



Treatment of COVID-19 disease in pregnancy and breastfeeding

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Abstract

The physiological and anatomical clinical characteristics of pregnant women make them susceptible to complications caused by coronavirus disease (COVID-19). Increased coagulation and risk of thromboembolic phenomena are common during pregnancy; they are further enhanced when associated with a thrombogenic pathology such as in COVID-19. The treatment of COVID-19 is controversial and limited, even for non-pregnant patients. During pregnancy, the options are even more restricted due to the teratogenicity of some drugs and anatomical and physiological difficulties, especially in advanced pregnancy in patients with respiratory failure. Therefore, the focus of treatment for pregnant patients should be centered on isolation, monitoring fetal and maternal vital signs, uterine activity, and general maternal–fetal well-being. The prescription of drugs and management orientation should be based on gestational age and maternal clinical conditions. The optimal type of delivery is guided by obstetric indications and COVID-19 disease severity. Breastfeeding should be encouraged with the use of masks and hand hygiene. The treatment of pregnant women with COVID-19 brings important peculiarities that should be considered in order to make better decisions for preserving the health of the mother and fetus.

Keywords: antivirals; corticosteroids; anticoagulation; enoxaparin; oxygen supplementation; labor management

MeSH terms:

PREGNANCY COMPLICATIONS, INFECTIOUS – DIAGNOSIS

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Лечение COVID-19 при беременности и кормлении грудью

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Аннотация

Анатомо-физиологические особенности беременных женщин делают их особенно восприимчивыми к осложнениям коронавирусного заболевания (COVID-19). Повышенная свертываемость крови с риском тромбозомболических осложнений характерна в период беременности, она еще более усиливается, когда ассоциирована с протромботическими состояниями, такими как COVID-19. Лечение COVID-19 является предметом дискуссии даже для небеременных. Во время беременности медикаментозная терапия ограничена из-за тератогенности некоторых препаратов и анатомо-физиологических особенностей, особенно в поздние сроки беременности у пациенток с дыхательной недостаточностью. Поэтому основное внимание в лечении беременных женщин должно уделяться изоляции, мониторингу жизненно важных показателей плода и матери, сократительной активности матки. Назначение препаратов и общие принципы ведения должны основываться на гестационном возрасте и клиническом состоянии матери. Выбор способа родоразрешения определяется акушерскими показаниями и тяжестью течения COVID-19. Следует сохранять грудное вскармливание при условии использования масок и средств для гигиены рук. Лечение беременных женщин с COVID-19 имеет важные особенности, которые необходимо учитывать для принятия лучшего решения с целью сохранения здоровья матери и плода.

Ключевые слова: противовирусные средства; кортикостероиды; антикоагуляция; эноксапарин; кислородная поддержка; ведение родов

Рубрики MeSH:

