

Pregnancy and risk of vertical transmission in Covid-19

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Abstract

Objectives: The current systematic review was planned to illustrate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections during pregnancy and to explore pregnancy outcomes, vertical and perinatal transmission as well as management of coronavirus disease-2019 (Covid-19) during pregnancy.

Methods: The multidisciplinary systematic review was conducted at the Department of Clinical Pharmacology and Therapeutic Medicine, Al-Mustansiriyah University, Bagdad, Iraq. The literature search was conducted in September 2021 and included databases as Medline, PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials and Science Direct databases related to articles on pregnancy and SARS-CoV-2 infections, published between December 2019 and July 2021.

Results: Of the 30 articles reviewed, 12(40%) were included. Major reasons for including a small number of studies in systematic review were that majority of the studies had insufficient description of study; analysis was duplicate across various publications, and inadequate explanation of impact of SARA-CoV-2 infection on the pregnancy outcomes. This review included 12 studies based on the assessment and estimation of risk of bias and quality of the eligible studies.

Conclusions: Findings revealed that pregnant women were predominantly susceptible to the respiratory viral infection and severe pneumonia due to physiological immune-suppression, immune adaptation and pregnancy-induced changes. The clinical presentation and management of pregnant women with Covid-19 is similar to that of non-pregnant women and there is no strong clinical evidence of vertical transmission. Also, only chloroquine and remdesivir have been found to be effective in the treatment of Covid-19 during pregnancy.

Keywords: SARS-CoV-2, Covid-19, Pregnancy, Vertical transmission.

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Introduction

In December 2019, a number of cases of unknown pneumonia emerged in Wuhan, China, and the World Health Organisation (WHO) notified this outbreak in late 2019. On January 7, 2020, a novel coronavirus (nCoV-19) was recognised as the causative agent of this undefined pneumonia.¹ Chinese researchers identified the genetic sequences of the virus and named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the genetic sequence of SARS-CoV-2 had 79% similarity with that of SARS in 2003 (Figure-1).² The WHO in January 2020 named this outbreak coronavirus disease-2019 (Covid-19) and regarded it as a global pandemic due to the rapid spread of this virus across the world. By April 5, 2021, more than 132 million subjects had been diagnosed with Covid-19 globally.¹ The clinical presentation of Covid-19 is dry cough, headache, fatigue, sweating and fever.³ The laboratory findings are leukocytosis, lymphopenia, high lactate dehydrogenase (LDH) and ferritin with bilateral or rarely unilateral pulmonary ground glass appearance on computed tomography (CT) chest scan. The diagnostic test of Covid-19 is real-time reverse transcription polymerase chain reaction (RT-PCR) and serological testing to detect immunoglobulin M (IgM) and IgG.⁴

Initially, there was insufficient information about Covid-19 in pregnancy due to limitation of published data, as only three case-series comprising 31 pregnancies with Covid-19 had been reported.⁵ Also, limited information regarding SARS and the Middle East respiratory syndrome (MERS) are available. Thus, the researchers and medical

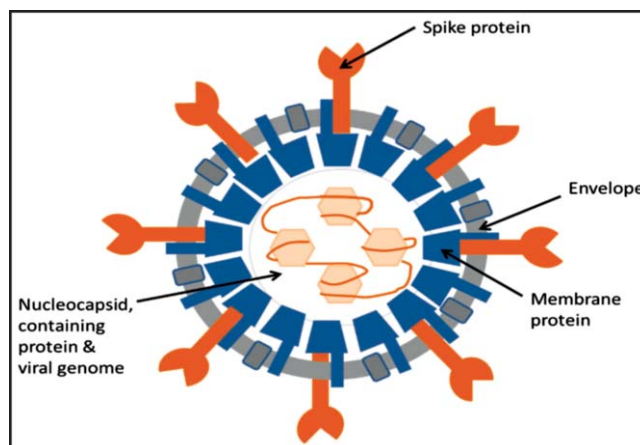


Figure-1: Structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

authorities faced a strong challenge in managing Covid-19 during pregnancy.⁵ Fortunately, the American College of Obstetricians and Gynaecologists (ACOG) guideline was published in the early phase of the outbreak to ensure a scientific approach for Covid-19 management during pregnancy.⁶ The case-fatality ratio of pregnant women with Covid-19 differed from country to country; high in Iran and low in China, since early estimation could over-estimate the numbers.⁷

