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REVIEW

Pregnant women and infants against the infection risk of COVID-19: a review of prenatal and postnatal symptoms, clinical diagnosis, adverse maternal and neonatal outcomes, and available treatments

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Abstract

Background The establishment of a risk-appropriate care approach for pregnant women and newborn infants under the COVID-19 pneumonia is vital to prevent the main pregnancy complications.

Objectives and design This study reviewed the vertical transmission (VT) potential of COVID-19 pneumonia in pregnant women. Key-related symptoms and adverse clinical outcomes for mothers and infants before and after childbirth were summarized. Some practical therapies and preventive health solutions were also proposed.

Results There was a high susceptibility in pregnant women to COVID-19 infection, especially in the third trimester of pregnancy. The most common symptoms in 22–40-year-old patients infected with COVID-19 were fever (87.6%), cough (52.3%), dyspnea (27.6%), fatigue (22.4%), sore throat (13.5%), malaise (9.4%), and diarrhea (3.4%), respectively. The viral infection led to an increase in preterm labor and cesarean delivery without any intrauterine infection and severe neonatal asphyxia. No infection in the newborn infants was reported despite a high risk of the VT phenomenon. The most important therapies were the reception of antiviral and antibiotic drugs, oxygenation therapy, psychological interventions, and food supplements with health-promoting effects. The best proposed medical strategies to control the COVID-19 infection were bi-monthly screening and following-up the mothers' and fetuses' health, not using the potent broad-spectrum antibiotics and corticosteroids, providing the delivery room with negative pressure for emergency cesarean section, and the immediate isolation of newborns after childbirth without direct breastfeeding.

Conclusion Babies with respiratory problems may be born to some mothers with COVID-19, who have weak immune systems. Thus, the virus transmission cycle should be disrupted to prevent adverse maternal and fetal outcomes by integrating individual health guidelines, efficient medical care therapies, and hospital preventive practices.

Keywords Novel coronavirus · 2019-nCoV infection · Clinical diagnosis · Pregnancy outcome · Neonates · Postnatal symptoms · Cesarean · Antiviral therapy · Health management · Computed tomography scan

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Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV	Severe acute respiratory syndrome coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
ARID	Acute respiratory infectious disease
UDs	Underlying diseases
VT	Vertical transmission
CT	Computed tomography
AMOs	Adverse maternal outcomes
ANOs	Adverse neonatal outcomes
G-HT	Gestational hypertension
IUI	Intrauterine infection

GDM	Gestational diabetes mellitus
PROM	Premature rupture of membrane
IUGR	Intrauterine growth retardation
ICU	Intensive care unit
WBCs	White blood cells
CRP	C-reactive protein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
PCT	Procalcitonin
GGO	Ground-glass opacity
ECS	Emergency cesarean section
IUGR	Intrauterine growth restriction
PMR	Progressive muscle relaxation
IVF	In vitro fertilization
ICU	Intensive care unit

Introduction

After 3 months since the outbreak of coronavirus disease 2019 (COVID-19) in Wuhan, China, this virus infection was affected 199 countries and territories around the world. The number of active cases and total death with COVID-19 infection was exponentially growing in the world (Fig. 1a). Since 9 March 2020, the number of COVID-19 daily cases outside of China has been increasing (Fig. 1b). To date, over 222 million coronavirus cases and ~ 4.6 million deaths have been recorded around the globe [1]. COVID-19 is the seventh coronavirus with human infection capability. It has a genomic similarity to the Middle East respiratory syndrome coronavirus (MERS-CoV, 50%), the severe acute respiratory syndrome coronavirus (SARS-CoV-1, 75–80%), and a bat coronavirus (96%) [2, 3]. COVID-19 is also called "SARS-CoV-2", because it like SARS-CoV-1 binds to the same cell receptor, namely angiotensin-converting enzyme II (ACE2) [4]. The most common clinical symptoms of this viral disease include fever and dry cough. Besides, some of the non-specific symptoms appeared in patients are fatigue, muscle soreness, dyspnea, headache, and diarrhea [5, 6]. The disease severity and mortality rate were reported to be ~ 20% and 3%, respectively [7]. Although COVID-19 pneumonia has become progressively severe, no definitive drug has so far evidenced the stemming potential of viral growth. The stronger transmission capacity of COVID-19 compared to the SARS-CoV-1 that emerged in 2003 makes an extremely serious need for the prevention and control of COVID-19. Accordingly, at the end of January 2020, the World Health Organization (WHO) declared a global health emergency to fight the COVID-19 outbreak.

