



## Assessment of Corona in Pregnant Women: Epidemiology, Clinical Signs, Prevention and Treatment

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### ABSTRACT

Coronaviruses are considered as viruses causing disease in humans and some animals. Some coronaviruses have mild symptoms similar to colds. On the other hand, some of them lead to acute respiratory complications. The new coronavirus known as Covid-19 is a seriously contagious viral disease infecting more than 10 million people during 6 months. This virus has signs close to SARS and this similarity led to public health hazard. There is a serious concern about pregnant women and their infants infected with this virus. Therefore, a lot of cares should be taken for these women during pregnancy and afterwards by obstetricians, nurses, and their close relatives. Findings indicated a possible vertical transmission of Coronavirus to the fetus through the placenta, but there is not any document confirming this report. This study reviews epidemiology, transmission, clinical signs, prevention, and treatment of Covid-19 disease with respect to the importance of pregnant mothers' health and coronal virus complications.

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### INTRODUCTION

Coronaviruses are a group of virus identified in the process of discovering several new human respiratory pathogens in the 1960s. These viruses possess special spikes structure on their surface (Figure 1).

One type of coronavirus known as CoV-SARS led to severe respiratory complications in humans or Acute Respiratory Syndrome in late 2002 and early 2003, after 40 years of identification. The mortality rate of this virus was 9.8%. In addition, the Middle East especially Saudi Arabia was another country under the effect of breaking out one these viruses known as CoV-MERS resulting in mortality rate of 35.5% in 2012 [1].

Some cases of lung infection without known origin and evident cause were identified in Wuhan, China in the late of 2019 [2]. Then, a new virus leading to acute respiratory infection was identified and

introduced as coronavirus 2 (SARS-CoV-2) by analyzing the sequence of lower respiratory tract of patients in January 2020 [3].

The Director-General of the World Health Organization introduced COVID-19 caused by SARS-CoV-2 as COVID-19 On February 11, 2020. In addition, this virus broken out in 114 countries and 118000 infected patients on March 11, 2020. This virus led to more than 4000 deaths. The World Health Organization (WHO) has declared an epidemic of the disease due to more than 4000 deaths [4].

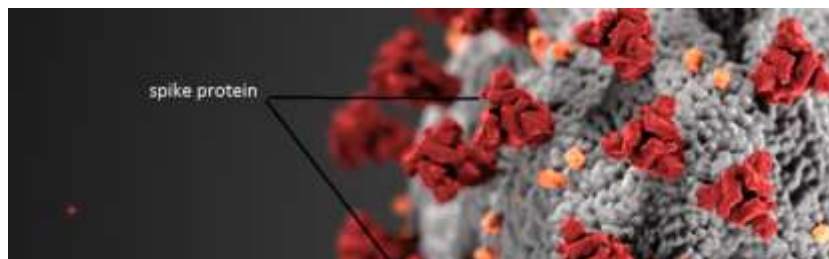
The emerging SARS-CoV-2 virus is a new strain of beta-coronaviruses. This SARS-CoV-2 possesses typical genomic structure of coronaviruses defined as spike structural proteins (S), envelope (E), membrane (M), and nucleocapsid (N), and several unique structural proteins [5]. This enveloped

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virus has a genome characterized by ribonucleic acid type with a length of 29.8 kilo base [6]. Pregnant women are one of the groups in the society prone to coronavirus. Pregnant women are in danger of this infection due to pregnancy, physiological changes in organs/ respiratory system, and blood circulation. Physiological changes consisted of decreased lung residual volume and modification in the immune

system result in increased susceptibility to viral infections and more severe consequences in pregnant women. Therefore, the importance of preventing this virus and treating pregnant women should be taken into account [8-10]. The present study evaluates Coronavirus in pregnant women according to epidemiology, clinical symptoms, prevention and treatment.



**Figure 1: Spike glycoprotein on coronavirus surface. Spike glycoprotein contains molecules in its structure assisting the virus's bind to the surface of epithelial cells [7].**

## METHOD

The present study investigates key points related to Coronavirus along with its' prevention and treatment in pregnant women during last decade. This examination was done in June 2020 and took advantage of database Nature, PubMed, Medline WHO NCBI, PsycINFO and other important databases.