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БЕРЕМЕННОСТИ ОСЛОЖНЕНИЯ ИНФЕКЦИОННЫЕ – ТЕРАПИЯ

COVID-19 – ДИАГНОСТИКА

COVID-19 – ОСЛОЖНЕНИЯ

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List of abbreviations

COVID-19 – COrona Virus Disease 2019

ACE2 – angiotensin-converting enzyme 2

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

HIGHLIGHTS	КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ
Due to the serious complications of COVID-19 during pregnancy, greater attention is needed in the care and treatment of the patients during the pandemic period.	В связи с возможностью развития серьезных осложнений COVID-19 во время беременности необходимо уделять большое внимание уходу и лечению пациентов в период пандемии.
Most pregnant women will have few symptoms; however, some of them may have more serious complications than non-pregnant women.	У большинства беременных женщин отмечено легкое течение заболевания; однако у некоторых из них осложнения COVID-19 могут быть более выраженными, чем у небеременных женщин.
Factors associated with adverse outcomes such as the following: diabetes mellitus, obesity, maternal age >40 years and third trimester of the gestational period.	К факторам риска неблагоприятного прогноза относятся: сахарный диабет, ожирение, возраст матери > 40 лет и третий триместр беременности.
The clinical findings of pregnant women with COVID-19 are similar to non-pregnant women. These symptoms are the following: fever, fatigue, myalgia, and dyspnea.	Клинические симптомы COVID-19 аналогичны таковым у небеременных женщин: лихорадка, слабость, миалгия и одышка.
Obstetric complications occur due to cytokine storm and the most frequent are: spontaneous miscarriage, fetal growth restriction, preterm birth, premature rupture of membrane, and stillbirth.	Акушерские осложнения могут развиваться как результат цитокинового шторма и наиболее частыми являются: самопроизвольный выкидыш, задержка роста плода, преждевременные роды, преждевременный разрыв плодных оболочек и мертворождение.
Treatment of pregnant women with COVID-19 is focused on early isolation, infection control, oxygen therapy, mechanical ventilation (when indicated), fluid control, laboratory tests, maternal and fetal monitoring, adequate delivery management, and multidisciplinary care team.	Лечение беременных женщин с COVID-19 проводится мультидисциплинарной бригадой и включает: изоляцию на ранних стадиях заболевания, контроль инфекции, кислородную поддержку, механическую вентиляцию (по показаниям), контроль водного баланса, лабораторный контроль, мониторинг состояния матери и плода.
Treatment of the viral phase is controversial in the literature.	Данные о возможности использования противовирусных средств противоречивы.
Corticosteroids for cytokine storm control as well as the use of low molecular weight heparin (enoxaparin) to decrease thromboembolism complications are indicated.	Показано использование кортикостероидов для контроля цитокинового шторма, а также низкомолекулярного гепарина (эноксапарина) для снижения риска развития тромбозомболических осложнений.
Breastfeeding protects both mother and child and should be encouraged.	Грудное вскармливание защищает как мать, так и ребенка, и его следует сохранять.
Knowledge of the available treatment to pregnant women can help achieve better perinatal outcomes.	Информированность о возможности адекватной терапии для беременных может помочь в достижении лучших перинатальных исходов.

The clinical and physiological characteristics of pregnant women make them vulnerable to coronavirus disease (COVID-19) and its complications [1]. It is believed that pregnant women have no greater risk of developing complications due to COVID-19; however, studies have shown an increased risk of morbidity, respiratory failure, mechanical ventilation, and death among these patients [2–4]. As an increase in maternal deaths has been reported, greater assistance for the maternal–fetal dyad during the COVID-19 pandemic is required [1]. It is known that the typical changes in pregnancy can lead to a greater impact on the respiratory, immune, coagulation and

cardiac systems [5]. Thus, pregnant women and newborns require greater attention and care in the prevention, diagnosis, and treatment of COVID-19 [1], and it is important to understand the treatment of pregnant women to reduce the impact of COVID-19 on this population [1]. This review aimed to bridge the knowledge gap on the association between COVID-19 and pregnancy as the available information on it is limited [6].

COVID-19 infects the respiratory mucosa and other target cells by adhering to angiotensin-converting enzyme 2 (ACE2), which is the functional receptor for severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) and severe acute respiratory syndrome coronavirus [1]. This triggers a major immune response, leading to a cytokine storm secondary to viral aggression and causes complications in pregnancy. The ACE2 are present particularly in the lung and intestinal cells; hence, these are the most commonly affected organs [1]. In the lungs the binding of SARS-CoV-2 to ACE2 causes alveolar damage and pulmonary consolidation. The presence of ACE2 receptors in the vascular endothelium explains the placental changes found in pregnant women affected by SARS-CoV-2 [1].

The disease caused by SARS-CoV-2 is divided into the following stages: the initial phase called viremia, the phase 2 or pulmonary phase, and lastly, the critical or severe phase, in which the disease progresses, especially in those who present with comorbidities [7]. The clinical picture can vary from asymptomatic to mild, and critical [3]. The disease is considered mild when it does not reach the lungs, and severe when patients develop pneumonia and dyspnea, respiratory rate greater than or equal to 30 breaths per minute, saturation less than or equal to 93%, and pulmonary infiltrate >50% in 24–48 hours. Critical patients include those with respiratory failure, septic shock and/or dysfunction, and multiple organ failure [8].

Most pregnant women will have a light course and will recover without the need to anticipate delivery [3]. One study found that 86% of pregnant women had mild illness, 9.3% had severe illness, and 4.7% had critical illness. These percentages are similar to those described for not-pregnant adults with COVID-19 (80% mild, 15% severe, and 5% critical) [9]. However, studies have shown that the risks of worsening and progressing to the critical stages of the disease, as well as the need for mechanical ventilation, are greater among pregnant women than among the general population [3]. The factors associated with a worse prognosis and increased mortality among pregnant women are diabetes, obesity, and age >40 years. Those in the third trimester also have a higher risk of admission to intensive care units, as well as being mechanically ventilated [3]. According to a study by Berry M. et al. [10], pregnant women with advanced pregnancies are at a greater risk. In two reports describing 18 pregnancies with COVID-19, all were infected in the third trimester [11]. Altered tests with leukopenia, anemia, C-protein reaction, procalcitonin, and ferritin were also related to the severity of the disease in pregnant women [10].