It has been demonstrated that patients with underlying diseases (UDs, such as cardiovascular diseases, hypertension, diabetes, and diseases related to the respiratory system, liver, and kidneys) more are at risk for severe respiratory symptoms and death caused by the virus [8]. In contrast, there is a milder condition for COVID-19-infected children than adults so that the pediatric populations showed a better prognosis, shorter duration of virus shedding, lower clinical severity, and faster rate of recovery. However, children with UDs are also tended to be severe and critical cases [9]. Among adults, pregnant women are one of the most important population groups at increased risk of this viral disease, particularly individuals with a history of gestational diabetes mellitus (GDM) and preeclampsia [10]. Pregnancy-induced changes in the cardiovascular and respiratory functions, such as escalated heart rate, stroke volume, and oxygen consumption along with the diminished capacity of lungs can considerably increase the SARS risk in pregnant women [11, 12]. The COVID-19 doubly develops some immunological and physiological changes during pregnancy, causing morbidity and mortality of pregnant women [13]. In other words, these changes can notably increase the rate of AMOs and ANOs. Siston et al. [14] earlier explained that although 1% of the whole patients infected with influenza A subtype H1N1 virus were pregnant women, 5% H1N1-related deaths belonged to this population group in 2009. It was also shown that the infection risk of SARS-CoV-1 and MERS-CoV during pregnancy could remarkably increase the maternal and neonatal complications, including spontaneous abortion, preterm delivery, intrauterine growth retardation (IUGR), use of endotracheal intubation or tracheostomy, consumptive coagulopathy, admission to the intensive care unit (ICU), and chronic renal disease [15–17]. Moreover, newborn infants will be at high risk of COVID-19 if they are born from mothers infected with COVID-19, or possess near contact with somebody with possible or definitive COVID-19, or live in or travel to the epidemic areas [18].

One of the most challenging questions is whether a pregnant woman with COVID-19 infection can vertically transmit and pose risks to her fetus and neonate or not. Furthermore, what are adverse maternal (AMOs) and neonatal (ANOs) outcomes and clinical strategies to control/reduce pregnancy complications in women with COVID-19 pneumonia? Answers to these questions will be useful to design new management principles and practices in the treatment and prevention of COVID-19 infection of pregnant women and their neonates. There is little information about abnormal pregnancy outcomes in pregnant women with COVID-19 [14]. Hence, this study was aimed to present the important findings on clinical outcomes and health recommendations for pregnant women with COVID-19 infection and their infants to set up some efficient preventive healthcare guidelines.

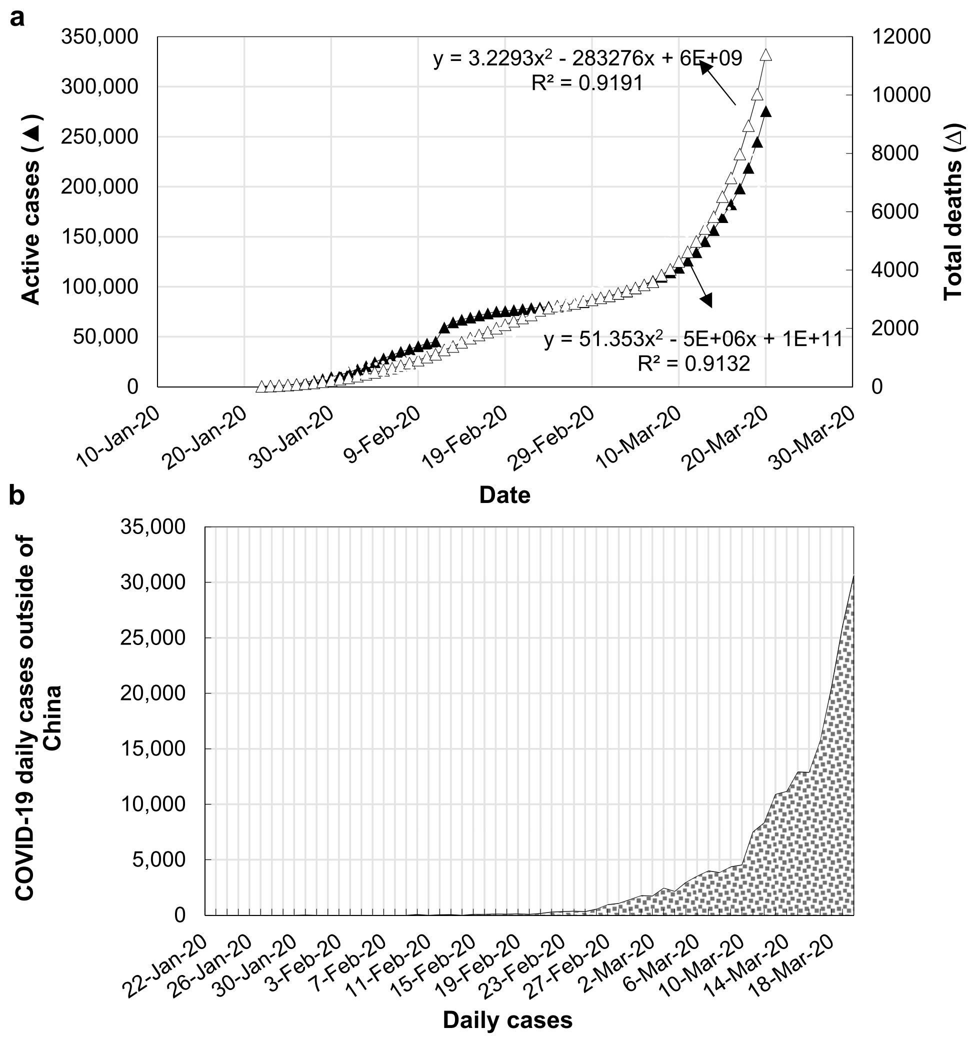

Fig. 1 **a** The number of active cases and total death with COVID-19 infection in the world, and **b** the COVID-19 daily cases outside of China from 22 Jan 2020 to 20 Mar 2020. Retrieved from https://www.worldometers.info/coronavirus

Primary symptoms of COVID-19 in pregnancy

Table 1 summarizes major symptoms related to COVID-19 infection in pregnant women. Figure 2 also depicts the different symptoms diagnosed in this population group. Fever (87.6%) was the most common sign of this viral disease. Other symptoms with the highest frequency among the patient cases were dry cough (52.3%), shortness of breath (27.6%), fatigue (22.4%), sore throat (13.5%), malaise (9.4%), and diarrhea (3.4%), respectively. Zhu et al. [18] reported that there were two main symptoms of fever and cough before, during, and after the delivery. In some cases, other signs like abnormally rapid breathing or tachypnea [19], nasal congestion [20], runny nose [21], vomiting [18, 22], skin rash in the abdominal area [20], pneumothorax [18], and abnormal liver function [18] were appeared.