Many examinations have been conducted on Coronavirus regarding the epidemiology of Coronavirus, concerns in pregnant women, Covid-19 vertical transmission from the placenta to the fetus during lactation, Covid-19 clinical signs in pregnant women, complications of the virus in each trimester of pregnancy, Immunity feedback to infection as well as prevention and treatment. For collecting data about Coronavirus, all key words including Coronavirus infections, Covid-19, prevalence in pregnant women, Corona and infant, prevalence of pneumonia, and pregnant mothers. This study covered almost 44 items out of 207 articles in harmony with the present examination.

## EPIDEMIOLOGY

COVID-19 disease began in Wuhan, China in early December 2019 and broke out gradually to many countries. The first patient infected and confirmed with this virus out of China was a case in Bangkok on January 13, 2020 [11]. It has been reported that 8565 patients were infected with this virus and 132 cases passed away in 67 countries on March 2, 2020. World Health Organization announced breaking out of this virus and called its epidemic in all over the world on March 11, 2020 [12]. The number of patients infected with this virus is increasing continuously in all over the world.

Specifying the number of cases suffering from this virus with the symptoms of mild to severe and asymptomatic cases is difficult [8].

According to daily statistics reported by WHO, almost 16000 cases was infected with this virus by the end of July. In addition, 650000 deaths and 9000000 improved cases were reported. The first five countries involved in this terrible virus were the United States, Brazil, Russia, India, and the United Kingdom; respectively. The ninth country involved in this disease is Iran with 288,195 definite cases, 16,084 deaths and recovered number of 251,164 [13].

## Concerns attributed to pregnant women

Pregnant women develop a special immunological adaptation to maintain fetal graft tolerance [14]. This transient state is modified with suppression of T cell activity and pregnant women are predisposed to viral infections [9]. In addition, observed physiological changes in the respiratory system and blood circulation may exacerbate the clinical results during pregnancy [15]. The importance of vulnerable populations is significant in the management of infectious diseases. A large number of pregnant women suffered from respiratory disease resulted in increased infectious complications and high mortality.

Although most infections caused by coronavirus streams are not severe in humans, almost one-third of pregnant women died due to Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Examination of COVID-19 revealed that early adaptive immune responses can control the severity of disease [10].

During pregnancy, physiological changes occur, such as a decrease in the residual functional capacity of the lung, the height of the diaphragm,

and changes in cellular immunity that lead to increased susceptibility to viral infections and more severe consequences in pregnant women.

Cellular immunity feels some modification such as physiological changes including decreased functional lung volume, and diaphragm height during pregnancy period. These changes lead to high sensitivity to viral infections and more severe complications in pregnant women.

Research showed that 35% to 41% of pregnant women infected with SARS and MERS have required mechanical ventilation and the mortality rate in these patients was 18% and 25%, respectively. On the contrary, most reports indicate that pregnant women with COVID-19 are asymptomatic or have mild symptoms. In addition, mechanical ventilation and hospitalization was necessary for a few numbers of these women in the intensive care unit (ICU) [16].

The influenza epidemic resulted in 2.6% mortality of the total population in 1918 and this value was equal to 37% in pregnant women. In addition, infection and complication of H1N1 flu virus was more in pregnant women and their hospitalization rate was four times more than other people in 2009. Although, these values were not attributed to pregnant women suffered from COVID-19 [17].

Recent examinations confirmed relatively high rates of preterm delivery and cesarean section in women affected by Coronavirus. However, it is required to collect more documents for dating of delivery and cesarean section simultaneous with the time of illness. Despite research on women who have had vaginal delivery, there is no evidence that the baby was infected.

It should be mentioned that it was not determined whether vaginal delivery increases the risk of infection or not.

More research is required for assessing the risk of delivery in patients suffered from COVID-19. Examinations on SARS virus indicated that this virus led to preterm birth, intrauterine growth restriction, and intrauterine fetal death by causing severe pneumonia during pregnancy. This notion necessitates screening suspected cases during pregnancy and continuous monitoring of affected mothers and their infants [15, 18-20].

### **Vertical transmission of COVID-19 from the placenta to the fetus**

COVID-19 is a highly contagious disease imposed destructive effects on infants' health and led to symptoms including shortness of breath, high heart rate and gastrointestinal disorder. Reports revealed that infants of infected mothers have symptoms such as shortness of breath, cough, and fever. Recent examinations confirmed a vertical transmission of the infection (transmission of the pathogen from an infected mother to the infant

before or after birth, especially through germ cells and placental blood) in France [21]. Delayed cord closure (DCC) and mother-infant contact are not suggested for reducing the risk of vertical transmission of the virus [22].