The clinical findings among pregnant women with COVID-19 were similar to those of non-pregnant adults, and the main symptoms were cough, fatigue, myalgia, shortness of breath, and fever [1, 3]. Obstetric complications can occur due to a cytokine storm, and the most frequently observed complications are spontaneous abortion, delayed intrauterine growth, fetal distress, premature birth, premature rupture of membranes, and stillbirth [1, 3].

Chest X-ray with abdominal protection and blood tests such as those for complete blood count, ultra-sensitive C-protein reaction, urea, creatinine, electrolytes (including Mg, K, Na, Ca), liver profile, and coagulation should be performed if the patient present with increased respiratory rate, decreased oxygen saturation (SO_2 ; <96%), increased body temperature; and dyspnea. Fetal auscultation obstetric ultrasound and cardiotocography should also be performed depending on the gestational age of the pregnancy to assess fetal well-being [12].

TREATMENT

The basic guidelines for the treatment of COVID-19 in pregnancy are focused on early isolation, infection control, empirical antibiotic therapy, oxygen therapy, mechanical ventilation in case of respiratory failure, prevention of excess fluids, laboratory tests, fetal and uterine monitoring, individualized approach to the type of delivery, and multidisciplinary care [11].

The first step to be performed by the attending physician is to classify the stage of the patient. The initial phase, also called viremia, usually covers the first 5 days of the disease, in which the patient has mild symptoms of upper airway infection such as sore throat, cough, anosmia, and ageusia with or without fever and myalgia [12, 13]. Most patients will have complete resolution of symptoms at this stage, but some progress to the moderate or pulmonary stage of the disease. In phase 2 or pulmonary disease, which usually occurs from the sixth day of illness onwards, with symptoms such as easy fatigability, cough, chest pain, and myalgia. If nothing is done during the initial and 2nd phase, the patient may progress to a severe condition in which she has organ failure, a drop in SO_2 < 90% sepsis, and septic shock [12].

TREATMENT OF THE INITIAL STAGE OF THE DISEASE

The treatment of patients with COVID-19 in phase 1 is controversial [14]. Many recommend that the patient stays at home and goes to the hospital only during desaturation [15]. However, there is a growing understanding that drugs should be used early to reduce viral aggression in order to reduce the damage caused by the virus, to decrease blood hypercoagulation, and to reduce the immune response [13, 16].

The most commonly used drugs to decrease viral load in non-pregnant women are hydroxychloroquine, ivermectin, and nitazoxanide. These drugs can be prescribed alone or in conjunction with antibiotics such as azithromycin and doxycycline [13], which have proven efficacy against the virus and immunomodulatory effects [17]. Additionally, vitamins and minerals have also been prescribed. The treatment of pregnant women is similar to that of non-pregnant women, and only the use of teratogenic drugs must be avoided.

Chloroquine and hydroxychloroquine have been used for more than 70 years, making it a safe drug

for use in SARS-CoV-2 [18]. The antiviral role of hydroxychloroquine includes blocking sialic acid receptors and restricting of pH mediated spike protein cleavage that occurs at the binding site of the angiotensin-converting enzyme ACE2 [19]. It also acts by altering the acidic environment in lysosomes and endosomes, thus preventing endocytosis and inhibiting cytokine storms [20]. Although studies show a lack of efficacy of hydroxychloroquine in advanced stages of COVID-19 [21], according to Risch, the use of hydroxychloroquine in critically ill patients with COVID-19 is not relevant; it has the greatest benefit in the early stages of the disease. Moreover, there are five studies including two controlled trials that have demonstrated significant efficacy in outpatient treatment of patients with COVID-19 [22]. Considering the systemic crisis caused by COVID-19, the use of hydroxychloroquine seems to be a good choice [20].