Clinical diagnosis of COVID-19 infection in pregnancy

As earlier mentioned, the travel history to epidemic areas, person-to-person contact, and precise clinical laboratory measurements [the nucleic acid or virus gene tests using real-time polymerase chain reaction (RT-PCR)] can give some clues to diagnose COVID-19. The viral load is usually detected in test samples collected from saliva, the secretion of upper (nasopharyngeal and oropharyngeal swabs), and lower (sputum, endotracheal aspirate, and bronchoalveolar washing fluid) respiratory tracts, urine, as well as feces. A primary choice among the different specimens is the nasopharyngeal swab, while the diagnostic positive rate of this sample is under 50%. This fact shows that the test repetition of nasopharyngeal swab samples is unavoidable to improve the positive rate. In contrast, the bronchoalveolar washing

Table 1 A summary of case reports on the infection risk of COVID-19 for pregnant women and newborns

Case (number, age)	Gestational age[a]	Major-related symptoms[b]	Key outcome(s)[b]	References
Pregnant woman aged 28 years	30th week	Intermittent fever	-Delivering a healthy preterm baby with weighing 1.83 kg without any evidence of COVID-19	[29]
15 pregnant women	Nr	Fever (86.6%), cough (60%)	-Achieving the good recovery of cases with lymphocytopenia (80% population) without any antiviral drugs -Clinical features and CT imaging progression pattern in pregnant women similar to those of non-pregnant women -No infection in the newborns from pregnant women with COVID-19 pneumonia	[28]
16 laboratory-confirmed and 25 clinically-diagnosed pregnant women	Nr	Initial normal temperature	-Vulnerable to more pulmonary involvement with an elevated neutrophil ratio and lymphopenia compared to non-pregnant women	[4]
9 pregnant women aged 26–40 years	3th trimesters (36–39th weeks) plus 4 days	Influenza virus infection, upper respiratory tract infection, fever (36.5–38.8 °C) without chills (7 cases), cough (4 cases), myalgia (3 cases), sore throat (2 cases), malaise (2 cases), shortness of breath (1 case)	-Observing the fetal distress and lymphopenia in 2 and 5 cases, respectively -No neonatal asphyxia in newborn babies -No development of severe COVID-19 pneumonia or death in patients -Negative for the virus after testing the amniotic fluid, cord blood, breastmilk, and neonatal throat swab samples -No evidence for IUI caused by VT in cases with COVID-19 pneumonia in late pregnancy	[26]
13 pregnant women aged 22 to 36 years	< 28th week (2 cases), 3th trimesters (11 cases)	Fever (37.3–39.0 °C) in 10 cases with fatigue, dyspnea (3 cases)	-A relatively high rate of cesarean delivery (38%) and preterm labor (46%) -Susceptibility of pregnant women to COVID-19 infection -No severe neonatal asphyxia and VT in livebirths -The probable rise of health risks to both mothers and infants during pregnancy	[6]
9 pregnant women aged 30 years	3th trimesters (36–39th weeks)	Fever and cough before (4 cases), during (2 cases), and after (3 cases) the delivery, diarrhea in 1 case	-Adverse impacts of perinatal COVID-19 infection newborns in terms of fetal distress, premature labor, respiratory distress, thrombocytopenia along with abnormal liver function, and death	[18]
3 pregnant women aged 30 to 34 years	3th trimesters (37–40th weeks)	Fever (37.0–38.0 °C), cough (2 cases)	-Fewer adverse maternal and neonatal outcomes -The possible risk of VT events of COVID-19 during late pregnancy or delivery	[30]

fluid showed a remarkable positive rate, although this sample is not appropriate for a high number of pregnant women because of the elevated cross-infection risk [23, 24]. It also is necessary to discriminate COVID-19 from other viral (e.g., influenza virus A and B, SARS-CoV-1, and respiratory syncytial virus) and bacterial (e.g., *Legionella pneumophila* pneumonia) infections by analyzing samples using specific kits.

Blood samples are one of medicine's most primary diagnostic tools in patients with COVID-19. Results showed that the infection of COVID-19 did not change the count of leucocytes significantly. Even so, Lai et al. [25] revealed the COVID-19 infection in most age populations caused an increase in the count of white blood cells (WBCs) and neutrophils. In a retrospective review of medical records, Chen et al. [26] showed that 77.7% of pregnant women with COVID-19 had a normal WBC count, while none of them had WBCs lower than the normal range. A case report of neonatal COVID-19 infection showed that the mother had lower lymphopenia and higher neutrophilia than the normal range [27]. Lymphocytopenia was also observed in some women with COVID-19 pneumonia [28, 29]. In another study, two-thirds of patient cases showed higher counts of neutrophils and lymphocytes than the normal range [30]. Normal WBCs (8.9×10^9/L) with 18.1% of lymphocyte was also recorded by Fan et al. [20]. However, Li et al. [22] in a case–control study reported that patients with COVID-19 compared to controls had lower WBCs and neutrophils counts. They also pointed out that the count of WBCs, neutrophils, and eosinophils in postpartum blood samples of patients was increased [22]. There were mild thrombocytopenia [30, 31] and creatine phosphokinase [32] in the selected patients. The decreased platelets were earlier reported in pregnant women infected with SARS-CoV-1 [33].

