Covid19 in pregnancy — a literature review

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Abstract

Coronavirus disease-2019, or Covid-19, was first reported in Wuhan, China, at the end of December 2019 as viral pneumonia. The causative agent, the Novel Coronavirus also known as severe acute respiratory syndrome Corona virus (SARS CoV-2), spread rapidly across the world to cause a considerable death toll. On March 11, 2020, the World Health Organisation declared Covid-19 a pandemic. For a little over a year, the coronavirus has been around. Pregnancy is an immunodeficient state predisposing women to an increased risk of respiratory viral infections. The risk is even higher in pregnant women who already have underlying health problems due to growing age, such as diabetes, hypertension, cardiac or respiratory diseases. The exact treatment of Covid-19 is still unknown. This narrative review was planned to summarises the current information on pathophysiology, diagnosis and effects of Covid-19 in pregnancy for better treatment plans.

Keywords: Coronavirus, Pneumonia, Pandemic, Pregnant women.

Introduction

Coronavirus disease-2019, or Covid-19, is the third outbreak of Coronavirus infection in the 20th century. Scientists have postulated that the bat - the primary host of the Coronavirus - undergoes mutation in a second host animal to infect human beings. The first outbreak of Severe acute respiratory syndrome Coronavirus (SARS CoV-1) occurred in 2003 in China due to virus mutation in civet cat. The second outbreak — the Middle East respiratory syndrome (MERS) — occurred in the Mediterranean region in July 2012 due to virus mutation in camel. By the end of December 2019, the Chinese authorities in Wuhan City discovered the novel coronavirus responsible for Covid-19.[1]

Covid-19 spread fast globally, and the World Health Organisation (WHO) declared it a pandemic on March 11, 2020.

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The causative agent of the novel coronavirus SARS CoV-2 has 80% genomic resemblance to SARS CoV-1, 50% to the MERS CoV, and 96% to the bat coronavirus. This time, the bat coronavirus, it is believed, has mutated in pangolin.[2]

Covid-19's effects on pregnancy have been a source of worldwide concern due to the physiological and immunological changes that occur during pregnancy. Several studies have found higher mortality rates among pregnant women than the general population during the previous Coronavirus outbreaks.[3-5] The influenza pandemic, also known as the Spanish flu, killed 37% of pregnant women in 1918 compared to only 2.6% of the general population.[3] Also, during the 2009 H1N1 influenza pandemic and the SARS CoV-1 and the MERS CoV epidemics, pregnant women experienced more deaths.[4,5] Based on such experiences, pregnant women were thought to be more vulnerable to Covid-19. The International Federation of Obstetrics and Gynaecology (FIGO) and the Centers for Disease Control and Prevention (CDC) have also urged pregnant women to be more vigilant about personal preventive measures.[6,7]

Obstetricians from various countries are reporting the outcomes of Covid-19 cases to raise understanding of the disease. The current narrative review was planned to summarise the available literature regarding pathophysiology, clinical characteristics, diagnosis and impact of the disease on pregnancy to build up the knowledge for better treatment plans of pregnant women.

Incidence

Pakistan at the time of the current review, was passing through the third wave of the coronavirus. Till then, the Covid-19 attack rate was estimated to be 2.3 per 100,000 Pakistani population.[8] Nonetheless, this infectious disease had resulted in a greater number of deaths worldwide than any other prior pandemic, with 114 million cases and 2.53 million deaths. In a recent study done in the United States, pregnant women had 3.5-fold higher Covid-19 related hospital admissions and 13.6-fold higher mortality rate than non-pregnant population; the majority of pregnant women being in their third trimester (56.3%) followed by second trimester (27.9%) and the first trimester (15.8%).[9] In an extensive systematic review, pregnant women with Covid-19 had increased odds of

maternal deaths than healthy pregnant women.[10] In view of this, the Centres for Disease Control and Prevention (CDC) has issued an alert about the increased risk of severe infection in pregnant women.[7]

Pathophysiology

SARS CoV2 is a single-stranded ribonucleic acid (RNA) coronavirus with a large encapsulated genome. The viral envelope contains at least three structural proteins: S, E and M proteins. Among these, the spike proteins form large protrusions from the virus surface and are considered mainly responsible for eliciting an immune response.[11]

At present, one of the primary goals of researchers is to create drugs that prevent the virus from infecting the host cells. The researchers are attempting to identify compounds that aid the virus's host cell invasion to develop their inhibitors as anti-Covid drugs.

