# Respiratory perspective of COVID-19 in pregnancy

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**Abstract**
The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic in March 2020 by the World Health Organization (WHO). By February 2022, the disease had infected more than 500 million people globally. COVID-19 frequently manifests as pneumonia and mortality is mainly caused by acute respiratory distress syndrome (ARDS). Previous studies have reported that pregnant women are at a higher risk of SARS-CoV-2 infection and complications can happen due to alterations in the immune response, respiratory physiology, hypercoagulable state, and placental pathology. Clinicians face the challenge of selecting the proper treatment for pregnant patients with different physiological characteristics compared with the non-pregnant population. Furthermore, drug safety for both the patient and the fetus should also be considered. Efforts to prevent COVID-19, including prioritizing vaccination for pregnant women, are essential to break the chain of COVID-19 transmission in the pregnant population. This review aims to summarize the current literature regarding the effect of COVID-19 in pregnant women, its clinical manifestations, treatment, complications, and prevention.

## Introduction

The coronavirus contains a single-chain ribonucleic acid (RNA) genome. This virus belongs to the Nidovirales order and is further classified into the Coronaviridae family and Coronavirimae subfamily [1]. The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019. It is known to be the etiology of coronavirus disease 2019 (COVID-19). Three months after the discovery of SARS-CoV-2, the World Health Organization (WHO) declared COVID-19 a pandemic due to its highly contagious nature and high mortality rate. In February 2022, the disease had infected 509,531,232 people globally with a 3–4% mortality rate [2]. The United States, India, and Brazil are among the countries most affected by COVID-19. The global situation is also reflected in Indonesia, with the highest daily new cases and death rates reaching 56,757 and 2,069 cases, respectively, in July 2021 [3,4].

The incidence of COVID-19 is higher in young adults than in the older age group, even though advanced age is associated with an increased mortality rate. Other risk factors contributing to higher mortality rates are obesity, diabetes, and hypertension. Interestingly, pregnancy is also known to be a contributing risk factor for mortality [5]. Based on a survey conducted by the Centers for Disease Control and Prevention (CDC) from January to June 2020, pregnant women with SARS-CoV-2 infection had a higher hospitalization rate (31.5%) than non-pregnant women (5.8%). Furthermore, COVID-19 increases the risk of preterm delivery [6]. The INTERGROWTH-21st Consortium conducted the INTERCOVID multinational cohort study and found that the mortality risk of pregnant women with COVID-19 was 1.6%, which is 22 times higher than that of pregnant women without the infection. Additionally, COVID-19 increases the risk of severe pregnancy complications, including preeclampsia/eclampsia/hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, intensive care unit (ICU) admission or referral to a higher tier of hospital care, infections requiring antibiotics, and low birth weight [7].

Pregnancy is a physiological condition that influences breathing as it increases oxygen demand.

Increased oxygen demand increases with gestational age [8]. This condition makes the pregnant state more susceptible to COVID-19. However, the diagnosis of COVID-19 in pregnant women is frequently delayed owing to the similar signs and symptoms of COVID-19 and the normal physiological changes in pregnancy, such as shortness of breath, fatigue, and muscle aches. Hence, prevention of SARS-CoV-2 infection and appropriate management of the disease in pregnant women are vital to reduce overall infection rates, maternal and infant morbidity, and mortality due to COVID-19 [9]. This review summarizes the current literature on the intriguing effects of COVID-19 on pregnancy and vice versa. The pathophysiology of COVID-19 in general and in regard to the physiological changes caused during pregnancy, as well as the clinical manifestations, diagnosis, intervention, complications, and prevention of COVID-19 in pregnant women, will be further elaborated in this review.

## Pathophysiology

### Life cycle and behaviour of SARS-CoV-2

SARS-CoV-2 is a single-chain, encapsulated, non-segmented RNA virus. The four genera of coronaviruses are Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. SARS-CoV-2 is classified into the genus Betacoronavirus. The virus has a spherical shape with some pleomorphism. The virion is approximately 60–140 nm in diameter. The capsid of the virus comprises an RNA genomic complex and a nucleocapsid protein N. The membrane surrounding the nucleocapsid consists of three proteins, spike protein S, membrane protein M, and small

**Figure 1.** Vascular damage mechanism in pregnant women with COVID-19.



ACE2 enzyme plays an essential role in converting angiotensin I to angiotensin-(1-9) and angiotensin II to angiotensin-(1-7). The SARS-CoV-2 spike protein will attach to the ACE2 receptor, resulting in down-regulation of the receptor, overproduction of vasoconstrictor angiotensin II, and decreases the amount of vasodilator angiotensin-(1-7).

envelope membrane protein E. Phylogenetic analysis has shown that SARS-CoV-2 belongs to the same subgenus as the virus that caused the SARS outbreak (SARS-CoV) [10].

SARS-CoV-2 enters host cells in two ways. The first method involves attaching the spike protein to the host angiotensin-converting enzyme 2 (ACE2) receptor, releasing the viral genome and nucleocapsid protein into the host cell cytoplasm. The second method is directly through the plasma membrane, in which exogenous proteases, such as transmembrane serine protease 2 (TMPRSS2), stimulate proteolytic activity by triggering the fusion pathway. The viral genome is then transformed into RNA-dependent RNA polymerase to produce more genomic RNA, messenger RNA, and viral proteins inside the cell. The proteins contained in the viral membrane are then arranged on the intracellular membrane. The protein and RNA complex forms a helical capsid structure, which buds between the endoplasmic reticulum and Golgi apparatus. Mature viral particles are packaged in vesicles and transported to the cell membrane, followed by the release of the virus from the cell [10].