One study examined ten infants born by nine mothers suffered from Covid-19 and found that vertical transmission of Covid-19 is not possible from mother to infant [18]. In addition, there is not any evidence confirming intrauterine transmission of SARS-CoV-2 [16]. It is better to quarantine infants for 14 days to not transfer disease from mother to infant. In addition, it is appropriate to use breast pumps during breastfeeding to minimize the risk of infection [22].

### **Transmission of COVID-19 during lactation**

The transmission of COVID-19 is possible from person to person through the respiratory particles or carriers and direct contact with infectious secretions of patients (eg sputum, blood and respiratory particles).

The Chinese National Health Commission stated that infants of mothers with or suspected of COVID-19 should receive intensive care. Although there is not any virus found in breast milk and no evidence of virus transmission, breast feeding or bottle feeding is not recommended [22, 23]. Examinations conducted in China did not confirm the increasing risk of infection in pregnant women in compare to non-pregnant ones [23].

### **Clinical signs of COVID-19**

Examining clinical characteristics of 41 patients with in vitro infection of COVID 19 revealed that the most common symptoms at the onset of the disease were fever, cough and fatigue or myalgia, sputum production and headache, respectively. Most patients in this sample required medical care. Among this sample, twelve patients (31%) affected by Acute respiratory distress syndrome (ARDS) and 13 patients (32%) required intensive care, and eventually 6 remaining cases (15%) died [2].

Similar study revealed that almost 20 to 30% of patients infected by COVID 19 required intensive care for respiratory support because of pneumonia. Among this sample, 4.42% of patients required supporting of advanced organs with endotracheal intubation and mechanical ventilation. Postmortem biopsies in an acute patient indicated severe pulmonary alveolar injury [24, 25].

Available literature classified patients into four groups regarding the severity of symptoms: mild, moderate, severe, and critical. (Table 1) the first level attributed to mild patients have only mild symptoms and no radiographic characteristics was observed. At the moderate level, signs of fever, respiratory symptoms, and radiographic features were seen. In the third group, severe patients

showed three criteria: (a) shortness of breath and RR <sup>1</sup> more than 30 times per minute (b) oxygen saturation less than 93% in ambient air and (c) PaO<sub>2</sub> / FiO<sub>2</sub><sup>2</sup> less than 300 mm Hg. At the last group,

severe patients (ARDS<sup>3</sup> possess three criteria: a) respiratory failure, b) infectious shocks (c) multiple organ failure [26].

**Table 1: Summary of clinical, laboratory, and radiographic signs of Covid-19 in some studies [24-28]**

Clinical signs	<ol style="list-style-type: none"> <li>1. Mild patients: low fever, mild fatigue and no pneumonia.</li> <li>2. Severe patients: Shortness of breath or hypoxemia one week after onset.</li> <li>3. Critical patients: ARDS (Acute Respiratory Distress Syndromes), facial shock. Shortness of breath, abdominal pain and anorexia. 80.9% of pneumonia was mild / common pneumonia, 13.8% were severe and 4.7% were critical.</li> </ol>
Laboratory tests	<ol style="list-style-type: none"> <li>1. Decreased lymphocytes, increased LDH, AST, ALT, blood urea and creatinine</li> <li>2. Most patients had high CRP and high red blood cell deposition and normal procalcitonin.</li> <li>3. Severe cases: D-dimer increases and cutaneous lymphocytes gradually decrease.</li> <li>4. Critical Patients: High Inflammatory Factors</li> <li>5. In fatal cases: the number of neutrophils, D dimer, blood urea and creatinine levels were very high</li> </ol>
Radiographic symptoms	<ol style="list-style-type: none"> <li>1. Two-way distribution of stained shades and opacity of background glass (prominent feature)</li> </ol>
Lung scan	<ol style="list-style-type: none"> <li>2. Radiological abnormalities occur in a significant number of primary patients. Pulmonary malignancy and protrusion are rare (one diagnostic method in pregnant women is lung ultrasound).</li> </ol>
Other side effects	Heart damage, arrhythmia, septic shock, liver dysfunction, acute kidney damage and multiple organ failure

Imaging examination in pregnant women can be done with ultrasound. Radiographic results indicate a two-way distribution of spotted shades and ground glass opacity in patients affected by

Coronavirus [29]. Sonography presents pathological lines B indicating sub pleural patchy diffuse consolidation and pleural thickening in patients with COVID 19 (Figure 2) [30, 31].