Hydroxychloroquine can also be considered a safer therapeutic option for pregnant women infected with SARS-CoV-2 [6, 23]. The clinical data for the use of chloroquine and hydroxychloroquine in pregnant women are reassuring [24]. According to the guidelines, the treatment should be initiated in the viral phase of the disease; therefore, in the first 5 days of symptoms, hydroxychloroquine 400 mg every 12 hours should be given on the first day and then reduced to 200 mg every 12 h for another 4 days [12]. Fesler M.C. and Stricker R.B. [4] have suggested that hydroxychloroquine can even be used prophylactically in the pre-exposure of pregnant women to COVID-19 as this drug is safe during pregnancy and could prevent gestational complications and serious evolution in this high-risk population. The proposal would be to offer hydroxychloroquine 400 mg weekly to this population [4]. However, the half-life of hydroxychloroquine is long, and the exposure period is 210 days for chloroquine and 420 days for hydroxychloroquine after interruption of intake. The most reported side effects are related to the eyes and heart rate. Pregnant women, especially those who are at risk of prematurity, should be monitored through ultrasound. After childbirth, ophthalmological monitoring of the child should be performed [24]. According to Fesler M.C. and Stricker R.B. [4], hydroxychloroquine should be prescribed during pregnancy with the aim of saving lives, in view of the expansion of the pandemic. However, use during this period must be decided based on a risk-benefit analysis [24].

Ivermectin for use in the viral phase has been shown to be safe and effective in treating adults with COVID-19 [25]. In fact, studies have shown a positive interaction between ivermectin and protein viral targets that lead to SARS-CoV-2. Ivermectin decreases mortality and reduces symptoms in patients with COVID-19, so it can be a potential drug for the treatment of COVID-19 [26]. The combination of ivermectin and doxycycline also appears to be effective against COVID-19 [26]. However, ivermectin, when used at doses 10-100 times

higher than the current doses used for humans, has been shown to be teratogenic in mammals, although among women who inadvertently used ivermectin, no neonatal deaths, prematurity, or maternal morbidity, although it is still unclear whether it increases the risk of miscarriage and stillbirth. The literature is scarce on the safety of using this drug in pregnancy, so the data are insufficient to ensure that ivermectin is safe during pregnancy [27].

Nitazoxanide has antiviral action against SARS-CoV-2 *in vitro* and suppresses cytokine production by controlling the cytokine storm. In addition, nitazoxanide has bronchodilator action on the airways [28]. Nitazoxanide is a category B drug used during pregnancy [29].

Regarding the use of antibiotics with antiviral actions against COVID-19, Azithromycin and doxycycline are frequently prescribed. Azithromycin has potential in the treatment of patients with COVID-19 due to its antiviral and immunomodulatory actions [30]. It can be used as monotherapy [30], or in combination with nitazoxanide or hydroxychloroquine. The use of both has been shown to be effective if used in the early phase of COVID-19 [31]. In addition, studies have shown that the combination of hydroxychloroquine and azithromycin may be a treatment option in pregnancy, and cases that have been successfully treated in the literature have been described [32]. The use of azithromycin in pregnancy is not associated with an increase in malformation above the 1–3% baseline; therefore, macrolides are generally safe during pregnancy [33]. In a national multicenter study, the use of macrolides during pregnancy was not associated with an increased risk of major congenital malformations [34]. The authors recommend the use of azithromycin 500 mg for 5 days for non-pregnant women [13]; for pregnant women, the guidance is to use azithromycin 500 mg on the initial day followed by 250 mg for another 4 days [32]. Breastfed newborns exposed to macrolides showed mild symptoms such as diarrhea, insomnia, loss of appetite, drowsiness, and skin rash [35].

Doxycycline is considered a class D drug in the Food and Drug Administration (FDA) pregnancy classification along with tetracyclines, although a systematic review has shown the safety profile of this drug in children and pregnant women, in contrast to tetracyclines [36]. Wormser G.P. et al. believes [37] that doxycycline can be prescribed selectively for pregnant women and nursing mothers in situations where other safer antibiotics are not available, but it should be used for the shortest possible period.