ACE2 receptors are highly expressed in the alveolar epithelium and in various cells of the maternal-fetal barrier and fetal tissues [5]. ACE2 converts angiotensin I (1-10) to angiotensin-(1-9) and angiotensin II (1-8) to angiotensin-(1-7). Angiotensin-(1-7) exerts its function by binding to the Mas receptor. It also provides vascular protection and acts as an anti-fibrotic, anti-proliferative, and anti-inflammatory agent. In contrast, angiotensin II (1-8) binds to the angiotensin type 1 receptor (AT1R) and stimulates vasoconstriction, hypertrophy, fibrosis, proliferation, inflammation, and oxidative stress [10]. During the process of SARS-CoV-2 entry into the cell by binding to the ACE2 receptor, the virus causes downregulation of the receptor, resulting in the overproduction of angiotensin II (1-8). Hence, this condition decreases the amount of angiotensin-(1-7). This low level of angiotensin-(1-7) plays a role in attenuating the inflammatory response observed in COVID-19, as summarized in Figure 1 [5,10].
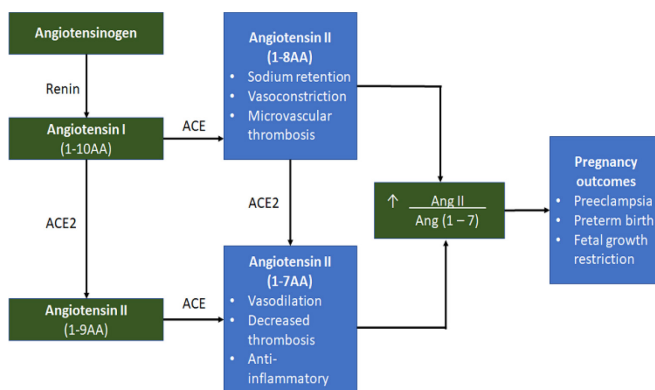
### Immune response to SARS-CoV-2 during pregnancy

A successful pregnancy requires a dynamic immune response. Since the fetus is considered a semi-allogeneic graft, the body must accommodate the fetus and reject it in the case of overwhelming infection. Consequently, local and systemic immunological changes occur during pregnancy to accommodate these functions [2]. While the body is in the pregnancy state, it promotes a humoral reaction rather than a cellular

immune response by shifting the population of CD4+ T cells to favor the T helper 2 (Th2) cytokine profile. This condition decreases T helper 1 (Th1) reactivity and may impair the clearance of virus-infected cells. However, it has been shown that excessive Th1 and Th2 responses were associated with severe forms of COVID-19. In these cases, there was an overproduction of cytokines such as interferon-gamma (IFN-γ), IL-1β, IL-4, IL-6, and IL-10 [6,11].

Another adaptation of the immune response during pregnancy is the decrease in circulating natural killer (NK) cells, especially in the third trimester. NK cells and the innate immune system promote viral clearance. Thus, a decrease in these immune cells may alter their ability to clear the virus. During pregnancy, the body also depletes circulating plasma dendritic cells, which reduces the production of virus-fighting agent type 1 interferon. In addition, the number of CD4+ and CD8+ T cells also reduces due to increased progesterone levels in the body. Moreover, pattern recognition receptors (PRR) such as toll-like receptors (TLR) are found in the placenta. As SARS-CoV-2 infection causes pyroptosis of host cells, the process results in the release of the damage-associated molecular pattern (DAMP). The presence of DAMP may increase the inflammatory process by acting as TLR ligands [11].

Proinflammatory conditions and mild activation of the systemic innate immune system occur primarily in

**Figure 2.** Immunological complications in pregnant women with COVID-19.



Proinflammatory conditions and mild activation of the systemic innate immune system are found in the first and third trimesters. Thus, pregnant women infected with SARS-CoV-2 in the first and third trimesters are at higher risk of experiencing more severe cytokine storms.

the first and third trimesters. During the second trimester, the immune system shifts towards Th2 to support the growth of the fetus in the womb [2]. Near the end of pregnancy, the body switches the immune system back towards Th1, which leads to a proinflammatory state known as the immune clock. The levels of CD25+FoxP3+ Tregs, CD4+, and CD8+ T cells increase in this phase. Thus, SARS-CoV-2 infection in the first and third trimesters poses a higher risk of developing a more severe cytokine storm, as shown in Figure 2 [12].

*Respiratory response*

In a normal pregnancy, hormonal changes and mechanical effects occur due to uterine distension. It affects lung function, breathing patterns, and gas exchange. Progesterone levels gradually increase throughout pregnancy. This hormone triggers the primary respiratory center to increase its sensitivity to carbon dioxide. Progesterone also alters the tone of the respiratory smooth muscle, and thus acts as a bronchodilator. Further, it can also stimulate mucosal edema, which causes nasal congestion. Progesterone receptors are mediated by estrogen. Therefore, estrogen levels increase during pregnancy. Estrogen increases the number and sensitivity of progesterone receptors in the hypothalamus and medulla [8].

Progressive distension of the uterus causes changes in the lung volume and the shape of the chest wall by elevating the diaphragm. The enlarged uterus increases the abdominal end-expiratory pressure and shifts the diaphragm upwards, increasing negative pleural or esophageal pressure, which then causes early closure of the small airways [8]. This results in a decrease in the functional residual capacity (FRC) and expiratory reserve volume (ERV). This condition occurs during the second half of pregnancy. The enlarged uterus also shortens the height of the thoracic cavity, consequently increasing inspiratory capacity (IC) to maintain constant total lung capacity (TLC). A decreased FRC is also associated with increased rib dimensions in the transverse and lower parts of the thorax. Chest wall compliance declines in the third trimester of pregnancy owing to increased abdominal content [8].

Minute ventilation (VE) increases significantly by up to 48% during the first trimester owing to a greater tidal volume (TV) with a steady respiratory rate. This ventilation pattern continues throughout the pregnancy. The increasing size of the uterus causes a shift in the resting position of the diaphragm by up to 5 cm. Consequently, changing the diaphragm's ability to
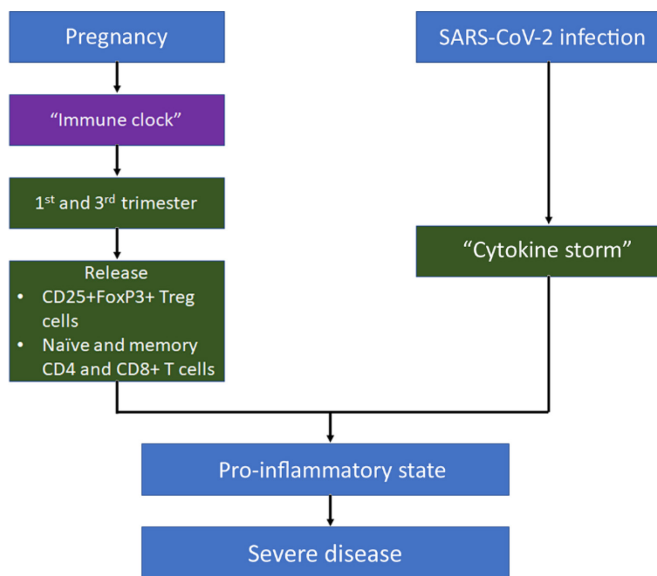
generate tension increases the apposition zone and radius of diaphragm curvature [8].