Coronavirus binds to its receptor, angiotensin-converting enzyme II on the respiratory cell membrane. S protein cleavage by the transmembrane serine protease and furins facilitate virus entry into the cells.[11]

Due to virus replication, inflammation and programmed cell death, called pyroptosis, occur, releasing more particles to invade. The damaged cell releases inflammatory mediators, including interleukin-6 (IL-6), chemokine 10, and alpha-1 (α1) interferon, which cause chemotaxis of monocytes, macrophages and T cells to the infected site, resulting in excessive inflammation and lung injury. In a non-pregnant state, cytotoxic cluster of differentiation-8 (CD8) T cells account for 80% of the infiltrating cells in Covid-19. In pregnancy, an immunodeficient state develops to allow foetal growth, which leads to a drop in CD4 and CD8 cells. Furthermore, the immune system's T-helper-2 (Th2) cells outnumber Th1 cells, which protect the foetus but leave the mother susceptible to viral infections. Although both T1 and T2 helper cells are involved in the immune response in severe disease, the decrease in natural killer cells and T1 helper cells moves the immune response more towards humoral than cellular immunity. The plasmacytoid dendritic cells that produce α1 interferon and clear viruses from the body also decrease in number during pregnancy. An abnormal immune response and a cytokine storm can lead to elevated interleukin plasma concentrations, septic shock and death in critical cases.[12] In the survivors, these aberrant and excessive immune responses lead to long-term lung damage and fibrosis, resulting in physical impairment and decreased life quality.[13]

It appears that changes in the immune system predispose pregnant women to severe viral infection due to low viral clearance. An increase in steroid hormones during pregnancy, on the other hand, can play a protective role by suppressing the exaggerated inflammatory response, thus preventing multiorgan damage. The significant increase in maternal blood progesterone may also promote lung repair and aids recovery from infection.[12]

The Covid-19 infection causes endothelial dysfunction and activation of coagulation pathways which can lead to disseminated intravascular coagulation (DIC) and thrombocytopenia. Due to high levels of coagulation and fibrinolytic factors, pregnancy has a synergistic effect on thromboembolism. Preeclampsia, diabetes and cardiac disease are all comorbid conditions of pregnancy that can aggravate endothelial dysfunction. A better understanding of the pathogenesis of septic shock to determine the optimum therapeutic choices would be helpful to decrease Covid-19 morbidity and mortality.

Changes in the shape of the chest and the elevation of the diaphragm during pregnancy exacerbate respiratory distress, resulting in a reduction in total lung capacity and the inability to clear secretions from the lungs, making pregnant women more vulnerable to respiratory infections.[12]

Clinical Features

In a retrospective case series, the most common symptoms at the onset of illness were fever (98.6%), fatigue (69.6%), dry cough (59.4%), myalgia (34.8%) and dyspnoea (31.2%). Other symptoms include headache, dizziness, abdominal pain, diarrhoea, nausea and vomiting. Patients may also complain of nasal congestion, rash, fever, loss of sense of taste and smell, malaise and appetite loss.[14] According to the US National Institutes of Health (NIH), the mild disease involves the upper respiratory tract with symptoms of flu, cough, myalgias and fever; the moderate disease involves both the upper and lower respiratory tract with oxygen saturation (SaO$_2$) >93%; in severe disease, the respiratory rate is >30 breaths per minute, SaO2 <93%, the ratio of arterial partial oxygen pressure to the fraction of inspired oxygen (PaO$_2$/FiO$_2$) is <300, or lung infiltration is >50%; and the critical disease comprises acute respiratory distress syndrome (ARDS), septic shock and multiorgan failure.[15] Table summarises the most frequently reported findings with Covid-19 in pregnancy from a few studies.[16-19]

According to a systematic analysis, fever (40%) and cough (39%) were the most common symptoms reported by pregnant women, whereas the commonest laboratory findings were lymphopenia (35%) and raised C-reactive protein (CRP) levels (49%).

Table: Common symptoms of coronavirus diseases (Covid) in pregnancy.

	Dashraath et al[16]	Yu et al[17]	Chen et al[18]	Elshafeey et al[19]
Fever	84	86	75	67.3
Cough	28	14	73	65.7
Dyspnoea	18	14	7	7.3
Diarrhoea	-	14	7	7.3
Lymphopenia	38	-	44	14
Leucocytosis	22	-	-	-
Others: nasal congestion, rash, sputum, headache, loss of appetite	-	-	6	<5

Adapted from Ryan et al., The journal of obstetrics and gynaecology research doi:10.1111/jog.14321.