Regarding vitamins and minerals, zinc deficiency is also strongly associated with conditions that increase the risk of developing severe COVID-19, which includes aging, immune deficiency, obesity, diabetes, and atherosclerosis. Therefore, zinc may have a protective effect as a preventive and adjuvant therapy against COVID-19 by reducing inflammation, improving mucociliary clearance, preventing lung injury, and modulating antiviral and antibacterial immunity [38]. Zinc sulfate 15 mg daily from

the 16th week of gestation until delivery [39]. Vitamin D studies have shown that low levels of vitamin D increase the risk of hospitalization and deaths caused by COVID-19 [40]. Moreover, the use of vitamin D in pregnancy can reduce the risk of pre-eclampsia, postpartum hemorrhage, gestational diabetes, and low birth weight [41]. The use of high doses of vitamin D (2,400 UI day) during pregnancy was associated with a lower risk of tooth enamel damage [42]. Popular belief suggests that vitamin C reduces the viral effects of the common cold; however, studies regarding this are controversial [43]; and with respect to COVID-19, the authors suggest the use of intravenous vitamin C to reduce the risk of virus-induced cytokine storms [44].

If pregnant woman develop fever, it should be controlled twice a day, and if necessary, paracetamol 500–1000 mg every 6–8 hours should be used [12]. Women with mild symptoms can be isolated at home and followed over the phone [12].

TREATMENT OF PULMONARY PHASE AND CRITICALLY ILL PREGNANT PATIENTS

For moderate and severe cases, the treatment of the disease does not differ between pregnant and non-pregnant patients. It is performed with the use of corticosteroids, anticoagulants, antibiotics, and other drugs depending on the conditions of the patient and the severity of the disease. Oxygen is prescribed in cases of oxygen desaturation, and if clinical conditions deteriorate, and the patient progresses to the critical stage of the disease, mechanical ventilation is indicated. According to López M. et al. hospitalization for critical patients is recommended to monitor vital signs such as blood pressure, respiratory rate, SO_2 , and heart rate [12]. The main drugs used in this phase are corticosteroids, anticoagulants, antibiotics, and antivirals.

Corticosteroids are the central and most important drugs in the treatment of patients with COVID-19. At the beginning of the pandemic, there were many questions regarding the use of corticosteroids in patients with COVID-19. It was believed that the use of corticosteroids could be associated with an increase in disease morbidity and mortality as it was thought to delay the elimination of the virus [12, 45]. However, a recovery study published in June 2020 broke this paradigm and showed that corticosteroids helped in the treatment of patients on mechanical ventilation or using oxygen [46]. Moreover, other studies have confirmed that in decompensated patients, in desaturation and with a high inflammatory response, corticosteroid use increases survival [47]. Recent research has shown that, although the recommendations of some studies indicate the use of corticosteroids only for patients in advanced stages of the disease, good results have been obtained with the use of corticosteroids starting at the beginning of phase 2 or from day 6 of symptoms at home without the need for hospitalization [13, 48].

Corticosteroids can be used routinely in pregnant COVID-19 patients for both fetal lung maturation and treatment of COVID-19 [49]. According to López, the use of corticosteroids for fetal lung maturation in patients with COVID-19 is safe [12]. These findings reiterate the safety of corticosteroids for use in pregnant women with COVID-19 and acute respiratory distress syndrome [50]. Corticosteroids are also indicated in pregnant women who require oxygen therapy or mechanical ventilation. Thus, pregnant women with $SO_2 < 94\%$ can use corticosteroids for both fetal lung maturation and treatment of COVID-19; in the first 2 days 4 doses of dexamethasone should be administered and then methylprednisolone should be administered for the remaining 8 days of treatment [51]. Methylprednisolone has been used in critically ill patients and has shown benefits in the management of COVID-19 [12], although dexamethasone is the only drug approved for use in pregnant women who require mechanical ventilation or supplemental oxygen [49]. Data on dexamethasone in breastfed babies are limited, and methylprednisolone may be indicated [51].

The gestation period is known to be prothrombotic. Pregnant women are in a state of hypercoagulability with an elevated risk for deep venous thrombosis and the development of disseminated intravascular coagulation, which could be life threatening [52]. Considering that COVID-19 is also a thrombotic disease, pregnant women affected by SARS-CoV-2 infection have a higher risk of developing thromboembolic complications [53]. Severe disease can complicate with disseminated intravascular coagulation, which is associated with high mortality. It is a systematic response to the virus and tissues damaged by the infection [54].