The oxygen consumption and basal metabolic rate increase by 21% and 14%, respectively, during pregnancy. Decreased FRC and increased oxygen consumption ($O_2$) can reduce oxygen reserves in pregnant women. The increase in VE reduces the carbon dioxide partial pressure ($PCO_2$) in the alveoli and arteries to 27 and 32 mmHg, respectively. As hyperventilation occurs, the $PCO_2$ level decreases, and the oxygen partial pressure ($PO_2$) in the arteries increases. $PO_2$ ultimately reaches 106–108 mmHg in the first trimester and 101–104 mmHg in the third trimester. Renal compensation causes blood pH levels to remain constant at 7.40–7.47, which is slightly alkalotic despite being in a hyperventilation state. Changes in respiratory physiology during pregnancy are summarized in Figure 3 [8].

Approximately 70% of pregnant women experience shortness of breath during daily activities. This condition is associated with an increased awareness of physiological hyperventilation sensations and increased central perception. These physiological changes further increase the risk of being infected by SARS-CoV-2. The effect of progesterone on the nasal mucosa facilitates the attachment of SARS-CoV- 2 and impedes its elimination. Increased uterine size is also a risk factor preventing lung expansion. A previous study has also shown that pregnant women have a higher risk of

requiring intensive care and mechanical ventilation in the event of SARS-CoV-2 infection [12].

*Coagulation response*

Coagulation increases during the peripartum period. Hormonal changes elevate coagulation factors, such as factor VII, factor VIII, factor X, von Willebrand factor, and fibrinogen. At the same time, the inhibition of protein C activation increases in the second and third trimesters. In addition, protein S activation decreases because of changes in the total protein S antigen levels. Several fibrinolytic pathway inhibitors are also known to increase, such as thrombin-activatable fibrinolysis inhibitors (TAFI) and plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2) [12].

Physical changes during pregnancy also enhance thrombotic conditions. Increased pelvic vein pressure is caused by an enlarged uterus and decreased blood flow to the lower extremities, which results in blood stasis. Relative compression of the left iliac vein by the right iliac artery leads to increased clot formation in the left iliac vein. The risk of developing deep vein thrombosis (DVT) during pregnancy is similar throughout all trimesters [12]. This hypercoagulability state might be exaggerated in SARS-CoV-2 infection, thereby increasing the risk of thrombosis-related mortality. Ahmed *et al.* confirmed this hypothesis while reporting basilar artery and lower lobe pulmonary embolism as

**Figure 3.** Respiratory physiology changes in pregnancy.
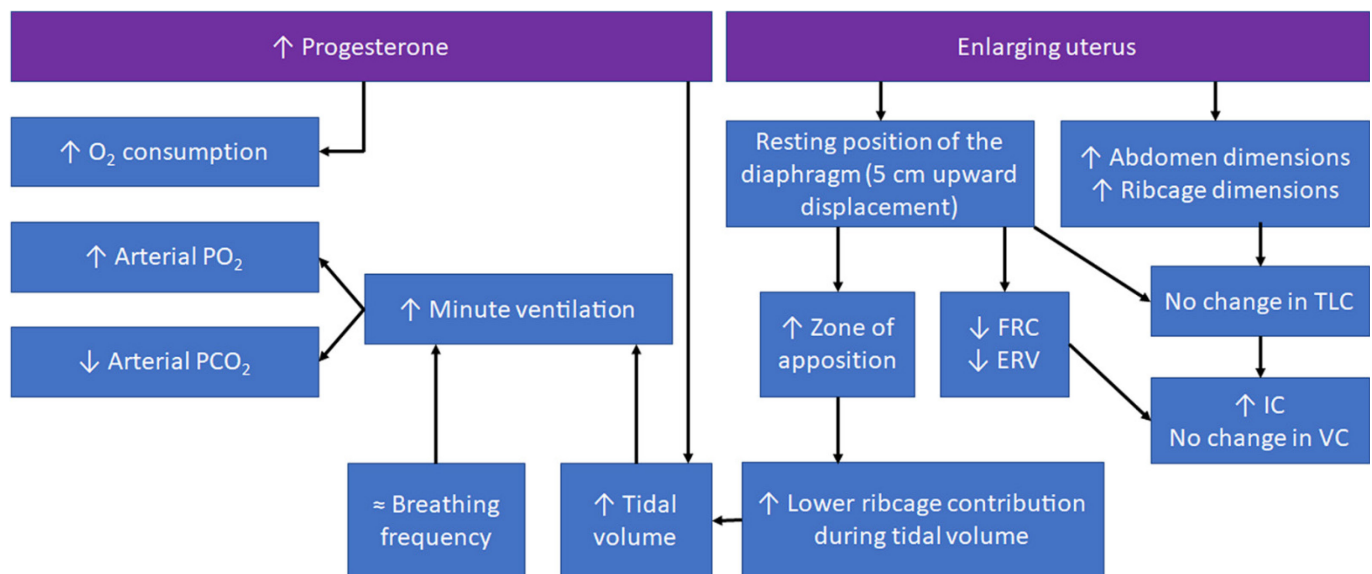


In normal pregnancy, hormonal changes and mechanical effects occur due to uterine distension. Progesterone which increases throughout pregnancy, alters airway smooth muscle tone and has a bronchodilator effect. Progressive distension of the uterus is the leading cause of lung volume and chest wall changes during pregnancy. Decreased functional residual capacity (FRC) and increased oxygen consumption (O2) play a role in decreasing oxygen reserves in pregnant women.

the cause of death in a 29-week pregnant patient with SARS-CoV-2 infection [2,11,14].

*The role of the placenta*

The placenta plays an essential role in physiological, immune, and endocrine functions to protect the fetus. The placenta is formed from cells derived from the mother and fetus. The fetal part of the placenta forms the chorionic sac, which includes the amnion, yolk sac, chorion, and allantois. The trophoblast is the outer layer of the placenta. It consists of two layers: the inner cytotrophoblast and outer syncytiotrophoblast. The maternal portion is derived from the endometrium, known as the decidua, with maternal blood vessels. The placenta provides protection against viruses by physically blocking viral entry routes and acting as an active antiviral and immunomodulator. Infection, hypoxia, and inflammation that occur during pregnancy stimulate the release of antimicrobial peptides and cytokines, activating the placental immune response [1].