Earlier researches have stated the same proportion of severe disease in pregnant women as in the general population; around 80% mild, 15% moderate and 5% severe.[20] However, in a later meta-analysis of approximately 400,000 patients with symptomatic Covid-19, the combined incidence of ICU admission, invasive ventilation, extracorporeal membrane oxygenation, and death was higher in pregnant women than in non-pregnant women.[10] The more frequent mild disease and ICU admissions among pregnant women indicate sudden respiratory deterioration in mild cases. The symptomatic women in home isolation and their close relatives must be educated about the severe symptoms which require hospitalisation, espeically dyspnoea, and to take continuous advice through telecommunication until complete recovery.

Diagnosis

Diagnosis of Covid-19 is based on the clinical characteristics, contact tracing, antigen detection by reverse transcription-PCR (RT-PCR), immunoglobulin M (IgM) serology, and computed tomography (CT) scan.

RT-PCR

Although a gold standard for the diagnosis of Covid-19, RT-PCR has a high false-negative (FN) rate.[21] Negative RT-PCR tests should be replicated within 24 hours to a few days. Two subsequent negative tests usually rule out the infection. RT-PCR should be conducted on all women admitted for induction or during childbirth.

IgM and IgG antibody serology

Serological monitoring detects anti-SARS-CoV-2 immunoglobulins when RT-PCR is not available. A clear advantage of these tests over RT-PCR is that they can identify individuals previously infected by SARS CoV-2 even if they never underwent testing while acutely ill.

Monitoring tests

There are two alternatives for follow-up of severe cases: RT-PCR having 59% sensitivity, and CT scans having 88% sensitivity.[21] There is little risk of foetal abnormalities or pregnancy loss, with a radiation dose of 0.0005 to 0.01 mGy of chest X-ray and ultra-low-dose CT. Therefore, in pregnant women with severe disease, ultra-low-dose CT strategies are required with about 10-fold decrease in CT dose to avoid congenital anomalies. Some authorities support an obstetric pulmonary ultrasound scan, which would be the quickest way to assess Covid-19 prognosis in mild cases without any detrimental effects. On ultrasonography (USG), a change in the texture of image can detect the severity of the lung disease.[21]

Other tests

In most Covid-19 patients, standard blood tests have shown normal or reduced lymphocyte count. The systemic elevation of pyrogenic cytokines is also present. D-dimer, blood urea nitrogen (BUN), creatinine, ferritin and neutrophil are also elevated in critical patients. All these tests may help to establish the prognosis and treatment of the disease.[21] Data sources are scarce regarding the significance of the varied antibody responses to Covid-19 during the follow-up period. Further research in this context may prove helpful in determining the prognosis.

Differential diagnosis

Symptoms of mild disease of Covid-19 are similar to other respiratory tract infections. Symptoms of headache and convulsions can also be present in epilepsy, sudden cerebrovascular disorder and eclampsia. In epilepsy, the disease history is diagnostic, whereas eclampsia and cerebrovascular disorders can be differentiated by hypertension, coronavirus testing, lab abnormalities of eclampsia, including haemolysis, low platelets and elevated liver enzymes, and brain magnetic resonance imaging (MRI). Several other pregnancy problems can cause renal failure in the critical phase, like placental abruption, preeclampsia and antepartum haemorrhage, requiring a detailed history and examination for appropriate diagnosis. In an analysis, only 18% patients among symptomatic pregnant women tested positive for SARS CoV-2.[10] Therefore, testing for other viral infections should also be considered while establishing a diagnosis.

Maternal complications of Covid-19

Pregnancy is considered a risk factor for hospital and ICU admission in Covid-positive women. The previous pandemics of SARS Cov-1 and MERS had significant adverse maternal outcome with 25.8% and 28.6% mortality, respectively. However, due to small sample sizes, with only
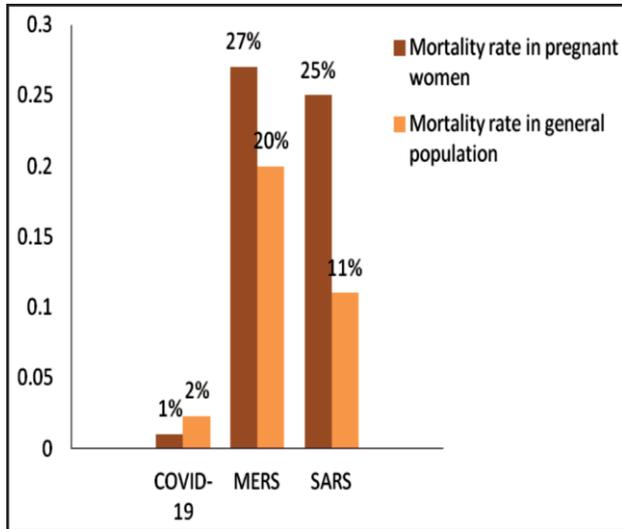
Adapted with written permission from Centers for Disease Control and Prevention (CDC) image gallery. Created by Alissa Eckert, MSMI, Dan Higgins, MAMSed.2020.[22-24]

