

Pregnant women were excluded from the early COVID-19 vaccine clinical trials [139]. However, an observational study based on the "v-safe after vaccination health checker" surveillance system did not show obvious safety signals among pregnant persons who received mRNA vaccines against SARS-CoV-2 [140].

The safety of COVID-19 vaccines in lactating women and the effects of mRNA vaccines on breastfed infants or milk production/excretion have limited data available. It seems that mRNA vaccines are not considered a risk for breastfed infants; therefore, it is recommended that breastfeeding women who are among the groups recommended to receive the COVID-19 vaccine should get vaccinated with mRNA vaccines [141].

### Treatment and Drug Safety

Considering the early struggle in treating COVID-19 patients, the researchers and clinicians have decided to try the previously available drugs according to their mechanisms of action. Hence, many antivirals, antibiotics, antiparasitics, and antipyretics such as chloroquine and hydroxychloroquine, azithromycin, remdesivir, lopinavir, favipiravir, interferon beta-1a, and baricitinib have been proposed [142,143].

After testing multiple candidate drugs, remdesivir is currently the only approved drug by the United States Food and Drug Administration (FDA) to treat COVID-19 during hospitalization. The reports of the successful treatment of COVID-19- positive pregnant patients with this antiviral drug are limited to case reports [144-146]. IMPAACT 2032 is a non-randomized study of the effects of Remdesivir on groups of pregnant and non-pregnant women that aims to evaluate the impact of Remdesivir in the treatment of COVID-19. Pregnancy is a common condition, so it is important to include pregnant women in the ongoing large-scale clinical trials [147]. As an experimental medication, no information is available on using Remdesivir during breastfeeding.

**Table 1.** Proposed drugs for COVID-19 treatment, their pregnancy safety categories, & the amount of excretion into human milk

| Drugs | Excretion into human milk | AU TGA pregnancy category | US FDA pregnancy category |
|---|---|---|---|
| Tocilizumab | Unknown | C | Not assigned |
| Remdesivir | Unknown | B2 | Not assigned |
| Dexamethasone | Unknown | A (oral); C (parenteral) | C |
| Hydrocortisone | Unknown | A (oral, rectal foam); C (parenteral) | C |
| Prednisolone | Yes | A | C/D |
| Prednisone | Yes | A | C/ D (delayed-release tablets) |
| Methylprednisolone | Yes | A; C (acetate suspension) | C |

Note. FDA: Food and Drug Administration & TGA: Therapeutic Goods Administration

On July 6th, 2021, the WHO recommended using interleukin 6 (IL-6) receptor blocker, Tociluzimab or Sarilumab, and systemic corticosteroids in severe or critical COVID-19 patients [148]. The animal studies have not proven the teratogenicity of Tocilizumab, and limited studies on pregnant patients have indicated no increase in spontaneous abortion or congenital abnormalities among rheumatic disease patients treated with Tocilizumab. However, the safety of administering this drug during pregnancy has not been adequately established so far [149-151]. Tocilizumab can cross the placenta at low concentrations [152].

In the case of short-term usage, limited evidence suggests that systemic corticosteroids increase the risk of premature birth, low birth weight, preeclampsia, and risk of cleft lip and palate [153, 154]. Also, steroids are generally considered safe for use by breastfeeding mothers. A very low level of prednisolone in breastmilk does not seem to harm the neonate during breastfeeding. Likewise, no adverse effects have been reported in infants with maternal use of any corticosteroid [155]. Although, compared to prednisolone, methylprednisolone achieves higher lungs concentrations [156], based on the RECOVERY trial findings, oral prednisolone, and intravenous hydrocortisone are recommended for moderate to severe cases of COVID-19 [157]. WHO recommends oral dexamethasone or intravenous hydrocortisone in severe cases of COVID-19, but studies have recommended against dexamethasone during pregnancy, which is linked with an increased risk of prematurity and adversely affects skeletogenesis [158,159]. Limited data support dexamethasone in postpartum patients; therefore, methylprednisolone is recommended instead [160]. Also, long-term prospective studies have found that administering low-dose maternal prednisone during pregnancy and breastfeeding is safe for the offspring [161,162]. **Table 1** presents the amount of milk excretion and pregnancy safety category of drugs proposed for COVID-19 treatment.

### Mental Health

Anxiety is a general mental health problem during pregnancy [163]. Moreover, the COVID-19 crisis potentially threatens almost everyone's mental health [164]. In addition to common fears, such as infection and quarantine, pregnant women face other anxieties like fear of probable vertical transmission and possible teratogenic effects of the virus [165]. Thus, women are still vulnerable to mental health disorders even after the delivery. Discontinuation of routing medical visits is another concern during pregnancy and breastfeeding [166-168]. This condition negatively affects mothers' personal development and harms children's development [169, 170]. A large multicentral survey including more than 9000 pregnant and breastfeeding women reported high levels of depression and anxiety during the pandemic [171]. A meta-analysis found a 3.8% to 17.5% rate of anxiety during this pandemic in pregnant women of Asian countries and 23.9% to 72% in Western countries. This study also reported a 5.2% to 40% rate of depression [172]. Also, studies found race, social and family support, being underweight during pregnancy, employment, primigravida, age lower than 35 years old, literacy, and low physical activity as potential associated factors with pandemic-related anxiety [167,173-175]. In addition, a higher prevalence of anxiety during the first trimester of pregnancy, compared to the second and third ones, has been reported in previous studies [176].

About one in every three individual reports moderate to severe anxiety. In general, it has been shown that females are prone to greater psychological impacts and are linked with higher stress, anxiety, and depression [63]. During pregnancy, mental health problems are associated with an increased risk of preeclampsia, nausea and vomiting, preterm labor, low birth weight, and low neonate APGAR score [177]. The addition of the COVID-19-related anxiety to pregnancy-related anxiety could affect the maternal and neonatal status [178, 179]. This concurrency suggests the need for psychosocial support for pregnant women during the pandemic [180]. The mental and emotional impact of COVID-19 should also be identified and supported because these people may spend much time at home and in quarantine and not meet anyone. In the hospital, people with coronavirus are kept isolated. Also, after the possible delivery, the newborn might be kept away from the mother for protection. This separation may cause anxiety and depression [181].

Moreover, the general anxiety and fear of the pandemic have also affected the healthcare workers, which could cause an additional burden on maternal care [182-184]. On this occasion, further actions should be considered when caring for pregnant COVID-19 patients, including implementing psychological support services for both health professionals and pregnant women [182].

## CONCLUSIONS

Pregnant women are among the vulnerable group of the population during the COVID-19 pandemic. Several physiological and environmental factors contribute to an increase in the susceptibility of pregnant women and fetuses, resulting in critical and undesired outcomes. Therefore, the diagnostic criteria should be modified accordingly, and the protocols should be applied more strictly. However, prevention is still the best approach for pregnant women during the pandemic. Along with developing the prevention strategies, more clinical studies should be conducted to include the pregnant population. Future studies should provide more clinical information about COVID-19 and

pregnancy. Since the safety of many COVID-19 treatments has not been assessed before, a large number of clinical studies have excluded pregnant patients [185]. Apart from treatment, more information should be provided about vaccination safety during pregnancy and breastfeeding. The impact of COVID-19 on the mental health of pregnant women, the long-term effects of coronavirus (long COVID-19) on pregnant women and newborns, and the outcomes of vaccination in pregnant women are unexplored research areas that require more studies.

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**Data sharing statement:** Data supporting the findings and conclusions are available upon request from the corresponding author.

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