<sup>1</sup> Respiratory rate

<sup>2</sup> Relative fraction of arterial oxygen (percentage) on inspiratory oxygen pressure

<sup>3</sup> Acute Respiratory Distress Syndrome

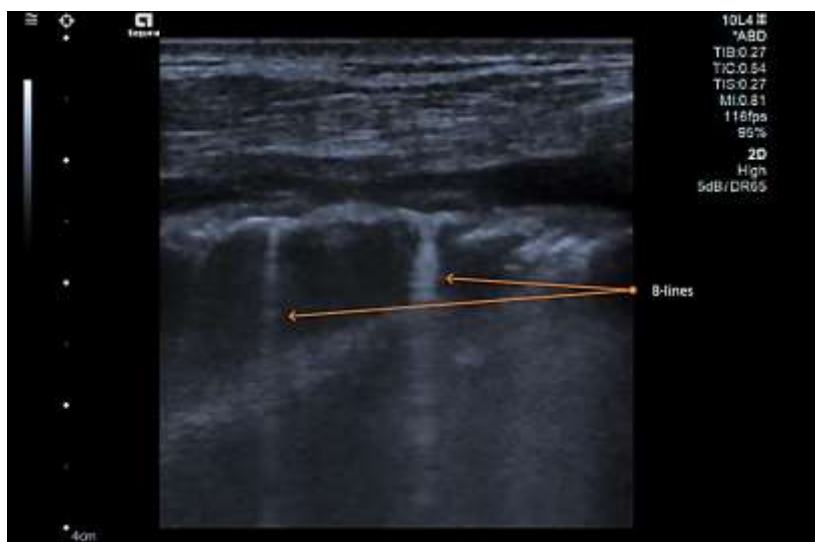


Figure 2: Ultrasound image of a person infected with Corona [31]

Coronavirus influences on the respiratory and cardiovascular systems with respect to secondary clinical signs. However, severe neurological symptoms (such as headache, dizziness, decreased sense of smell and taste, and nerve pain) and consequences including acute illness cerebral palsy, cognitive impairment and musculoskeletal damage were not observed [32].

#### Clinical signs of COVID-19 in pregnant women

Conducted studies revealed the same pattern of COVID 19 symptoms in infected pregnant women and non-pregnant women [17]. A systematic review indicated the most common symptoms such as fever (48%) and cough (46%), muscle aches (17%), and shortness of breath (16%), fatigue (15%) and headache (9%) in 538 pregnant women infected with Corona. Pregnant women had fewer symptoms of sore throat, nasal congestion, anorexia, nausea, vomiting, and olfactory and taste disorders [33]. Another study conducted on 326335 pregnant women showed that the risk of hospitalization, ICU admission, and mechanical ventilation was more in pregnancy period. However, the rate of mortality was not significant [34].

#### Complications of COVID-19 in each pregnancy trimester

One study done on pregnant woman affected by Covid-19 indicated that the clinical signs in the

early second trimester of pregnancy (second trimester) were mild and similar to non-pregnant patients. This patient has no acute lung damage or inflammation resulted from infection. This study confirmed that pregnancy does not exacerbate signs and complications of this disease. In addition, long-term infection of mother (for three weeks) will not impose any significant effect on the fetus [35]. A large number of studies of COVID -19 have been conducted in the third trimester of pregnancy. It should be mentioned that mild infection in the late second trimester for one patient [36] and one case of miscarriage in the early second trimester have been reported [37]. One study examined the possibility of intrauterine transmission of Covid-19 on nine pregnant women affected by Covid-19. This study found that main symptoms in the third trimester were the same for pregnant and non-pregnant women. The frequency of symptoms occurred in fever, cough, and fatigue, weakness, and sore throat; respectively. In addition, this study revealed no mortality and acute complications of COVID-19 in the third trimester of pregnancy (third trimester). Moreover, no infant was born with shortness of breath. This study did not confirm any document regarding spreading COVID-19 through vertical intrauterine transmission resulting in adverse neonatal complications and fetal infection [17].