Figure-1: Mortality in pregnant women and the general population due to coronavirus diseases (Covid), severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS).

12 recorded cases of MERS in pregnancy and 26 cases of SARS Cov-1, the results of these studies cannot be generalised to the whole pregnant population.[12] Mortality in pregnant women and the general population in SARS Cov-1, MERS and Covid-19 have been compared in (Figure-1).[22-24]

Respiratory failure

In most cases, disease severity is determined by respiratory failure, as it is the commonest symptom in women with pneumonia. Only a few patients have other
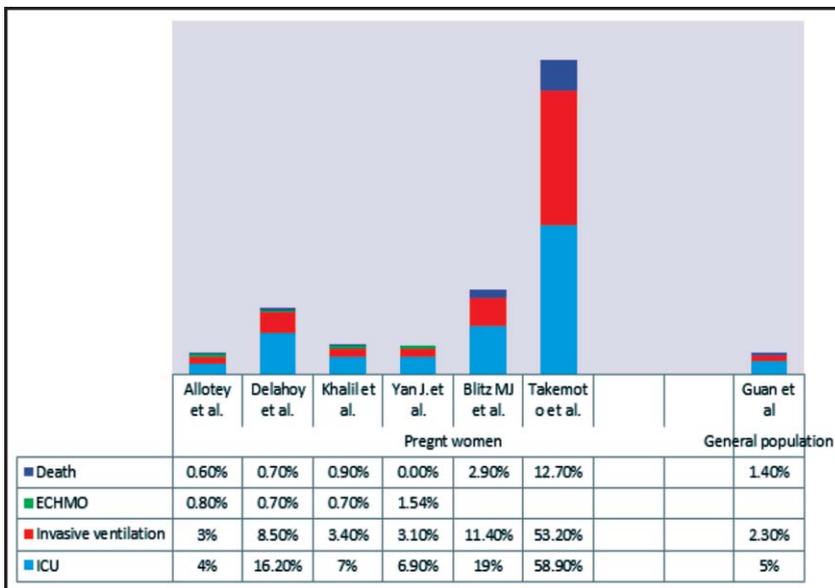
organ dysfunction before the onset of dyspnoea.[25] Multiorgan involvement is less common and indicates a poor prognosis. The likely underlying mechanism of organ failure is postulated to be a direct inflammation and a cytokine storm. The characteristics of Covid-positive pregnant women admitted in ICU can be compared on the basis of a few studies (Figure-2).[10,23,24,26-29]

In a study of the general population comprising 1099 Covid-positive patients, 15% required hospital admission due to severe disease, 5% were admitted to ICU, 2.3% needed ventilator care, and 1.4% lost their lives.[23] Similar findings were reported in a meta analysis of pregnant women in which 16% patients were admitted to ICU, 8% received mechanical ventilation, and 1% expired.[24]

The ICU admission rates in various studies are comparable albeit with a few differences.[26-28] However, a recent study from Brazil has shown a much higher ICU admission rate (21.2%) and death rate (12.7%) among postpartum women.[29] The high prevalence of the severe disease in Brazil may be secondary to environmental factors, socio-economic factors, and noncompliance with preventive measures. Besides, the high death rate of the affected population raises a question about ICU care.

Multiorgan dysfunction

Studies have observed myocardial injury and arrhythmias related to Covid-19 among the general population. Pregnant Covid-positive patients can also develop moderate cardiac dysfunction and reduced left ventricular ejection fraction (LVEF), but the data is sparse. In a general population-based study in the US, 33% patients with severe disease had myocarditis and cardiomyopathy, while in a study of 7 pregnant women, 28.6% patients had myocarditis.[30] In another study, 9.7% pregnant patients developed cardiac dysfunction.[31] A study reported that cardiomyopathy was the commonest cardiac problem with a maternal mortality rate of 14.9%.[32] These studies reveal a lower proportion of myocardial changes in pregnant women than in the general population, which may be due to the pregnant women's younger age group and pregnancy hormones' protective effect which needs further exploration.