Preliminary data suggested that pregnant women with Covid-19 were not severely affected compared to the general population since the number of reported affected pregnant women was small and not compared with matched non-pregnant women. Furthermore, studies confirmed that pregnant women with Covid-19 were at a higher risk compared to non-pregnant women.^{8,9} Besides, earlier data concerning perinatal and intrauterine transmission of SARS-CoV-2 is also unknown as there was no strong evidence of transmission to the neonate. The reason behind this phenomenon was that nearly all the infected pregnant women were in the third trimester, and the effect of the virus earlier in pregnancy was mostly unknown. The pregnant women during Covid-19 pandemic are at a higher risk for infection with SARS-CoV-2 due to frequent prenatal care requirements, including routine healthcare visits, which could expose them to a greater risk of having contact with infected persons.¹⁰

The current systematic review was planned to illustrate SARS-CoV-2 infection during pregnancy and to explore pregnancy outcomes, vertical and perinatal transmission as well as management of Covid-19 during pregnancy.

Methods and search strategy

In the present Systematic review, Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA),¹¹ was applied as a guideline for extracting data and results. Experimental, preclinical and clinical studies were searched on electronic databases including Medline, PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials using medical subjects heading (MeSH) terms, key words and title words for the period, December 2019 to July 2021. The terms used for these searches were: [Pregnancy] AND [Covid-19 OR SARS-CoV-2 OR nCoV-19] OR [perinatal transmission, vertical transmission, pregnancy complications],

[pregnancy] AND [hyperinflammation OR cytokine storm]. The reference lists of the articles were reviewed. Articles published in English were considered and case reports were also reviewed. The key features of the shortlisted studies were summarised in a systematic review study. The authors performed the search in September 2021.

Results

Of the 30 articles reviewed, 12(40%) were included (Figure-2).

Major reasons for including a small number of studies in systematic review were that majority of the studies had insufficient description of study; analysis was duplicate across various publications, and inadequate explanation of impact of SARA-CoV-2 infection on the pregnancy outcomes. This review included 12 studies based on the assessment and estimation of risk of bias and quality of the eligible studies. Taken together, these studies were conducted between 2019 and 2021. All included studies were reviewed and evaluated. Furthermore, there were some contradictions regarding diagnostic criteria and the variability in testing accuracy of SARA-CoV-2 infection during pregnancy across studies.

Findings of the present study illustrated that the pregnant

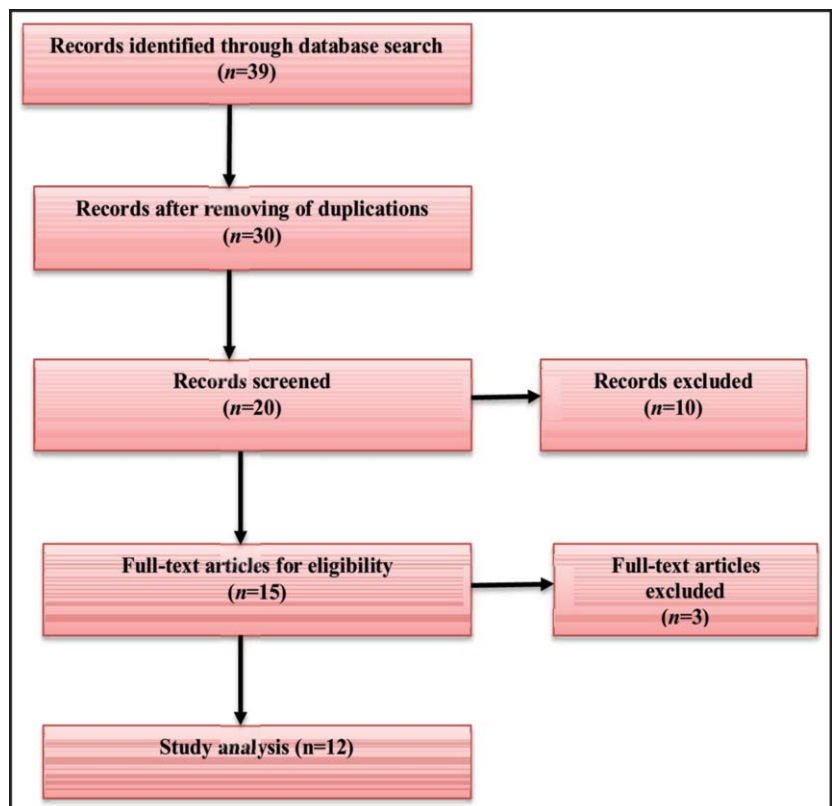


Figure-2: Flow-chart of the present study.