Table 2: Some studies related to pregnant women and Covid-19

Row	Author	Topic	Sample, age, symptoms	Results
1.	Panichaya et al. (2020) [35]	Prolonged viral persistence in COVID-19 second trimester pregnant patient	Sample: A 43-year-old woman with Covid-19 with a gestational age of 18	The results showed that although abortion was occurred in this case, it was due to the

			weeks (early second trimester).	diagnosis of Down syndrome in the fetus because the fetal swab test was negative for Covid-19. This indicates that the mother had a long-term infection with COVID-19 (for three weeks) with no obvious effect on the fetus.
2.	Liu et al. (2020) [36]	Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy	<p>Sample: A 30-year-old woman with Covid-19 with a gestational age of 34 weeks (early third trimester).</p> <p>Patient Symptoms: Mild symptoms, no fever, no lung lesion, and inflammation of the pelvis from infection.</p>	The results indicated that intrauterine fetal death which may be due to the spread of Covid-19 infection from mother to fetus.
3.	Baud et al. (2020) [37]	Second-Trimester Miscarriage in a Pregnant Woman With SARS-CoV-2 Infection	<p>Sample: A 28-year-old woman with Covid-19 with a gestational age of 19 weeks (second trimester).</p> <p>Patient symptoms: Severe symptoms of coronavirus infection, liver and kidney failure, need for mechanical ventilation, and hospitalization in the intensive care unit (ICU)</p> <p>Patient symptoms: fever, fatigue, muscle aches, mild swallowing disorder, diarrhea and cough</p>	<p>The patient initially referred to the hospital due to fever, fatigue, muscle pain, mild dysphagia, diarrhea, and cough.</p> <p>The nasopharyngeal swab test was positive for SARS-CoV-2 and he was discharged with oral acetaminophen, but after 2 days patient returned to the hospital due to severe uterine contractions, which eventually resulted in a miscarriage in the second trimester due to a placental infection caused by SARS-CoV-2.</p>
4.	Della Gatta et al. (2020) [38]	Coronavirus disease 2019 during pregnancy: a systematic review of reported cases	<p>Sample tested: 51 pregnant women. 49 patients were in the third trimester and 2 patients were in the second trimester of pregnancy.</p>	<p>In three patients (2 in the second trimester and 1 in the third trimester) the symptoms were still ongoing and delivery had not taken place. In the remaining 48 patients, two</p>

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Patients' symptoms in terms of frequency: fever, cough, sore throat, shortness of breath, fatigue, muscle pain and weakness, respectively.	underwent normal vaginal delivery and 46 underwent cesarean section. The results showed one stillbirth and one infant death from Covid-19 infections.
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A systematic review performed on 538 pregnant women suffered from coronavirus indicated that 20% women delivered in a gestational age of less than 37 weeks and 85% of this sample had cesarean deliveries. Among this sample, 3% women have been hospitalized in ICU and approximately 14% felt acute clinical symptoms. In addition, infant mortality was 0.3% and not death in mothers was reported [33].

**Immune responses to viral infection**

Innate and adaptive immune responses play a significant role in defending body against microbes. The innate immune system diagnoses and defends against invasive microbes. In addition, this system protects rapidly against infections. Innate immune response to viral infections such as influenza is performed by neutrophils, macrophages, and dendritic cells (DCs). Host microbial sensors known as pattern recognition receptors (PRRs) are responsible for detecting viral components and inducing an innate immune response. PRR is included in various kinds of cells especially in dendritic cells (DCs). DCs are the most significant cells containing antigen. In addition, they have the ability in inducing CD4 + and CD8 + lymphocytes regulating subsequent adaptive immune responses [39].

Examinations revealed that pregnancy increases the damages resulted of influenza. These damages are due to disrupting the immune system against the virus, expressing granulocyte colony-stimulating factor (G-CSF), and increasing

physiological stress in the lungs due to changes in progesterone levels and Prostaglandin [10]. Physiological changes and disorders in cellular immunity result in increased susceptibility to viral infections during pregnancy [16].

**Prevention and treatment**

Although a lot of antiviruses are used in animal for controlling the complications and infections caused by SARS-CoV-2, but there is not any drug or vaccine for inhibiting SARS-CoV-2 transmission. However, dexamethasone is one of the proven therapies in the treatment of hospitalized patients affected with Covid-19 and reduces mortality in patients requiring mechanical ventilation [15]. The best way in preventing the transmission of this disease is implementing non-pharmacological methods such as rapid identification and isolation of patients, tracking of carriers, travel restrictions and prohibitions, reducing direct contact with people, social distance, hygiene and frequent hand washing [40].

Fever and other signs of respiratory infection should be evaluated in all patients and pregnant women. The process of screening for pregnant women before admitting in the maternity unit and care clinics should be conducted. In addition, the number of visit sessions for pregnant women should be reduced and the program of routine screening should be changed. In addition, table 4 indicates a simple model suggested by the World Health Organization in Corona prevention during pregnancy [41].

Table 3: Guide for pregnant women at the time of corona virus [42].