Chen et al. [34] also found that one-third of pregnant women with COVID-19 had high levels of ALT and aspartate aminotransferase (AST). However, Liu et al. [28] reported no change in ALT and AST concentrations among pregnant women infected with COVID-19 during pregnancy. On the contrary, Li et al. [22] realized that patients with COVID-19 showed lower ALT levels compared to the healthy controls. In general, the low level of serum albumin (< 40.0–55.0 g/L) or hypoalbuminemia was detected in pregnant women with COVID-19 [11, 29, 30]. The analysis of C-reactive protein (CRP) confirmed elevated levels of C-reactive protein (> 10 mg/L) in pregnant women with COVID-19. [26, 30, 34]. Conversely, Li et al. [22] reported a lower CRP concentration in patient pregnant women than the non-pneumonia controls. In 2003, the SARS-CoV-1 infection led to an elevated level in the liver enzyme of alanine aminotransferase (ALT) in five Chinese primagravidas [33]. As a biomarker, the peptide precursor of the hormone

Table 1 (continued)

Case (number, age)	Gestational age[a]	Major-related symptoms[b]	Key outcome(s)[b]	References
Pregnant woman aged 27 years	36th week	Fever, dry cough, fatigue, tachypnea	-CT scan of lungs: patchy peripheral and subpleural ground-glass opacities (left lobe), and minor subpleural opacity of rough thickness and blurred borders (right middle lobe) -An uncomplicated elective Cesarean delivery with a healthy newborn infant	[19]
2 pregnant women aged 29 and 34 years	3th trimesters (36–37th weeks)	Fever (37.3 °C–38.5 °C), skin rash, nasal congestion, and sore throat	-CT scan of lungs: multiple patchy infiltrates and consolidation on left side of the lung(s) -Low risk of IUI by VT of COVID-19	[20]
9 hospitalized infants aged < 1 year	–	Fever (4 cases), mild upper respiratory tract symptoms (2 cases)	-A possibility of more susceptibility of female infants to COVID-19 infection compared to male ones	[21]
Boy infant of a 34-year-old pregnant woman	3th trimesters (40th week)	Mother's fever (37.8 °C)	-The favorable health of male infant and afebrile with no cough or vomiting -No special treatment for the newborn	[27]

[a] *nr* not reported, [b] *VT* vertical transmission, *IUI* intrauterine infection, *CT* computed tomography

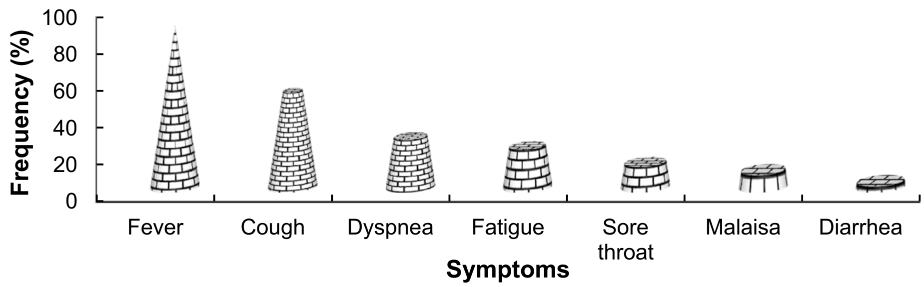

Fig. 2 The most common symptoms detected in pregnant women with COVID-19 infections

calcitonin or procalcitonin (PCT) is typically used to diagnose bacterial infections. It seems that the high serum PCT levels (≥ 0.5 ng/mL) can be considered as a valid indicator in patients with COVID-19. High serum PCT levels in 6.1–13.7% of the adult populations infected with COVID-19 were shown [35–37]. But, this test could not discriminate pregnant women with COVID-19 from healthy cases [30]. Liu et al. [30] determined much more concentration of interleukin-6 (43.72–44.18 pg/mL) in patients with COVID-19 compared to the normal range (0.0–7.0 pg/mL). Thus, this multifunctional pleiotropic cytokine may be a good indicator of COVID-19 in suspected cases.

Chest computed tomography (CT) scan analysis

Today, it has been discovered that the use of the chest computed tomography (CT) scan is an efficient diagnostic tool to assess the extent of damage to lungs infected by COVID-19. Ai et al. [38] realized that the chest CT scan compared to RT-PCR had a higher sensitivity (~ 1.4 times) to diagnose COVID-19. Hence, a comparison between repeat chest CT scans can be an ongoing criterion to evaluate the illness progression or recovery. Overall, the most common radiologic result on the chest CT (56.4%) on admission is ground-glass opacity (GGO) [31, 39]. However, crazy paving patterns and consolidations can be seen in the chest CT images with the COVID-19 progression [31, 40]. Figure 3 illustrates the CT scans of a case of COVID-19 in an Iranian pregnant woman at 36th gestational week. At admission time, the lesions as GGOs with blurred borders are mainly distributed in the middle and lower lobes of both lungs. After 3 days of antibiotic-antiviral therapy, lesions were notably resolved by reducing GGOs in both lungs. However, further progression of the COVID-19 pulmonary manifestations in Chinese cases caused multiple lesions on their initial CT scan.