Studies have shown that thromboembolism as well as coagulopathies are in fact increased in pregnant women affected by COVID-19; therefore, these women must be closely monitored for the greatest risk of deterioration [53]. Moreover, the risk of thromboembolism and pulmonary embolism in pregnant women is highest during the puerperium period; hence, prophylaxis should be considered in this period [55]. The D-dimer, a blood clotting marker, grows progressively during pregnancy and peaks on the first day after delivery. Then, it decreases rapidly within 3 days, then linearly thereafter, and becomes normal in the 42 days after delivery. If the D-dimer does not start to decrease in the postpartum period, thromboembolism is considered [52]. The D-dimer is a product of fibrin degradation which is elevated during thrombus formation and breakdown in COVID-19 patients. As COVID-19 infection progresses, the clotting system is activated to stop viral infection [54]. The levels of D-dimer and fibrinogen increase during all pregnancies, with 98% of patients showing an increase at 36 weeks [56].

Although COVID-19 is a thromboembolic disease, there is no consensus on the use of anticoagulants, whether therapeutic or prophylactic, as well as

the precise moment when they should be used. Studies have found that the use of prophylactic anticoagulation reduces mortality in patients with COVID-19 when admitted to the hospital [57]. With regard to COVID-19 and gestation, the prophylactic use of enoxaparin has been oriented especially to those who are at greater risk, such as obese women [58]. On the other hand, other studies have found that the therapeutic use of enoxaparin in COVID-19 has led to a 2.3-fold increase in mortality, so some studies say that anticoagulation may not be effective in this syndrome. Moreover, some authors agree that most patients who died did so due to hypoxia secondary to acute renal failure, shock, and multiple organ failure. Although thrombosis may have contributed to mortality, it did not appear to be specifically related to it [59]. Anticoagulation therapy with enoxaparin appears to have a better prognosis in critically ill patients, especially those with markedly high D-dimer levels [60].

Researchers advocating the use of anticoagulation have used enoxaparin for the treatment of hypercoagulable states in patients with COVID-19 [57]. Low-molecular-weight enoxaparin has been used for >20 years in pregnant women and is the anticoagulant of choice to be used in pregnancy in patients at risk for thrombosis [61]. The best-known indications are those for the prophylaxis of thromboembolism, prevention of abortion in thrombophilia patients, and prevention of arterial thrombosis in patients with heart valve disease. Enoxaparin does not cross the placenta; hence, it is safe for the fetus [61]. The mechanism of action of enoxaparin involves the action of anti-factor Xa in maternal blood, inhibition of tissue factor by placental trophoblasts, and anti-inflammatory action. The main side effects associated with the use of enoxaparin are localized mild allergies (2%) and increased bleeding (2%); the severity is dose dependent [61].

Assessments for detecting coagulation changes as well as the use of low-molecular-weight heparin should be considered and discussed between the attending physician and the patient [2]. The prophylactic dose of subcutaneous enoxaparin is 30–40 mg/day. The dose of subcutaneous heparin is 5,000 μ L for every 8 hours [59]. Thromboprophylaxis should be performed considering the severity of the disease, the outpatient or hospital situation with associated morbidities, and contraindications to the use of anticoagulants [49]. The use of low molecular weight enoxaparin prophylactic doses during hospitalization for up to 2 weeks after independence of D-dimer levels is recommended [12]. There is no contraindication for aspirin use during pregnancy [49].

Remdesivir decreases viral load by inhibiting SARS-CoV-2 replication in patients affected by the virus, reducing inflammation, mild symptoms, and lung damage associated with COVID-19. It has been used in a compassionate manner [62]. Remdesivir inhibits COVID-19 *in vitro* [18]. Remdesivir, lopinavir, and ritonavir can be used during pregnancy and lactation, but data on non-pregnant women

showed no benefit [49]. However, according to López M. et al. [12], tocilizumab, a monoclonal antibody with inhibitory action on IL-6, or remdesivir (an RNA polymerase inhibitor with *in vitro* action against SARS-CoV-2) have shown good efficacy in critically ill patients, but there is concern about the use of these drugs during pregnancy. The role of immunomodulatory monoclonal antibodies (tocilizumab), immunomodulators (tacrolimus), interferon, inhaled nitric oxide and convalescent plasma during pregnancy and lactation require further evaluation [49].

In case of a suspicion of alveolar infiltrate or increase in procalcitonin (indicates bacterial superinfection), intravenous ceftriaxone 1–2 g/day and teicoplanin 400 mg every 12 hours in 3 doses followed by 400 mg/day should be given [12]. Even for drugs that are not contraindicated during pregnancy, the patient must be asked to sign the informed consent for compassionate use [12].