ACE2 expression and activation in the placenta, uterus, and kidneys increase during pregnancy. In one study, angiotensin-(1-7) and ACE2 were detected in the subplacental syncytiotrophoblast, endothelium, and myometrium [15]. Zheng *et al.* reported that ACE2 expression is low in various cell types found in the placenta, except in decidual perivascular cells [16]. On the other hand, the coexistence of ACE2 and TMPRSS2 in the human placenta and chorioamniotic membrane during pregnancy is rare [1]. This underlies the hypothesis that the placenta is a potential site for SARS-CoV-2 infection. Hence, a vertical transmission may occur. However, the exact mechanism requires further investigation.

## Clinical manifestations

In general, the clinical symptoms of COVID-19 in pregnant women are similar to those in nonpregnant women. The most common clinical manifestations of COVID-19 in pregnant women are fever and cough, followed by other symptoms such as shortness of breath and malaise [17]. The 2020 CDC report estimated that the number of asymptomatic COVID-19 infections is approximately 40% of the general population. Pregnant women with COVID-19 are asymptomatic at the beginning and then worsen rapidly [9]. In some cases, it is challenging to distinguish shortness of breath due to COVID-19 from shortness of breath due to increased maternal oxygen demand and oxygen consumption by the fetus [18]. In addition to shortness of breath, pregnant women are less likely to report fatigue, muscle

aches, or gastrointestinal symptoms. This has led to delays in the diagnosis of COVID-19 [9].

The clinical spectrum of COVID-19 in pregnancy is classified similar to the general population, namely asymptomatic, mild, moderate, severe, and critical. Mild symptoms refer to symptomatic patients without evidence of pneumonia or hypoxia. Moderate symptoms refer to patients with clinical signs of pneumonia (fever, cough, shortness of breath, and rapid breathing) without signs of severe pneumonia and room air oxygen saturation $(SpO_2) \geq 93\%$. Severe symptoms refer to clinical signs of pneumonia with one of the following symptoms: respiratory rate $> 30$ breaths per minute, severe respiratory distress, or room air $SpO_2 < 93\%$. Critical symptoms refer to acute respiratory distress syndrome (ARDS), sepsis, and septic shock [17]. In a WHO cohort study involving 147 pregnant women with COVID-19, approximately 8% of cases were classified as severe and 1% as critical [17].

## Investigation

*Laboratory examination*

The most common laboratory findings in pregnant women with COVID-19 are lymphopenia (35-69.6%), elevated C-reactive protein (CRP) (48-69%), and increased D-dimer (82-84.6%). However, the change in the D-dimer level is not specific because its value typically increases during pregnancy [9]. Oshay *et al.* conducted a systematic review of 67 articles covering 427 pregnant female patients with COVID-19 [18]. The analysis found that 150 patients showed an increase in CRP, 128 patients had lymphopenia, 97 patients had neutrophilia, 73 patients had leukocytosis, 51 patients showed an increase in D-dimer, 24 patients had anemia, and 24 patients showed an increase in procalcitonin [20].

*Chest computed tomography (CT) scan*

Studies have reported that there are four stages of COVID-19 according to chest CT scan images: the early stage (0–5 days after the onset of symptoms), the progressive stage (5–8 days after the onset of symptoms), peak stage (9–13 days after the onset of symptoms), and late-stage (14 or more days after symptom onset) [21]. Oshay *et al.* reported that pregnant women exhibited more severe COVID-19 findings on CT scans than the general adult population [20]. The most common findings were ground-glass opacity, posterior lung involvement, multilobar involvement, bilateral lung involvement, peripheral distribution, and consolidation (Figure 4). Compared with the general population, pregnant women with

COVID-19 also frequently have features of consolidation (40.9% versus 21%) and pleural effusion (30% versus 5%), respectively [22].

Chest CT has a high sensitivity for diagnosing COVID-19 (~97%). Owing to the possible side effects of radiation, informed consent must be obtained in advance. Radiation shields are used to cover the abdomen during CT scan procedures. Chest radiography may be an alternative if a CT scan is unavailable. According to the American College of Radiology and the American College of Obstetricians and Gynecologists, the radiation dose received by the fetus when a pregnant woman undergoes a single chest X-ray is 0.0005–0.01 mGy which is negligible. Even though the radiation dose received from a chest CT scan is much higher (0.01–0.66 mGy), fetal growth retardation, microcephaly, and intellectual impairment are only observed when exposed to radiation doses above 610 mGy [23].

*Lung ultrasound*

Ultrasonography is another chest imaging modality for diagnosing COVID-19 in pregnant women. This test can be considered when both chest radiography and CT scans are unavailable. The examination starts from the basal zone to the superior thorax. For a systematic examination, the imaging is performed along four vertical lines, the right midaxillary, right parasternal, left parasternal, and left midaxillary lines. When the

**Figure 4.** Chest CT scan in pregnant patients with COVID-19 pneumonia.



(**a**) 28-year old, 39 week: bilateral, circular ground-glass opacity in the lower lobes, (**b**) 30-year old, 34 week: single peripheral ground-glass shadow with air bronchograms in the right upper lobe, (**c**) 33 year-old, 38 week, 5 days after onset of symptoms, focal ground-glass shadow associated with smooth interlobular and intralobular septal thickening in the right lower lobe, (**d**) 28-year old, 38 week, 6 days after onset of symptoms, patchy consolidation and fibrous stripes in the lower lobes.
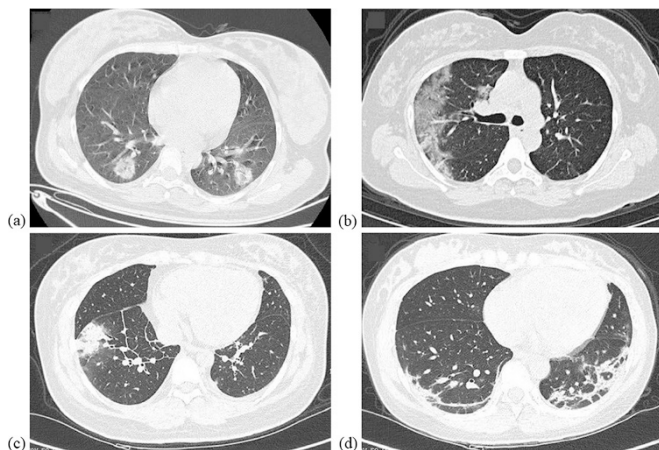
patient is seated, the posterior thoracic paravertebral surfaces should be examined from the basal to the superior zone or along the posterior axillary line [24].