Li et al. [22] based on the typical image of CT confirmed that COVID-19 pneumonia could cause some abnormalities in both lungs of 15 out of 18 suspected patients. Chen et al. [34] detected multiple patchy GGO on chest CT scans of nine positive parturients with COVID-19, without any typical symptoms such as fever and dry cough. The chest CT scan of a 28-year-old pregnant at 30 weeks gestation showed subpleural patchy consolidation and ground-glass opacities in the left and right lung sides, respectively [29]. Chen et al. [19] after taking CT scans of a 27-year-old pregnant woman suspected to COVID-19 found that this viral infection could cause some patchy peripheral and subpleural ground-glass opacities in the left lower lung lobe, whereas a minor subpleural opacity with irregular blurred margins was observed in the right middle lobe. The chest CT imaging of three pregnant cases with COVID-19 was examined by Liu et al. [30]. Even though there was normal auscultation of the patient's lungs on their admission time, several typical and atypical CT manifestations as a result of the COVID-19 invasion were observed in terms of bilateral infiltrates, localized emphysema, subsolid patchy, GGO, and linear fibrotic patterns. They also signified that the lung abnormalities in two cases were progressed, while another patient

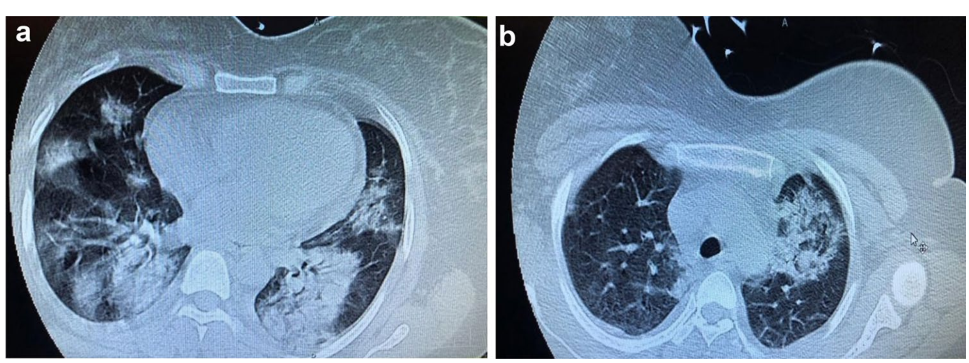

Fig. 3 Chest CT scans of a 32-year-old Iranian pregnant woman with COVID-19 at 36 weeks gestation at admission time (**a**), and 3 days after starting antibiotic-antiviral therapy (**b**)

was recovered on the 16th day by visualizing improvements in the appearance of CT scans [30].

Adverse maternal outcomes and intrauterine transmission of COVID-19

Schwartz [11] evaluated the maternal–fetal transmission of COVID-19 in 38 pregnant women as affected by adverse maternal outcomes. Although some patients had co-morbid conditions (e.g., GDM, preeclampsia, pregnancy hypertension, uterine scarring, and uterine atony), no cases were found with severe pneumonia or maternal deaths. It was thus concluded that these AMOs could not be risk factors for intrauterine transmission of this virus to fetuses. Chen et al. [26] also reported some complications gestational hypertension (G-HT), preeclampsia, and premature rupture of membrane (PROM) in four cases among nine pregnant women infected with COVID-19. However, they showed that these AMOs did not cause any intrauterine infection (IUI) by vertical transmission (VT) during the late pregnancy. Liu et al. [30] reported a 30-year-old third gravid patient with COVID-19, who had a history of G-HT during her first pregnancy. Not only RT-PCR results of anal swab and vaginal mucus for COVID-19 was negative but also no IUI by VT was found. Similar findings were obtained by Li et al. [22] who showed no risk of maternal-to-neonatal intrapartum transmission of COVID-19 among patient populations with a diverse range of gestational complications on admission, such as GDM, preeclampsia, PROM, G-HT, sinus tachycardia, and hypothyroidism.

Generally speaking, no significant association was observed between COVID-19 severity and mentioned AMOs. However, the delivery time and type of pregnant women with COVID-19 can be variable depending on the gestational age, disease severity, pregnancy comorbidities (e.g., GDM, G-HT, preeclampsia, etc.), obstetric history, and embryonic factors [41]. The best surveillance assessments for pregnant women with COVID-19 during pregnancy are temperature, blood pressure, arterial blood gases, electrolytes balance, heart rate, respiratory effort, and pulse-oximetry oxygen saturation (SpO_2), as well as the management of ultrasonically detected fetal anomalies [32]. Although the pregnancy duration in patients with mild and stable conditions can be extended under regular pre-emptive monitoring, an emergency cesarean section (ECS) is required to deliver babies from mothers with more severe illness risk [32, 42, 43]. Many research groups have reported an ECS for cases with COVID-19 to deliver preterm babies due to the septic shock or sepsis, acute organ dysfunction, and fetal distress [11, 18, 19, 22, 27–30, 34, 39, 41, 42, 44]. Hence, ECS is one of the most important risk factors for cases with COVID-19. According to the patient's clinical condition and receiving the consultation from obstetric anesthetists, one of regional and general anesthesia may be chosen for the ECS [31]. However, the safe and efficient anesthesia procedures for ECS of cases with severe symptoms of COVID-19 were general anesthesia with tracheal intubation, spinal, and combined spinal-epidural [29, 46].