Visit	Who	What	Modifications
Booking visit	All women	Full history, initial screening for medical, psychological and social risk factors.	Virtual booking where possible, or one-stop visit, with dating scan and all testing in maternity unit.
Dating scan	All women	Combined antenatal screening, all blood tests, BP and urine testing to be taken at dating scan appointment.	
16 weeks	All women	Review results of screening review, discuss and record the results of all screening tests.  Reassess planned pattern of care for the pregnancy and identify women who need additional care.  Give information about ongoing care.	Virtual appointment unless attendance required for additional testing or other concerns
18-20 weeks	All women	Routine anomaly scan.  Check BP and urine at this visit instead of 16-week appointment.	Maternity unit or community unit with ultrasound facilities.
25 weeks	Nulliparous women	Measure fundal height, BP and urine; review scan results.	Maintain if staffing allows or additional concerns.
28 weeks	All women	Discuss current health.  Enquire about fetal movements.  Discuss mental wellbeing, and offer advice and sources of further support and information. Follow up any safeguarding concerns.  Discuss plans for antenatal classes (remote access).  Measure fundal height, BP and test urine; repeat blood tests to screen for anaemia and RBC allo-antibodies; anti-D prophylaxis for Rh negative women.	Maintain appointment.
31 weeks	Nulliparous women		Omit – replaced with 32/40 for all.
32 weeks	All women	Measure fundal height, BP and test urine; discuss results of investigations at 28 weeks; discuss plans for birth.  Discuss wellbeing, fetal movements.  Follow up safeguarding issues.	Maintain appointments as far as possible. If need to reschedule due to illness/quarantine, see or contact all women within 3 weeks of previous contact.
36 weeks	All women	Measure fundal height, BP and test urine; discuss fetal movements and wellbeing; discuss plans for birth and all usual care.	
38 weeks	Nulliparous women only	Measure fundal height, BP and test urine and all usual care.	
40 weeks	All women	Measure fundal height, BP and test urine; give information about options for prolonged pregnancy.	
Post dates from 41+0'  (Locally agreed protocol)	All women	Measure fundal height, BP and test urine; discuss fetal movements and wellbeing.	Appointment to be co-scheduled with offered outpatient / inpatient IOL to avoid a further attendance <sup>T</sup>



**Table 4: Model proposed by the World Health Organization in the prevention of Corona during pregnancy [41]**

WHO FANC model	2016 WHO ANC model
<i>First trimester</i>	
Visit 1: 8-12 weeks	Contact 1: up to 12 weeks
<i>Second trimester</i>	
Visit 2: 24-26 weeks	Contact 2: 20 weeks Contact 3: 26 weeks
<i>Third trimester</i>	
Visit 3: 32 weeks	Contact 4: 30 weeks Contact 5: 34 weeks
Visit 4: 36-38 weeks	Contact 6: 36 weeks Contact 7: 38 weeks Contact 8: 40 weeks
Return for delivery at 41 weeks if not given birth.	

Some strategies should be done in managing Covid-19 during pregnancy. These important strategies are SARS-CoV-2 tests on time, initial isolation of patients, methods of controlling acute and invasive infections, oxygen therapy and use of mechanical ventilation if it is required, administration of antibiotics (due to the risk of secondary bacterial infection), monitoring, and controlling uterine contractions. Infants whose mothers were affected by COVID-19 should be isolated from other infants. Moreover, the relationship between mother and infant should be avoided temporarily as it was suggested for H1N1 influenza [15]

**Tocolysis Prescription**

Pregnant women with Coronavirus 2019 (COVID-19) are in the increased risk of preterm delivery [41]. Preterm birth (birth before the 37<sup>th</sup> week of gestation) is one of the main reasons for death in infants and pregnant women. Tocolytics are various drugs prescribed for delaying preterm labor by stopping uterine contractions. In addition, these drugs allow infant to stay more in the uterus. On the other hand, Tocolytics provide this situation for specialists to prescribe corticosteroids stimulating the development of the lungs and other body's organs.

Some tocolytic medications have severe side effects. It is evident that combination of some tocolytic medications may be more effective than one tocolytic drug. Moreover, this combination cannot impose negative effect on mother or infant [43].

There are concerns about the use of NSAIDs and the effects of beta-sympathomimetics on increased rate of heart in women with or suspected COVID-19. Regarding these concerns, the best tocolytic is nifedipine because it is a suitable alternative for indomethacin [44].