Ultrasound examination of the normal lung shows a hyperechoic subcutaneous layer and a horizontal pleural line that moves horizontally with breathing, known as lung sliding. Horizontal A-lines are the hallmarks of normal lungs. In viral pneumonia, interstitial lung disease, pulmonary fibrosis, or pulmonary edema, decreased aeration of the lungs is observed, even though they are not fully consolidated. These images appear as vertical artifacts of various shapes and lengths called B-lines. When the density of the peripheral lung parenchyma increases but has not reached consolidation, as in ARDS, ultrasound shows white areas without A-lines or B-lines, known as the white lung. The consolidation appears as an irregular hypoechoic area, as shown in Figure 5 [23,24].

*Diagnostic test for SARS-CoV-2 infection*

There are three methods for diagnosing SARS-CoV-2 infection that has been recognized by the WHO: detection of viral RNA, viral antigens, and host antibodies. Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) detects viral RNA and is the gold standard for diagnosing SARS-CoV-2 infections. Viral antigens are detected using the lateral flow assay (LFA) technique, often referred to as the rapid antigen detection test. This examination provides the best result if carried out 1–3 days before or 5–7 days after the onset of symptoms. Detection of host antibodies against

**Figure 5.** Lung ultrasound patterns in pregnant women.
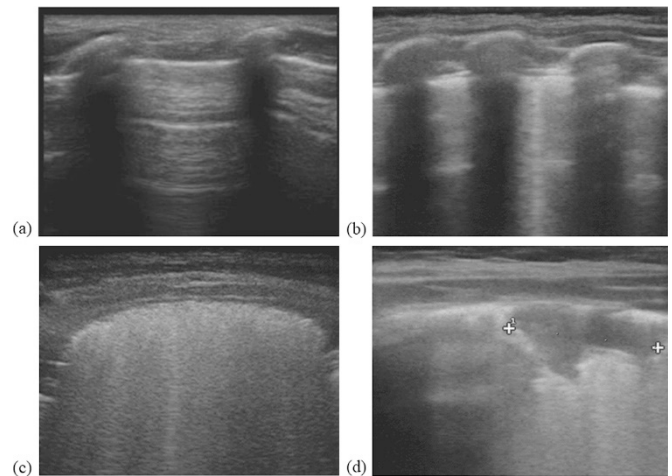


(**a**) A-lines in normal lung, (**b**) B-lines in patient suspected with COVID-19 pneumonia, (**c**) white lung appearance in severe COVID-19 pneumonia and (**d**) subpleural consolidation in severe COVID-19 pneumonia.

SARS-CoV-2 can be performed using serological techniques, such as enzyme-linked immunosorbent assays (ELISA). Typically, the production of host antibodies takes 10–30 days from the first day of symptoms. These examinations can be performed on pregnant women as well [6,25].

## Treatment

### General treatment

Treatment is administered according to the degree of the clinical symptoms. Patients with mild symptoms may undergo self-isolation. Patients should be able to maintain adequate hydration, monitor their body temperature, and administer antipyretics if needed. Prolonged bed rest is not recommended, because it can increase the risk of thrombosis. Routine antenatal examinations should be postponed until the end of the isolation period (four weeks from the onset of symptoms) or after a negative PCR result is obtained two weeks from symptom onset. Patients with moderate or severe symptoms must be hospitalized. These patients require vital sign monitoring in the isolation ward. Oxygen therapy is administered to maintain the $SpO_2$ above 94%. Fluid administration is recommended for fluid balance to minimize the risk of fluid overload [26].

### Antiviral therapy

The definitive treatment for COVID-19 is still being investigated. Remdesivir, an adenosine analog incorporated into the RNA polymerase chain, when metabolized in cells prevents viral replication [27]. Grein *et al.* showed clinical improvement with a significant reduction in oxygen therapy in patients with severe COVID-19 who were given remdesivir [28]. In May 2020, the United States Food and Drug Administration (FDA) authorized the emergency use of remdesivir in severely ill patients with suspected or laboratory-confirmed SARS-CoV-2 infections. The WHO also listed a conditional recommendation for remdesivir in patients with severe COVID-19 and non-severe COVID-19 at the highest risk of hospitalization. Due to the limited data on pregnant women, the decision regarding use of remdesivir should be made between the pregnant women and their health care provider while discussing whether the potential benefit justifies the potential risk to the mother and fetus [29].

Favipiravir is a selective viral RNA polymerase inhibitor that is used against various RNA viruses. Several clinical trials have been conducted on this drug for the treatment of COVID-19. To date, there is insufficient data on the safety of favipiravir in pregnant women. Therefore, the use of favipiravir in pregnant women has not yet been recommended. Another antiviral, oseltamivir, works by inhibiting the neuraminidase enzyme, thus preventing viral replication. Several studies conducted in Wuhan, China, found that some SARS-CoV-2 cases were co-infected with influenza A or B. This finding justified the use of oseltamivir. Based on previous observational studies in pregnant women, the use of oseltamivir is not associated with teratogenic effects [6,27,30].

Molnupiravir is a prodrug of β-D-N4-hydroxycytidine (NHC) and is included with nucleoside drugs. The NHC is incorporated by the SARS-CoV-2 RdRp into the genomic or subgenomic RNA during RNA template genome copying. The NHC-containing RNAs resulting from the process would be used as a template for the production of subsequent RNAs which could not form functional viruses. A conditional recommendation is stated by WHO for molnupiravir for patients with non-severe COVID-19 at the highest risk of hospitalization. Molnupiravir should not be given to pregnant or breastfeeding women and decisions around treatment with this drug must be made using a shared decision-making model [29].

### Corticosteroid

Based on the Randomized Evaluation of COVID-19 Therapy (RECOVERY) clinical trial, dexamethasone was associated with a reduced risk of mortality in COVID-19 patients who require mechanical ventilation and a slightly statistically significant reduction in mortality risk in patients requiring oxygen therapy. This study suggests that the benefits outweigh the risks of steroid exposure in the fetus. Therefore, the Society of Maternal-Fetal Medicine (SMFM) recommends dexamethasone use in pregnant women with COVID-19 who require oxygen therapy or mechanical ventilation. The dexamethasone dose for fetal lung maturation is 6 mg every 12 h for two days intramuscularly, followed by 6 mg/day orally or intravenously for up to ten days. For indications other than lung maturation, the dose is 6 mg/day orally or intravenously for ten days [31]. The WHO living guideline also stated a strong recommendation for systemic corticosteroids in patients with severe or critical COVID-19 [29].