Clinical postnatal symptoms of newborn infants

Zhu et al. [18] reported the pediatric critical illness score below 90 (6 cases), gastrointestinal signs such as gastric bleeding, milk refusal, and bloating and feeding intolerance (4 cases), breath shortness (6 cases), febrile (2 cases), and rapid heart rate (1 case) for Chinese infants born from mothers with COVID-19. Based on the chest CT scan data, some major complications including respiratory distress syndrome, infection, and pneumothorax in seven infants were diagnosed, however, molecular tests showed no positive result of SARS-CoV-2 nucleic acid in all cases. Yang et al. [47] have recently reported two infants born to mothers infected with COVID-19 presented mild neonatal respiratory distress syndrome. However, samples of pharyngeal swab, amniotic fluid, and umbilical cord blood of these cases were tested by RT-PCR, while no positive sign of SARS-CoV-2 nucleic acid was found.

A low blood platelet count along with liver dysfunction in two infants was observed. Although no infant case was reported for the COVID-19 infection, one premature infant on the 9th day after birth died by exhibiting symptoms such as breath shortness, refractory shock, multi-organ dysfunction syndrome, and disseminated intravascular coagulation. According to the detected symptoms, laboratory examinations, sputum culture, and CT imaging data, Zhang et al. [44] confirmed bacterial pneumonia in three infants born from women with COVID-19. Nonetheless, no neonatal illness or death was reported after discharging the hospitalized newborns and follow-up evaluations [44]. Another research group realized the mild neonatal pneumonia and lymphopenia in a newborn from the mother infected with COVID-19. Treating this infant with antibiotic drugs for 48 h led to an improvement in hematological and clinical responses [20]. In contrast, no severe complications for infants born from pregnant women with COVID-19 were found by Wei et al. [21], so that none of them needed mechanical ventilation and intensive care. Chen et al. [26] diagnosed a mild rise in the levels of myocardial enzymes on the birthday such as myoglobin (170.8 ng/mL) and creatine kinase-myocardial band (8·5 ng/mL), while no clinical symptoms appeared. It seems that the mothers at the risk of COVID-19 could produce adequate neutralizing antibodies (e.g., IgG) in response to the virus invasion [48, 49]. The passive antibodies by breastfeeding can be transferred to the infants' bodies, as there was no COVID-19 in breastmilk samples collected during follow-up examinations.

Adverse neonatal outcomes by the COVID-19

The ANOs such as preterm delivery and low-birth-weight are prevalent for newborns of mothers with viral pneumonia. Wong et al. [15] previously explored that there was a high risk of intrauterine growth restriction (IUGR), preterm delivery, and spontaneous miscarriage in pregnant women with SARS-CoV-1. The study of Chen et al. [50] also revealed that mothers with pneumonia than healthy ones could potentially intensify the risk of low-birth-weight, preterm labor, restricted fetal growth/size, and a 5-min Apgar score lower than 7. There are similar concerns about the potential effect of COVID-19 on fetal and neonatal outcomes.

Chen et al. [26] realized that all the studied pregnant women ($n=9$) underwent ECS, while two of four preterm newborns delivered at the 36th gestational week weighed fewer than 2500 g. Not only no fetal and neonatal deaths, as well as neonatal asphyxia, were reported, but also no neonatal samples were positive for the COVID-19 [26]. Similar ANOs such as bacterial pneumonia and preterm delivery were reported for newborn infants from pregnant women with COVID-19 in Hubei province, China [44]. Moreover, one of nine newborn infants in the study of Zhang et al. [44] was preterm (36 weeks 2 days). Preterm labor (6/13) and abortion (1/13) were also reported by Liu et al. [41]. In a case–control study, meaningfully more preterm births (21.1–23.5% vs. 5.0–5.8%) and low-birth-weight (10.5–17.6% vs. 2.5%) were detected for the newborns born from mothers with confirmed or suspected COVID-19 compared to the controls. However, there were no significant differences in the 5-min Apgar score and fetal distress between the two newborn groups [22]. Although Li et al. [22] observed severe neonatal asphyxia and deaths for infants of mothers with COVID-19, no report by Chen et al. [34] on intrapartum death, neonatal death, or serious neonatal asphyxia was assessed. Furthermore, Liu et al. [30] showed favorable neonatal outcomes for one infant delivered by meconium-stained amniotic fluid. Overall, the ANOs of COVID-19 infection were less severe than those of SARS-CoV-1 and MERS-CoV. For instance, a high rate of preterm delivery (80%) accompanied by required critical care (> 50%) and death (~ 30%) was declared for pregnant women with SARS-CoV-1 in Hong Kong [17, 51].