In pregnant women with $SO_2 < 94\%$ saturation, oxygen support with a nasal cannula of 1–6 L/min should be offered in order to achieve SO_2 between 94% and 96% [50]. If the cannula is not sufficient, switch to a Venturi mask, and if necessary, indicate a positive pressure mask [12]. Another option would be high flow with a 60 L/min nasal cannula for patients who do not improve with nasal flow, in cases where intubation would be indicated. It is similar to a conventional cannula in that it offers oxygen flow as high as 60 L/min and the air is humidified and heated. However, patients should be stable, aware, and have a normal cough reflex [50]. The identification of severe cases allows the use of O_2 support and an indication for an intensive care unit. Careful monitoring is recommended as many patients have sudden deterioration [12]. The assistance in this stage must be provided by an anesthesiologist, clinician, or intensivists, as intubation [12] may be necessary. The patient should be in prone position if possible. Pregnant women with refractory hypoxemia can be in prone position as long as physiological changes and gestational risks are considered, taking into account the pregnant physiology and anatomy [50, 63].

Mortality among non-pregnant women who require mechanical ventilation is 88%. However, Lucarelli E. et al. [64] reported three cases of pregnant women who were intubated due to respiratory failure and pneumonia due to COVID-19. After several days, they were extubated and were able to continue monitoring their pregnancies with no proven adverse effects. Pregnant patients on mechanical ventilation should use neuromuscular-blocking agents for a minimum time [49].

Obstetric management in intubated patients can be as follows: before 23–24 weeks of gestation, fetal monitoring is not recommended for pregnant women with respiratory failure caused by COVID-19, as an emergency cesarean would bring more risks to the mother than fetal benefits [50]. After this gestational age, evaluation of each case is recommended as delivery under general anesthesia presents significant risks for the mother and the health

team. At 24–28 weeks, monitoring depends on fetal weight and neonatal conditions [50]. Over 28 weeks of pregnancy the maternal-fetal monitoring must be continuous. If maternal conditions deteriorate, the delivery is indicated, probably by cesarean section [50].

In pregnant women, due to the risk of pulmonary edema from inflammation, fluids must be controlled especially in those with desaturation. If saturation deteriorates in a patient with a positive fluid balance, use of furosemide is indicated [50].

LABOR MANAGEMENT

Pregnant women should be isolated for 2 weeks or, after negative RT-PCR (reverse transcription polymerase chain reaction), taking measures to avoid lying in bed due to the risk of thromboembolism caused by COVID-19, and by pregnancy, daily consultation by telehealth [12]. Perform obstetric examinations and in-person consultation only if indispensable cardiotocography is carried out to assess the fetus, depending on maternal conditions and gestational age [12].

At the beginning of the pandemic, the indication for cesarean delivery was common due to the lack of knowledge of vertical transmission [65]. However, studies have shown that cesarean sections should be indicated according to the usual obstetric conditions, as the risk of vertical transmission is not an indication for cesarean section [12]. Moreover, maternal infection with SARS-CoV-2 is not an indication for cesarean section. The timing and type of delivery should be based on obstetric indications, clinical and fetal conditions such as gestational age, obstetric history, maternal comorbidities, and disease severity [1]. With regard to maternal indication, in a patient with respiratory failure, childbirth may worsen the pulmonary situation, and maternal hypoxia may increase the risk of fetal impairment. In this case, indicate a cesarean section between and 32–34 weeks in severely critically ill patients, when the risk of prematurity can be assumed by the service. Before 32 weeks, balance maternal–fetal risks, especially in intubated patients or those who need them [12], and perform continuous monitoring by cardiotocography and, if fetal distress is suggested, indicate delivery immediately by the most appropriate method that conditions permit [12].

Minimize the frequency of maternal exams, do it every 2–4 hours, and with the least number of professionals. Monitor SO_2 , respiratory rate and temperature every hour [12]. Do not indicate delivery for a stable patient with COVID-19. The ideal is to schedule when a patient is negative [12], and seek to establish a safer delivery for the mother, baby, and health team [65]. Women should be instructed on the most appropriate type of delivery for each case, respecting the correct indications to reduce unplanned cesarean sections and the psychological impact of childbirth during the pandemic. One study showed that 68.9% of women had a cesarean delivery and COVID-19 was the main indication for it. COVID-19 is

also associated with premature birth, although neonatal outcomes are generally favorable [65].