Scientists have also observed neurological symptoms in Covid-19 patients related to cytokine storm. In a case series of six patients with severe Covid-19, results were indicative of prolonged hypoxemia than

	Allotey et al.	Delahoy et al.	Khalil et al.	Yan J.et al.	Blitz MJ et al.	Takemoto et al.			Guan et al
				Pregnt women					General population
■ Death	0.60%	0.70%	0.90%	0.00%	2.90%	12.70%			1.40%
■ ECHMO	0.80%	0.70%	0.70%	1.54%					
■ Invasive ventilation	3%	8.50%	3.40%	3.10%	11.40%	53.20%			2.30%
■ ICU	4%	16.20%	7%	6.90%	19%	58.90%			5%

Figure-2: Characteristics of Covid-positive pregnant women admitted to intensive care unit (ICU).

the virus infection.[33] Other complications include hepatic and renal failure, viral meningitis, cerebrovascular disorder, epilepsy, thrombotic disease, and septic shock in critical patients. Therefore, recovering patients of severe Covid-19 should be followed closely as these patients are at risk of developing long-term sequel of the disease.

Increased Caesarean section rate

The available evidence about the risk of Caesarean section (CS) in Covid-affected women is diverse. In a multicentre study in China, the overall CS rate was similar before and after the pandemic, although in the severely affected regions, the CS rate was high.[34] However, according to the available data, patients with a severe and critical illness are managed only by CS delivery if maternal condition worsens. A study has presented an equal incidence of CS among Covid-19 and non-affected populations.[35] Another study has also asserted that CS in Covid-19 patients can increase foeto-maternal complications.[36] The findings of these later studies suggest CS only for routine obstetric indications.

Preeclampsia and eclampsia

An observational study described a pre-eclampsia-like syndrome in five out of eight women with severe Covid-19; one of the women remained pregnant after recovery from the disease. She developed proteinuria and hypertension during Covid-19 and a Hellp syndrome-like picture which could be distinguished from pregnancy-induced hypertension by the presence of raised Lactate dehydrogenase (LDH) >600 and a normal uterine Doppler pulsatility index. Her pregnancy continued after recovery from Covid-19, but her preeclampsia findings were resolved.[37] It can be assumed that the hepatorenal involvement in the disease and endothelial damage might cause hypertension and protein urea in Covid-19 pregnant women, which will resolve as the infection subsides.

Psychological effects

In a study of psychosomatic effects of Covid-19, approximately one-third of respondents reported moderate to extreme anxiety.[38] Owing to rising economic challenges in developing countries, there is proof of increased abuse and violent behaviour towards women, requiring attention by law-enforcing authorities.

Foetal effects

Women with Covid-19 also had a greater chance of neuro-developmental defects during conception or their first trimester.[39] During the third trimester, women with Covid-19 pneumonia had an elevated risk of pregnancy complications, including missed abortion (2%) and preterm membrane rupture, intrauterine growth retardation (IUGR; 10%), preterm birth (39%), foetal tachycardia, and an increased CS rate.[40] Another study reported that women with pneumonia had a greater chance of low birth-weight (LBW), preterm birth, and a low APGAR (Appearance, Pulse, Grimace, Activity and Respiration) score of <7 at 5 minutes.[41] These findings suggest severe pneumonia and fever being linked to the risk of poor foetal outcomes in Covid-positive mothers.

Placental effects

Several studies have used histochemical analysis to assess the impact of Covid-19 infections on the placenta. One study looked at five placentae from Covid-positive women with term pregnancies. One of the subjects had dyspnoea; her placenta was viral RNA-positive with pronounced lymphohistiocytic villitis and intervillositis as well as signs of malperfusion.[42] In foetal demise cases in Covid-19 patients, a study found retroplacental haematoma and villous oedema on placental histopathology.[43]

A study discovered SARS CoV-2 in foetal and placental tissue in a first-trimester case report; villi were avascular, with decidual and peri-villus fibrin deposition, substantial leukocyte infiltrate, and massive blood-filled vessels, and all were suggestive of inflammation.[44] A study evaluated third-trimester placenta from 8 Covid-positive patients for histological changes and inflammatory cells, and found the feature of maternal malperfusion in all the cases and increased perivillous fibrin deposition in 7 cases although inflammatory changes of chronic intervillocitries or increased macrophages, T cells, B cells, and plasma cells were non-significant. The monoclonal antibody testing against spike protein and SARS Cov-2 were negative in samples from all the placenta.