Available treatments and therapies

There have been some therapies to treat physical and mental disorders of pregnant women with COVID-19 pneumonia. Antiviral therapy is the primary practice to eradicate a wide span of viruses. The antiviral treatment type of pregnant women with COVID-19 should be carefully determined after discussing this issue with a virologist. Also, the patients should be recommended about the negative effects of antiviral treatment on their health and the risk of fetal growth restriction [31]. A broad-spectrum group of antivirals in animal models of MERS-CoV has been utilized to assess their activity against COVID-19 [52]. The most common antiviral agents used to treat pregnant women with COVID-19 included moxifloxacin (0.4 g intravenously, q.d.) [27], ganciclovir (0.25 g intravenously, b.i.d.) [27, 30], abipenem (0.3 g intravenously, b.i.d.) [27], umifenovir (arbidol) (0.2 or 3.0 g orally, q.i.d.) [29, 30], lopinavir/ritonavir (Kaletra®, 400/100 mg or 200/50 mg orally, q.i.d.) [29, 32], oseltamivir (75 mg orally, b.i.d.) [9, 18, 20], atomized/nebulized inhalation of interferons (e.g., recombinant human interferon α1b, 40 μg, b.i.d.) [9, 18, 24, 27, 30], remdesivir (a nucleotide analog) [25, 53, 54], and chloroquine (an antimalarial agent) [25, 53]. Fan et al. [20] also used a traditional influenza-treating drug to cure COVID-19 symptoms, namely capsules of Lianhua-Qingwen (1.2 mg orally, q.i.d.).

If the selected antiviral therapy could not prevent the substantial damage of lungs, the risk of secondary bacterial pneumonia would be enhanced. Under this condition, the instant administration of antibiotics is necessary to control bacterial sepsis [32]. However, the use of potent broad-spectrum antibiotics should be abstained [55], because premature use and unnecessary treatment with antibiotics may lead to a secondary infection [56]. Due to the COVID-19 progress and the prevention of secondary bacterial infections, Wong et al. [15], Li et al. [22], and Chen et al. [26] used antibiotic therapy for all the patients. Other researchers reported the reception of empirical antibiotics to treat pregnant women with COVID-19 [20, 30]. Fan et al. [20] stated that the case with COVID-19 within 3 days of delivery received empirical antibiotics such as methylprednisolone (20 m. IV daily), ornidazole (0.5 g. IV b.i.d.), and cefotiam hydrochloride (2.0 g, IV b.i.d.). Also, Wang et al. [27] intravenously administered 15 wu q.d penicillin G to prevent neonatal COVID-19 infection in China.

Since corticosteroids may retard the virus clearance from the body [57], the clinical application of corticosteroids to treat patients infected by COVID-19 is not proposed [52, 58]. Moreover, the premature use of corticosteroids similar to antibiotics may increase the risk of secondary infections [56]. But, Liang and Acharya [32] claimed that the administration of methylprednisolone (1–2 mg/Kg daily, for 3–5 days) was performed to improve lung inflammation and to stop the acute respiratory distress syndrome in Chinese patients with severe dyspnea and hypoxemia. In addition to this treatment, they recommended that the daily intramuscular administration of 12 mg Betamethasone could recover the lung maturity of fetuses with preterm delivery [32].

Oxygenation therapy or oxygen support (nasal cannula) is another procedure to treat pregnant women with COVID-19. How to perform this treatment is depending on the hypoxemia severity so that the oxygen concentration with an inhalation rate of 40 L/min is variable from 60 to 100% [59]. Chen et al. [26] and Wong et al. [15] also provided a nasal cannula for all pregnant women with COVID-19. In general, about a quarter of pregnant women with pneumonia will be hospitalized in intensive care units (ICUs) with a need for ventilatory support [48]. Rasmussen et al. [42] explained that 5 of 13 pregnant women with COVID-19 admitted to ICUs required a mechanical ventilator. They also found that there was a three-fold need for ventilation support in pregnant than non-pregnant women. The use of endotracheal intubation and extracorporeal membrane oxygenation was also recommended to improve the clinical outcomes of mothers with multiple organ dysfunction syndromes during pregnancy [31, 32, 39, 41, 60].

Psychological intervention in terms of emotional and mental counseling services is an urgent need to reduce the depressive and stress risk of pregnant women [61, 62]. It was shown that the progressive muscle relaxation (PMR) for half an hour per day during 5 consecutive days could significantly promote sleep quality with a decrease in anxiety scores in 51 patients with COVID-19 [63]. Recently, the positive effect of PMR on the reduction of anxiety levels in young women and prenatal has also been reported [64, 65]. Charkamyani et al. [66] explained that the risk of developing GDM, preeclampsia, and mental disorders in women undergoing in vitro fertilization (IVF) is much greater than with women who conceived naturally. These underlying diseases can highly increase the risk of COVID-19 pneumonia [10]. Thus, changing the lifestyle by performing moderate physical activity and relaxation techniques can be also related to reduced AMOs, improved immune and psychological systems, and reduced risk of COVID-19 infection [10, 67]. Therefore, online mental health programs based on an Internet-based guided self-help therapy should be implemented during the COVID-19 outbreak for pregnant women in the world [10, 68]. Under the outbreak of this viral disease, self-quarantine or self-isolation of pregnant women can remarkably reduce the intake amount of vitamin D from sunlight exposure. This fat-soluble vitamin plays a key role in reducing the GDM and depression of pregnant women [69, 70]. Nonnecke et al. [71] mentioned that the decreased quantity of fat-soluble vitamins such as D and E in cattle resulted in the infection propagation of bovine coronavirus. Thus, supplementing the daily diets with vitamin D is essential to prevent COVID-19 pneumonia with promoted psychological well-being [72]. In addition, a moderate supplementation of vitamin C through increasing the body's immunity not only can reduce the susceptibility of respiratory tract infection induced by COVID-19 [6, 72], but also can notably reduce the neonatal bilirubin levels in the last month of pregnancy [73, 74]. Moreover, the remote follow-up route should be set up to monitor bilirubin levels under severe quarantine and control measures to avert hyperbilirubinemia development [75].