**Corticosteroids Prescription**

Consuming betamethasone showed advantages between pregnancy weeks of 20 + 0 to 33 + 6 in patients at risk of preterm delivery for seven days. Regarding these benefits, the American college of obstetricians and gynecologists (ACOG) recommends it in pregnant women with or suspected to Covid-19. Taking betamethasone is not prescribed for patients that are in pregnancy weeks of 36 + 0 to 36 + 6 and at risk for preterm delivery for seven days.

In addition, pregnant women suffered from COVID-19 are treated with corticosteroids and candidate for steroids for inducing fetal lung development before birth. With respect to these cases, dexamethasone or betamethasone for inducing fetal pulmonary development is prescribed. Then, the process of treatment continues with Prednisolone (40 mg daily and orally) or hydrocortisone (80 mg intravenously twice daily) for completing steroid course of mother [44].

**Sulfate therapy in preterm labor in patients with Covid-19  
Efficacy of magnesium sulfate as a tocolytic**

One study examined the effect of magnesium sulfate as a tocolytic with several doses including low-dose (4 g loading dose and 2 g per hour), medium dose (4 g loading dose and more than 2 g per hour storage), and high dose (loading dose of 6 g and more than 2 g per hour of storage).

Employing doses of magnesium was effective in 69.2% patients with low dose, 79.2% with moderate does, and 88.7% with high does. In addition, this medication inhibited preterm labor and showed side effects on cardiovascular system, anemia and high blood pressure. Nausea, muscle weakness, chest tightness, and hot flashes were observed in some cases[45].

Moreover, prescribing magnesium sulfate (4 g and 2 g per hour) can delay preterm labor in pregnant women suffered from COVID-19 [43]. Studies indicated that prescription magnesium sulfate before week 32<sup>th</sup> pregnancy should be taken into account regarding standards for neuroprotection in fetus.

This medication is capable of dilating the lungs in bronchospasm after intubation. Prescription of magnesium sulfate for each pregnant patient should be done separately with respect to the effect of respiratory depression on mothers with Coronavirus. Regarding consuming magnesium sulfate, it is suggested that fluid intake be minimized and the total amount of fluid injected be limited to 125 ml per hour or less because of the potential for additional pulmonary edema [46, 47].

### **Thromboprophylaxis in COVID-19**

Thrombotic complications were observed in 31% of Covid-19 patients admitted to ICU. Pulmonary thromboembolism with 81% prevalence was the most significant consequences in these patients [48]. Heparin drug (5000 units) is prescribed subcutaneously every 12 hours for prenatal preventing of thrombosis in women with mild symptoms or the date of their delivery may be the next few days [44].

### **Drug safety in COVID-19**

Different medications including chloroquine, nelfinavir, lupinavir / ritonavir, and remdesivir were employed for treating Coronavirus. These drugs were effective in responding viruses such as AIDS and Hepatitis and their efficiency against Corona was evident. In addition, Remdesivir played significant role in compare to other drugs [49-53].

This drug imposed a remarkable effect in the treatment of pregnant women with Ebola and Marburg. Nowadays, this drug is employed for treating pregnant women suffering from COVID-19. The American College of Obstetricians and Gynecologists (ACOG) allowed low-dose of aspirin (a drug used to prevent high blood pressure) for

pregnant women without COVID-19. There is not any document on negative effect of nonsteroidal anti-inflammatory drugs. ACOG recommends an individualized approach for continuing or discontinuing this drug for suspected or definite patients affected by COVID-19 taking low-dose aspirin [44].

### **Labor management**

Screening should be done before admitting pregnant women to maternity unit and clinics [15]. The initial evaluation of patients may be done by telephone for reducing face-to-face visits (telehealth). Generally, it is suggested to minimize face-to-face examinations. Attending in medical centers depends on patients suspected to COVID-19. Suspected or definite patients with COVID-19 should be transferred to a separate examination area without anyone except to care staff. Personal protective equipment (PPE) such as mask should be used.

The patient's companions and care staff must use a mask. In addition, companions must wait in a waiting room and in an isolated area or outside the hospital. Medical history and physical examination defined as blood pressure, body temperature, oxygen saturation (SO<sub>2</sub>), heart rate, and respiration. The fetal heart rate should be checked regarding gestational age and symptoms of mother for confirming infant's health. Chest radiography with a shield should also be done and considered as one the precautions strategies for protecting fetus [54]. Pregnant women suffered from COVID-19 should be hospitalized in rooms with proper ventilation (eg, negative pressure) with special equipment during pre-delivery, during and post-delivery similar to what was done for other adult patients with Covid-19 in specific units or hospitals [44].