On the other hand, maternal vascular malperfusion was present in all eight cases. No maternal decidual arteriopathy was noted in any case.[45] These findings explain the risk of uteroplacental insufficiency and poor parental outcome even if the placental tissue is not infected with SARS CoV-2.

Infant care and risk of vertical transmission

Ideally, the neonates of infected mothers should be tested for Covid-19. Initial studies have also recommended infected mother-infant separation for at least two weeks to prevent vertical transmission which needs to be balanced against the risks of prolonged seperation, i.e., maternal distress, and failure to establish lactation mother-infant bonding.[46] However, despite the fact that the presence of coronavirus has been identified in breast milk in a study in 9 of 49 samples, there is no

evidence of the disease in the infants. Therefore, testing of neonates of infected mothers for Covid-19 or prolonged mother-infant separation is not commendable. In another study done across the US, scientists examined 64 breast milk samples from 18 women infected with SARS CoV-2. Although one sample tested positive for viral RNA, subsequent tests found that the virus could not replicate and could not cause infection in the breastfed infant.[47] It appears that breast milk might have protective antibodies against the disease. There is now consensus that breastfeeding should be encouraged in maternal Covid-19 infection because the infant may receive passive immunity through breast milk against the virus.

The World Health Organisation (WHO) recommends that mothers with suspected or confirmed Covid-19 should use physical barriers, like a curtain between the mother and the newborn, and the mother should wear a face mask and practice hand-hygiene when feeding the infant.[48]

Prevention of Covid-19 in pregnancy
The incubation period of coronavirus is five days (range: 2-14 days). The victims are infectious, but asymptomatic during the incubation period and stay infectious for 21 days and more.

The social distancing of six meters, wearing a mask in public areas, hygienic measures, like hand-washing, sanitising, and avoiding touching face, are preventive steps for all pregnant women with or without Covid-19. Contact tracing and isolation of contacts help slow the progression of the SARS CoV-2, so that the increasing number of cases do not overload the healthcare system. In developing countries of Southeast Asia, like Pakistan and India, lower infection rates were correlated with Bacillus Calmette-Guérin (BCG) vaccination at birth. Nevertheless, epidemiological studies could not prove the preventive role of the BCG vaccine.[49] The current severe wave of coronavirus in these countries also turns away such findings.

Herd Immunity
WHO advises Covid-19 vaccination for pregnant women and breastfeeding mothers in order to achieve herd immunity. Active immunity provided by vaccination can help prevent severe disease, hospitalisation, maternal death, and antibodies transferred from the mother can protect the foetus or newborn from coronavirus infection. According to the Ministry of National Health, and the Society of Obstetricians and Gynecologists Pakistan (SOGP), pregnant women should consult their physicians in this regard, and getting vaccinated is a personal choice.[50,51]

Pakistan has thus far licenced five Covid vaccines; Sinopharm, Cansino, Sinovac, Sputnik and AstraZeneca. The Sinopharm and Sinovac are inactive Covid-19 vaccines, while AstraZeneca, Sputnik V and Cansino use deoxyribonucleic acid (DNA) viral vectors to transfer the required genome into the host cell. There is evidence that as new virus strains evolve, the protective effect of vaccines against some of them may wane, and, as a result, booster doses are necessary regularly, such as during the winter or when the number of recorded cases of the disease increases. The CDC has established an online portal for reporting adverse reactions to vaccinations and the WHO has formed the Global Advisory Committee on Vaccine Safety to review vaccine-related adverse events. So far, there have been no safety issues raised in animal trials or among pregnant lectating women receiving the vaccine as reported by CDC.[51,52]

Conclusion
Even one year after the start of the pandemic, the coronavirus infection is associated with uncertainties. The general protective measures, blocking virus entry into the body, suppressing inflammatory changes, and boosting active and passive immunity may be helpful in eliminating the infection. In pregnancy, the disease is more severe with psychological effects. Severe pneumonia may be associated with multiorgan dysfunction and congenital birth defects, and infection of the placenta. The virus transmitted through breastfeeding is inactive due to the effect of antibodies transferred from the mother, but there is a possibility of neonatal disease by droplet infection from the mother by direct contact. Therefore, breastfeeding mothers with Covid-19 infection should strictly practise preventive measures before handling the baby. Further research is required for the correct diagnosis, adequate immunisation, treatment during pregnancy, and follow-up during the recovery phase to bring forth late sequelae of the disease.

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