Health management strategies during pregnancy and delivery

There are some available health management strategies for pregnant women against the COVID-19 outbreak during pregnancy and delivery. The first instruction is the potential exposure reduction to COVID-19 with home self-isolation and quarantine. Compliance with basic cleanliness strategies according to the WHO recommendations can significantly minimize the contagion risk of COVID-19 from infected people. Regular washing hands with soapy water or sanitizer agents, avoiding touching the mouth, nose, or eyes, spraying the contact surfaces with 70% isopropyl alcohol are some efficient self-care practices to improve the health of pregnant women at the outbreak and exposure time to the virus [6, 10, 76]. Under the COVID-19 outbreak, it is necessary to frequently screen and follow-up on the health of mothers and their fetuses in pregnancy months. This care strategy provides a possibility to rapidly identify clinical symptoms and risk factors and to perform early medical treatments after hospital admission [18, 22, 25, 42, 48, 77]. During the hospitalization of the patients, all the involved medical staff must be worn with required protective equipment, such as fluid-resistant gowns, eye protection, disposable gloves, and shoe covers, full-face shield, and fit-tested N95 respirators [13, 22, 29, 46, 78, 79]. They should stick to the standard, contact, and airborne safety measures [34, 42]. Besides, the number of patient-related personnel in isolated rooms should be decreased to minimize the virus transmission risk [13, 55]. The use of a negative-pressure isolation room in an ICU can highly reduce the virus diffusion rate [6, 29, 31, 42]. Also, a negative-pressure operating room in the labor ward should be set up for the safe ECS delivery of newborns [31]. Thus, there is a need for transferring infants to the neonatal isolation room immediately after delivery [27]. If the newborn infant is exposed to any person infected with COVID-19, the neonate as a suspected case should be admitted to a single isolation room for at least 2 weeks after birth and settled in an incubator [75]. It has been proposed that the suspected/confirmed mothers with COVID-19 did not breastfeed their infants during this period to avoid any close contact, inhalation of contaminated aerosols, and finally the virus transmission [9, 27, 46, 80]. Altogether, a planned workflow and care coordination should be organized with participating nurses, obstetricians, neonatologists, and midwives to guarantee the safety of mothers and their babies [6]. Eventually, the mothers can be discharged from hospitals only after their full recovery.

Conclusions and future directions

The present review addressed the most critical public health problem in 2019–2020 “COVID-19”. Pregnant women, especially in the third trimester of pregnancy, were much more susceptible to the consequences of COVID-19 infection than the general population. The most common symptoms in pregnant women after this viral infection were fever, dry cough, dyspnea, fatigue, and sore throat. Some primary actions for the control of this ARID were the use of oxygen support (nasal cannula) and empirical antibiotic treatment. The CT imaging progression pattern could successfully determine COVID-19 severity. The CT images visualized a variety of multiple patchy, peripheral, bilateral subpleural opacities accompanied by light consolidation in both lungs. The main obstetric complications were preterm labor and cesarean section. Fortunately, most studies showed that the COVID-19 infection from mothers to infants did not transmit vertically or during childbirth. However, this viral disease is able to enhance AMOs (e.g., GDM) and ANOs (e.g., respiratory complications) probably due to the weakness of the immunological responses of the positive mothers with COVID-19.

The suspected cases of COVID-19 should be regularly monitored to confirm or control the disease during pregnancy. The administration of the potent broad-spectrum antibiotics and corticosteroid drugs for pregnant women with confirmed COVID-19 infection, particularly during late gestation, was not recommended. The use of personal protective tools (such as gloves and masks) and proper hand hygiene by patients and personnel were associated with the reduction of the COVID-19 outbreak. Other effective preventive measures considered in the clinical decision-making context were isolation rooms for mothers and newborns with negative-pressure airflow, the delivery preparation through an emergency cesarean section, the reduced number of caregivers and hospital’s personnel in isolated rooms, no direct breastfeeding by infected mothers, as well as discharging hospitalized patients with COVID-19 after removing their clinical signs and symptoms. However, the local healthcare facilities may change the effectiveness of proposed guidelines on the outbreak and recovery rate of COVID-19 in pregnant women. Thus, an updated practice guideline is required concerning the implementation of standard precautionary measures at each stage of disease progression. Due to the high psychological stress of mothers under the COVID-19 outbreak, the online setting of psychological-based training programs not only alleviates adverse mood symptoms in pregnant women during pregnancy, but also promotes their immunity to prevent the COVID-19 infection, preterm labor, and cesarean section. More data with a high number of gravid women with COVID-19 are needed for a more comprehensive understanding of the clinical effect of COVID-19 infection on maternal and neonatal outcomes. Another issue is the sharing of knowledge and expertise among healthcare centers to conclude the best management and therapeutic strategies in the face of the virus prevalence among pregnant women. Lastly, future efforts should be directed towards the design of COVID-19 vaccines and safe therapies, as well as the implementation of clinical trials to examine them during pregnancy. The pathogenesis evaluation of COVID-19 through pathological tests and molecular characterization of the viruses isolated from infected tissues would be helpful to achieve this target. Besides, the assessment of risk factors in determining the most appropriate treatment is so important by considering the patients’ age, disease severity, and gestational age.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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