### Immunomodulator

Tocilizumab is an Interleukin-6 (IL-6) inhibitory monoclonal antibody that plays a role in severe inflammatory and autoimmune responses. In severe SARS-CoV-2 infection, cytokine release syndrome is

mediated by severe inflammatory conditions and the production of large amounts of cytokines, which lead to multiorgan dysfunction and ultimately death. IL-6 is one of the cytokines involved in cytokine release syndrome. A study in Wuhan reported that the use of tocilizumab was beneficial in preventing cytokine release syndrome in COVID-19 patients with high IL-6 levels [27]. The WHO living guideline included strong recommendation for tocilizumab in patients with severe or critical COVID-19. On the other hand, the data of tocilizumab use in pregnant population is still scarce. The drug may cross the placental membrane, although it is uncertain whether it would effect transient immunosuppression in the fetus and this should be weighed against the potential benefit for the mother [29].

*Anticoagulant*

Severe COVID-19 increases the risk of thromboembolic events. Critically ill patients or patients on mechanical ventilation should receive prophylactic anticoagulants such as unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), if not contraindicated. Data on anticoagulants for the treatment of severe COVID-19 are limited. It is recommended to use anticoagulants guided by CRP and/or D-dimer levels. However, no data have demonstrated the benefits of full-dose anticoagulants in these patients. Since pregnancy increases the risk of thrombosis, especially in the third trimester and immediately after delivery, anticoagulation can be considered for hospitalized pregnant women with COVID-19 [31].

The American Society of Hematology recommends administering a prophylactic dose unless other indications such as venous thromboembolism (VTE) are confirmed. The anticoagulant dose should be adjusted for each patient according to the hospital protocol. However, the increased risk of bleeding during labor due to inflammatory conditions could be worsened by the administration of therapeutic anticoagulants. UFH is recommended for critically ill pregnant women without confirmed thrombosis because of its short half-life and reversibility. Activated partial thromboplastin time (aPTT) should be monitored while administering intravenous heparin [31].

D'Souza *et al.* stated that LMWH is the thromboprophylaxis of choice for pregnant women with COVID-19. However, there is insufficient evidence to recommend a therapeutic dose of LMWH in pregnant women with COVID-19. The administration of LMWH and UFH after hospitalization is debatable, particularly in pregnant patients. However, healthcare workers should consider risk factors such as obesity, pregnancy, immobilization, and congenital thrombophilia when administering VTE prophylaxis in outpatient settings [31].

*Vitamins*

Vitamin C and ascorbic acid are potent antioxidants that aid immune response. Vitamin C is required for adequate innate and adaptive immune responses, the maintenance of epithelial integrity, increased phagocytic ability, differentiation and proliferation of T and B lymphocytes, and antibody production. Several studies have reported improved respiratory parameters in critically ill COVID-19 patients after receiving intravenous vitamin C at a dose of 2–10 g/day. The use of vitamin C during pregnancy and lactation is considered safe. However, no studies have examined the impact of high vitamin C doses on pregnancy [27].

Studies have reported a potential association between low vitamin D levels and high COVID-19 mortality rates in the United States, United Kingdom, France, and other countries. Cytokine storms are more

**Table 1.** Recommendations of COVID-19 therapy in pregnant women[27].

| Drug | FDA category | Transplacental passage | Recommendations |
|---|---|---|---|
| Remdesivir | B | Crosses the placenta | No adverse effect on embryo-fetal development in animals, under investigation in humans |
| Lopinavir-ritonavir | C | Crosses the placenta | No increased rate of congenital malformation or miscarriage, safe for use in pregnancy |
| Favipiravir | No data | No data | No data |
| Oseltamivir | C | Crosses the placenta | No increased rate of congenital malformation or miscarriage, safe for use in pregnancy |
| Corticosteroid | C/D | Crosses the placenta | No increased rate of congenital malformation or miscarriage, safe for use in pregnancy |
| Tocilizumab | C | Crosses the placenta | Discontinue during pregnancy |
| Heparin | B | Does not cross the placenta | Safe for use in pregnancy |
| Vitamin C | A | Crosses the placenta | Safe for use in pregnancy |
| Vitamin D | A | Crosses the placenta | Safe for use in pregnancy |

commonly found in individuals with vitamin D deficiency, which underlie the use of vitamin D in COVID-19 cases. Animal studies have shown a teratogenic effect of high doses of vitamin D. However, data on human subjects are unavailable. Prophylactic or therapeutic doses of vitamin D are considered safe during pregnancy and lactation. Toxic levels above 150 ng/mL are rare in individuals taking this vitamin [27]. The recommendations for using antivirals and other COVID-19 drugs in pregnant women are summarized in Table 1.

*Pregnancy delivery timing*

The SMFM recommends that a positive PCR result in a clinically stable pregnant woman without signs of fetal distress is not an indication of labor. Therefore, delivery can be performed according to the routine obstetric indications. In pregnant women with asymptomatic or mild COVID-19 at 37–38 weeks of gestation without indications for delivery, it may be considered after 14 days from the first positive PCR result or seven days after the onset of symptoms plus three days after symptom improvement. Otherwise, delivery may be considered at 39 weeks of gestation or later to reduce the risk of deteriorating maternal status [31].

Delivery in patients with refractory hypoxemia should be considered at $\geq$ 32 weeks of gestation. An earlier delivery date should be considered for more severe symptoms. Neonatal mortality was 0.2% at 32 weeks and remained constant or decreased with each subsequent week. The incidence of significant morbidity was 8.7% at 32 weeks, 4.4% at 34 weeks, and 1.8% at 36 weeks. Early delivery might be beneficial in reducing the physiological burden of myocarditis, refractory hypoxemia, or prolonged recovery [31].

The timing of delivery in critically ill patients must be individually adjusted. Decisions should be made based on maternal status, other underlying pulmonary diseases, critical illness, ability to be weaned off of ventilator or mechanical ventilation, gestational age, and discussion between the patient and their family. In the third trimester, uterine pressure reduces expiratory reserve volume, inspiratory reserve volume, and functional residual capacity. This condition increases the risk of severe hypoxemia in pregnant women, especially critically ill patients. However, it remains unclear whether early delivery is beneficial in all cases. If the only indication for labor is severe hypoxemia, other options might be helpful, such as the prone position, extracorporeal membrane oxygenation

(ECMO), and other ventilation methods, especially when the gestational age is less than 30–32 weeks [31].

There is no evidence to support the superiority of specific delivery methods. Therefore, this decision is made according to obstetric indications and patient preferences. A positive COVID-19 result does not affect the delivery method, unless the patient's respiratory condition requires urgent intervention. In mild cases without signs of fetal distress, vaginal delivery is considered the safest option. One way to prevent the transmission of SARS-CoV-2 in the delivery room is to use personal protective equipment for both patients and healthcare workers [12,31,33].