Managing the first and second stages for delivery should not change. When the patient has spontaneous labor and a slow progression in the first stage of labor, augmentation with oxytocin and premature amniotomy are suggested for reducing duration of labor [55]. Although there is not enough research regarding the best time specified for delivery in pregnant women affected by COVID-19, it is better to specify and consider the best time for delivery. Acceleration in delivery with COVID-19 may be acceptable with mild symptoms since the peak of COVID-19 occurs in the second week [55]. Specifying the time of delivery for pregnant women with severe COVID-19 is controversial. Delivery was supported after 32 to 34 weeks. Some researchers have specified the time of delivery after 32 to 34 weeks for decreasing the risk of pregnancy if pregnant women had worse condition. Others believed that delivery between 24-34 weeks is suitable for women suffered from refractory

hypoxemia resulted from respiratory failure or for patients with critical and severe symptoms. Researchers mentioned that protecting mothers should be continued until mother's recovery. In addition, screening fetus should be continuous to prevent its' death and possible complications for mothers [56].

### Postpartum management

Infants their mothers suffer from COVID-19 should be checked, isolated from other healthy infants, and took enough care due to possible infection. Decision about preventing venous thromboembolism (VTE) after delivery in women with Covid-19 is depend on risk assessment. In addition, postpartum thrombosis prevention will not be provided for pregnant women with COVID-19 whose delivery was uncomplicated and had mild symptoms.

Patients that received prenatal thrombosis prevention should discontinue these drugs after discharging in the case of disappearing risk factors. On the other hand, prevention should take long for 7 to 14 weeks (even up to 6 weeks) with respect to acute and critical cases. Mother's vital signs are controlled for 24 hours after a natural delivery, 48 hours after cesarean section and checked every 4 hours. The amount of oxygen is measured regularly for 24 hours or until disappearing disease's symptoms.

All infants should be checked according to possible SARS-CoV-2 infection within the first 24 hours of birth by available molecular assays in the case of laboratory facilities. The relationship between mother and infant should be inhibited to reduce the risk of transmission infection by mother, although it may impose undesirable effects. Isolating mother from infant and preventing relation between them can be stressful for mothers and lead to distraction in breastfeeding. In addition, this situation may have negative consequences on infant's nutrition [44].

### Vaccine

A large number of examinations and efforts are made for producing a vaccine for SARS-CoV-2. All approaches have their special advantages and disadvantages. A lot of aspects should be taken into account in the process of producing vaccine. These effective vaccines are similar to the structural proteins subunits of coronaviruses (spike (S), envelope (E), membrane (M) and nucleo-capsid (N)). All attentions have been focused on Spike(S) for more development in vaccine production among the four structural proteins attributed to this virus.

- 1) This subunit is common among all kinds of coronaviruses
- 2) The exposure of this subunit to individual's immune system induces immune responses

3) It provides subsequent immunity against this virus

4) It can prevent the entrance of virus into sensitive cells and being infected by this virus. Some vaccines passed human clinical trials while others just have been tested [40].

Vaccination was efficient in the process of influenza treatment. The American College of Obstetricians and Gynecologists and controlling and preventing centers announced that the passive flu vaccine is immune in all pregnancy's trimesters. Therefore, all pregnant women should receive this vaccine. Findings revealed that pregnant women that injected the flu vaccine felt a reduction of 25% in their preterm labor and delivering infants with low weight. In addition, 63% of influenza infections in infants and 36% respiratory infections and fever in mothers was reduced by vaccination [39]. It is hoped that to experience a significant decrease in COVID-19 consequences in pregnant women and children by finding and producing Covid-19 vaccine, we will see a reduction in the complications of this infection in pregnant women and children.

### CONCLUSION

The number of definite patients of COVID-19 and death of these patients is increasing in all over the world. Pregnant women and their infants are the most vulnerable cases against this disease. Although there is not any document confirming the vertical transmission of SARS-CoV-2 and infection through breast-feeding, precautions should be considered and infants should be kept in quarantine for 14 days. In addition, breast pumps should be used for reducing the risk of infection while breastfeeding.

There is not any special drug or vaccine for preventing the transfer of SARS-CoV-2. Considering personal/ social health and reducing direct contact with others are the main solutions in non-transferring this virus. The present study suggests that pregnant women should receive more care and more precautionary measures should be taken. Treatment is still evolving and changing, especially in pregnant women whose pregnancy physiology may alter viral behavior.

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