At delivery, opioids and remifentanyl are used with caution because of the risk of respiratory depression. Nitrous oxide can be used for labor analgesia [49]. Neuraxial analgesia is indicated, as it can also be used for cesarean section in cases of conversion [12]. Histopathological examination of the placenta should be required [1]. Prophylactic enoxaparin should be taken daily 40–80 mg or 60 mg if greater than 80 kg due to the risk of thromboembolism in the puerperium and COVID-19 [60]. Discharge is the same as any patient with COVID-19, and after discharge, the puerperal woman was followed up via telehealth. If there is a need for evaluation during the contagious period, all precautions should be taken [12].

All patients, and even asymptomatic patients, should be tested before elective procedures, and the correct protective equipment, such as an N95 mask, one or two gloves, a long-sleeved lab coat, and eye protection, should always be worn [12]. The room should have negative pressure. Pregnant women must wear surgical masks during delivery. After delivery, leave the patient in the same room as before and, if possible, she should be assisted by the same team of health professionals. Offer contact with the newborn. All materials must be considered contaminated [12].

The transmission of COVID-19 from person to person occurs through respiratory droplets after contact with an infected person (<2 m or direct contact with an infected surface) [12]. One study showed that there was no vertical transmission in 206 newborns [65]. Vertical transmission being possible has not yet been conclusively proven [3].

BREASTFEEDING

Breastfeeding protects the mother and child, and the benefits are unquestionable and should be encouraged. The decision to continue breastfeeding during COVID-19 should be made considering the clinical peculiarities of COVID-19 and the protective effects of breastfeeding [66]. As COVID-19 is not transmitted by breast milk, the benefits of breastfeeding outweigh the risks and can even protect the mother and newborn. For breastfeeding to be safe, infection control protocols must be strictly adhered to [66]. The mother must wear an N95 or surgical mask and perform hand hygiene when in contact with her newborn, especially during breastfeeding [12]. The mother should undergo hand disinfection and respiratory hygiene [1]. Neonates should be tested and isolated to avoid contact with contaminated droplets [12]. The mother and baby should be together and maintain skin-to-skin contact during the COVID-19 period. If the mother is very sick and unable to breastfeed, she can express the milk, and a healthy person should breastfeed the newborn [66]. Another option, if feasible, is to discharge the asymptomatic newborn to be cared for by a relative who does not have the disease, but if

he is symptomatic and needs to stay in the hospital due to prematurity, for example, he must remain isolated in the intensive care unit [12]. Newborns should be monitored for suspicious symptoms of COVID-19 [1].

CONCLUSION

As the risks of COVID-19 complications are higher in pregnant patients, a knowledge of the behavior that can help in better decision-making to preserve the health of the maternal–fetal dyad is encouraged. The patient must remain in isolation and be monitored and treated

AUTHOR CONTRIBUTIONS

Salete da Silva Rios researched and analyzed the literature on the review topic. Juliana Rios Chen, Ceres Nunes de Resende, Ana Carolina Rios Chen and Alberto Borges Peixoto, participated in writing the text of the manuscript and its interpretation. Edward Araujo Júnior developed the general concept of the article and supervised its writing. All authors participated in the discussion and editing of the work. All authors approved the final version of the publication.

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according to the stage of the disease, taking into account the obstetric conditions, the anatomy and physiology of the gestational period, and the severity of the disease. The type of delivery should consider this information. The health team must be preserved from unnecessary exposure to viral contamination, and breastfeeding must be guided by encouraging early mother–child contact as long as hygiene rules and the use of masks are respected. Knowledge of the treatment available today for pregnant patients with COVID-19 will help leading to better evolution and maternal–fetal outcomes.

ВКЛАД АВТОРОВ

С.С. Риос провел поиск и анализ литературы по теме обзора. Ю.Р. Чен, Ц.Н. Резенде, А.К.Р. Чен и А.В. Пейшото участвовали в написании текста рукописи и его интерпретации. Э. Араухо-мл. разработал общую концепцию статьи и руководил ее написанием. Все авторы участвовали в обсуждении и редактировании работы. Все авторы утвердили окончательную версию публикации.

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