*Postpartum care*

Vale *et al.* recommended a distance of two meters between the patient's and the baby's bed in the postpartum ward. The patient's bed can be separated by curtains. The patient should also wear a mask in the room. A systematic review that included 666 neonates did not show a high rate of SARS-CoV-2 infection after vaginal delivery, during breastfeeding, or during mother-infant interactions. Breastfeeding is not contraindicated for patients with COVID-19, as long as the patient can breastfeed and is clinically stable. Symptom severity, breast hygiene, and mask use should be considered both before and during breastfeeding. Hand and Noble reported a high SARS-CoV-2 immunoglobulin A (sIgA) antibody level in breast milk in 12 of 15 patients who previously had COVID-19 [12].

## Complications
*Acute respiratory failure*

Acute respiratory failure occurs in up to 8% of COVID-19 cases and is the leading cause of death in COVID-19. Pregnant women are more susceptible to this complication than non-pregnant women. The risk is heightened owing to increased oxygen consumption, decreased functional residual capacity, and physiological hyperventilation with compensated respiratory alkalosis. The target oxygen saturation for pregnant women with COVID-19 is > 95% and should be maintained between 92% and 95%. This oxygen saturation level ensures that the partial pressure of oxygen ($PaO_2$) is > 70 mmHg to maintain adequate oxygen for the fetus. The recommended prone position for COVID-19 patients to increase oxygen levels can be difficult for pregnant women, especially in the later trimester. Alternatively, a semi-prone or left lateral position can be performed. Patients can place a pad above and below the abdomen to minimize

compression of the abdominal aorta and inferior vena cava [9].

### Thromboembolism

Previously, COVID-19 has been associated with disseminated intravascular microthromboembolism and coagulopathy. The disease also increases the risk of VTE because it causes endothelial injury, imbalance of procoagulants and anticoagulants owing to the inflammatory and immunological effects of the disease, and immobilization of hospitalized patients (Virchow's triad). VTE occurs in one-third of COVID-19 patients admitted to the intensive care unit (ICU). The most common diagnoses included deep vein thrombosis and pulmonary embolism. Pregnancy is known to induce hypercoagulable conditions, thereby increasing the risk of VTE when pregnant women contract COVID-19, especially hospitalized patients. Thus, pregnant women with COVID-19 should be administered prophylactic anticoagulation during hospitalization, unless contraindicated. Subsequently, the use of therapeutic anticoagulation can be considered according to the VTE risk score and presence of other indications [9].

### Cardiac complications

Cardiac complications found in COVID-19 patients include acute myocardial injury, cardiomyopathy, acute coronary syndrome, arrhythmias, and acute heart failure. These complications may result from direct viral myocarditis, cytokine-mediated indirect cardiac injury, microvascular thrombosis, cardiac overload during infection, or multiple organ system failures. Acute myocardial injury is defined as an increase in troponin levels above the 99th percentile and can occur in up to 16% of COVID-19 patients. Myocardial injury in pregnant women with COVID-19 has a high mortality rate of approximately 13%, most of whom die from fatal arrhythmias. This increase in the mortality rate results from hyperdynamic circulation, increased blood volume, and cardiac output caused by physiological changes during pregnancy [9].

### Pregnancy complications

Pregnant women with COVID-19 have a higher risk of preterm deliveries. However, the cause is usually not spontaneous preterm birth. The vast majority of preterm births are iatrogenic with relevant medical indications. The pathogenesis of spontaneous preterm birth may be related to hypoxia, placental pathological changes, and uteroplacental insufficiency. A study reported a higher prevalence of pre-eclampsia in pregnant women with COVID-19 than in those without COVID-19, with incidence rates 7.7% and 4.3%, respectively. Pre-eclampsia in pregnant women with COVID-19 may be associated with the downregulation of ACE2 receptors, decreased conversion of angiotensin II to angiotensin-(1-7), endothelial cell dysfunction, and complement activation. Further studies are needed regarding the incidence of pregnancy-related complications in pregnant women with COVID-19 [11].

### Vertical transmission

Vertical transmission refers to the transmission of the virus from the mother to the child during intrauterine, intrapartum, or postpartum periods. Mother-to-fetal transmission of SARS-CoV-2 is possible because ACE2 receptors are expressed in the placental villi of cytotrophoblasts, syncytiotrophoblasts, and extravillous trophoblasts. Several possible routes of vertical transmission include: 1) intrauterine, either transplacental through aspiration of infected amniotic fluid or due to maternal viremia; 2) intrapartum, through contact with maternal blood or secretions; or 3) postpartum, through breast milk or droplets via the respiratory route [9].

The possibility of vertical transmission has not yet been ruled out. Previous studies have detected SARS-CoV-2 via PCR in the placental tissue, umbilical cord blood, and amniotic cavity. A systematic review involving 50 studies also reported that the virus was detected in infected neonates and in the placenta and amniotic fluid of pregnant women [12]. Another study conducted on this issue estimated that the probability of neonates contracting SARS-CoV-2 from a mother with COVID-19 was approximately 2.5% [34].

A classification system categorizes congenital infection in a live-born neonate into confirmed, probable, possible, unlikely, and not infected. Confirmed infection occurs when PCR detects the virus in cord or neonatal blood collected within the first 12 h of birth. Probable infection is defined as the detection of the virus in amniotic fluid collected prior to membrane rupture and not detected in umbilical cord blood or neonatal blood collected within the first 12 h of birth. Possible infection is defined as anti-SARS-CoV-2 IgM in umbilical cord blood or the virus detected by PCR in placental tissue in the absence of the virus in umbilical cord blood, amniotic fluid, and neonatal blood in the first 12 h of birth. If PCR does not detect the virus in cord blood or neonatal blood in the first 12 h of birth or amniotic fluid prior to membrane rupture without a serology test, the infection is unlikely. The neonate is considered uninfected if the virus is not

detected by PCR in the absence of anti-SARS-CoV-2 IgM in the cord blood [35].

## Prognosis

The risk factors for ICU admission in pregnant women with COVID-19 are similar to those in the general population, including old age, obesity, and comorbidities, such as diabetes mellitus and hypertension. Turan *et al.* stated that as many as 83.6% of pregnant women with COVID-19 treated in the ICU received mechanical ventilation [36]. Additionally, they have a higher risk of preeclampsia or eclampsia (RR 1.76; 95% CI 1.27 – 2.43), ICU admission (RR 5.04; 95% CI 3.13 – 8.10), mortality (RR 22.3; 95% CI 2.88 - 172), and preterm birth (RR 1.59; 95% CI 1.30 – 1.94) [7].

A systematic review conducted by Allotey *et al.* stated that the mortality rate of pregnant women with COVID-19 was 0.6%, with 73 deaths per 11,580 cases [37]. The CDC report in November 2020 stated that the pregnant population with COVID-19 had a slightly increased risk of death compared to the non-pregnant population (1.5–1.2 per 1,000 cases), with an adjusted risk ratio of 1.7. Mortality is primarily due to ARDS, with consequent cardiopulmonary and venous thromboembolism [9,38].

## Prevention

The ideal approach for infection prevention in epidemics and pandemics is through social mechanisms and vaccination. The CDC and WHO recommend that all individuals wear masks in public places to reduce disease transmission, maintain social distancing, and perform hand hygiene through proper handwashing and alcohol-based hand sanitizers [39]. As of October 21, 2022, the WHO lists 48 vaccines in phase 3 clinical trials and 9 vaccines undergoing or have completed phase 4 [40]. Emergency use authorizations (EUA) have been issued by the WHO for the following vaccines: Pfizer/BioNTech Comirnaty (BNT162b2) vaccine, SII/COVISHIELD, and AstraZeneca/AZD1222 (ChAdOx1-S) vaccines, Janssen/Ad26.COV 2.S vaccine, Moderna COVID-19 (mRNA 1273) vaccine, Sinopharm COVID-19 (BBIBP-CorV) vaccine, Sinovac-CoronaVac vaccine, Bharat Biotech BBV152 COVAXIN vaccine, Covovax (NVS-CoV2373) vaccine, and Nuvaxovid (NVX-CoV2373) vaccine.

The COVID-19 vaccine is being developed more rapidly than other vaccines. Thus, the inclusion of pregnant women in clinical trials is considered unsafe. In June 2020, the FDA recommended that pharmaceutical companies perform developmental and reproductive toxicology (DART) testing before enrolling pregnant women or individuals planning to become pregnant in clinical vaccine trials. All vaccines administered by the EUA and WHO have completed DART trials in animals and have shown no harmful effects during pregnancy. Vaccines including mRNA-1273, Ad26.COV2-S, and BNT162b2 have participated in clinical trials for pregnant women [41]. The CDC collects data on pregnant women in the v-safe COVID-19 Vaccine Pregnancy Registry and analyzes related COVID-19 vaccinations for pregnant women and babies. Records of at least 23,000 pregnant women are included. As many as 827 people per 3,958 who received the COVID-19 mRNA vaccine did not show a clear safety signal [42].

Several studies have shown that vaccine-derived antibodies are transferred to neonates during pregnancy and lactation. A study in 17 states of the United States of America showed a decrease in the number of infant hospitalizations (the first 6 months of life) for COVID-19 in mothers who had received 2 doses of the COVID-19 vaccine during pregnancy. In a smaller study evaluating the antibody response in infants, it was found that most infants had detectable anti-S IgG antibodies at 2 months after maternal vaccination and 57% were still detectable at 6 months of age. This compares with only 8% of infants who had antibodies in mothers who developed SARS-CoV-2 infection during pregnancy. However, the antibody concentration needed to provide a protective effect on infants is still not known. When newborns have severe COVID-19 and there is currently no COVID-19 vaccine that can be given to infants under 6 months of age, these results provide the support that infants may receive the protective benefits of maternal vaccination [43]. The IgG concentrations in pregnant women and the placental IgG transfer ratio is also known to increase with time. The degree of maternal protection through placental antibody transfer is most likely dependent on the maternal antibody concentration. In some studies, transplacental transfer of antibodies begins in the second trimester although it was more efficient in the third trimester [44].

The risks post-vaccination in the early stages of pregnancy have also been studied. The mRNA vaccine could cause antibody and cellular immune responses causing suppression of cells on the development of the placenta and fetus. A positive study of the reduced incidence of stillbirth was reported in the vaccinated group, especially in the delta period [45]. A study in Scotland compared perinatal mortality rates between

the vaccinated versus unvaccinated COVID-19 groups. In the unvaccinated group, the mortality rate was 22.6 per 1000 live births, whereas no cases of perinatal death were found in the vaccinated group. However, it should be noted that this study is an observational study with significant heterogeneity and possible other confounding factors which should be considered before drawing conclusions [46].

Based on WHO interim data regarding the six COVID-19 vaccines that have received the EUA, these vaccines are recommended for use in pregnant women only if the benefits of vaccination outweigh the potential risks. Prior to vaccination, patients should be informed of the risk of developing COVID-19 during pregnancy, such as developing a more severe infection. They should also be informed about the benefits of vaccination in reducing disease incidence, and that limited data are currently available regarding the safety of vaccines in pregnant women. In addition, the vaccines Ad26.CoV2.S and ChAdOx1 Nov-19 might cause thrombotic thrombocytopenia, although this is rare. Pregnancy tests are not routinely performed prior to vaccination. The WHO also does not recommend that women delay or terminate the pregnancy because of COVID-19 vaccination [47]. However, further research is needed on high-quality studies with low risk of bias showing evidence related to multiple vaccine types, timing of pregnancy, vaccine effectiveness against newer developing variants eg omicron, and with uniform reporting of important clinical outcomes. Studies on several types of vaccines are important to increase vaccine coverage in low-income countries.

## Conclusions

Pregnancy is a physiological condition that increases the risk of SARS-CoV-2 infection and complications due to changes in the immune response, respiratory physiology, hypercoagulable state, and the presence of ACE2 in the placenta. Pregnant women with COVID-19 are initially asymptomatic and their condition worsens rapidly. The symptoms of shortness of breath due to COVID-19 may overlap with respiratory physiology alterations due to pregnancy. Laboratory findings in pregnant women with COVID-19 include lymphopenia, elevated CRP, and increased D-dimer levels, which are typically observed during normal pregnancy. The frequent radiological findings in pregnant women with COVID-19 are ground-glass opacities and features of consolidation. Administration of antivirals, corticosteroids, and anticoagulants should be considered in pregnant women if the benefit outweighs the risk. Pregnant women with COVID-19

have an increased risk of ICU admission, mechanical ventilation, and a higher mortality rate. EUA-listed COVID-19 vaccines are recommended for pregnant women, considering the benefits and risks to the patient and fetus.

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