women are highly vulnerable to the risk of respiratory viral infection and severe pneumonia.¹² SARS-CoV-2 infection during pregnancy may lead to serious complications with a higher mortality rate.¹³ Covid-19 pneumonia in pregnant women is associated with the higher expression of the protective angiotensin converting enzyme 2 (ACE2) during pregnancy.¹⁴ Viral infections during pregnancy is associated with intrauterine growth retardation (IUGR), preterm birth, abortion and poor perinatal outcomes.¹⁵ The pathways of vertical transmission are intrauterine transmission (IUT), transmission during normal vaginal delivery, and transmission through breast feeding. IUT is the least manageable and has a higher risk for both the mother and the foetus.¹⁶ However, there is no evidence that Covid-19 pneumonia during pregnancy leads to foetal infection by IUT depending on the negative results by RT-PCR of cord blood, placental blood, and amniotic fluid and vaginal secretions.¹⁷ As well, the present study revealed that vertical transmission of SARS-CoV-2 infections during pregnancy is low.¹⁸ Regarding breastfeeding, no positive RT-PCR findings have been reported in the breast milk of the infected mother.¹⁹ Concerning the type and timing of delivery, these are decided by the obstetricians, depending on the gestational age, foetal and maternal health, and specific health conditions of each pregnant woman.²⁰

The general principles in the management of Covid-19 during pregnancy are the same for the non-pregnant women unless there is any contraindication for drug therapy during pregnancy. Though, frequent monitoring and consultations for detection of early and late complications, such as premature rupture of membrane and preterm delivery, should be assessed.²¹

Discussion

Pregnancy and Covid-19: During pregnancy there is a state of immune suppression, which makes the pregnant women more susceptible to viral infections. Therefore, SARS-CoV-2 infection during pregnancy leads to serious complications with higher rates of substantial mortality mainly with underlying co-morbidities.²² Interim guidance has been disclosed by the Centres for Disease Control and Prevention (CDC) for the management of Covid-19 during pregnancy depending on related findings in the context of previous coronavirus outbreaks. CDC has issued different recommendations regarding the pathogenesis, epidemiology, clinical course and disease progression of Covid-19 in pregnant women.²³ Even though clinical experience in managing pregnant women with Covid-19 was limited initially, different complications were reported, including preterm delivery, premature

rupture of membrane and foetal distress in the pregnant women with Covid-19.²⁴

It has been reported that pregnant women are predominantly susceptible to the respiratory viral infection and severe pneumonia due to physiological immune-suppression adaptation and pregnancy-induced changes, such as intolerance to hypoxia and high oxygen consumption.²⁵ Previously, a study reported that about 50% of pregnant women with SARS needed intensive care unit (ICU) support and mechanical ventilation, with approximately 25% mortality. Besides, pregnant women during the 2009 swine influenza (H1N1) carried four times more risk than non-pregnant women for hospitalisation.²⁶ However, a recent study illustrated that Covid-19 in pregnant women is not different from that among non-pregnant women though the pulmonary consolidations and ground glass appearance are more evident at both lower lobes on low-dose CT imaging. Furthermore, the study showed that Covid-19 pneumonia is mild and characterised by mild fever and cough in 11 patients. In those patients, one pregnant woman delivered vaginally, while the remaining 10 patients delivered by caesarean section (CS).²⁷ The mild presentation of Covid-19 pneumonia in pregnant women might be linked to the expression of angiotensin converting enzyme 2 (ACE2) during pregnancy.²⁸ Higher expression of ACE2 during pregnancy, particularly in the foeto-maternal interface, may increase the risk of severe Covid-19 pneumonia. Also, renin-angiotensin-aldosterone system (RAAS) is highly activated during pregnancy which plays a potential role in pulmonary vasoconstriction and development of acute lung injury (ALI). Therefore, a higher expression of ACE2 is to overcome the deleterious effect of activated RAAS.²⁹

The association between over-expression of ACE2 and severity of Covid-19 is weak, since ACE2 protein is located on the X chromosome, which is more abundant in women. However, the Covid-19 fatality is higher in men and the severity of Covid-19 in elderly patients is high despite low expression of ACE2.³⁰ Therefore, definitive association between the severities of Covid-19 pneumonia during pregnancy with the over-expression of ACE2 should be revised.

Vertical transmission of SARS-CoV-2 during pregnancy: Viral infections during pregnancy are mostly concerned by obstetricians regarding the possibility and likelihood of vertical transmission from mother to the foetus. It has been reported that viral infections during pregnancy is linked with intrauterine growth retardation (IUGR), preterm birth, abortion and poor perinatal outcomes.³¹ The pathways of vertical transmission are

intrauterine transmission (IUT), transmission during normal vaginal delivery, and transmission through breast feeding. IUT is the least manageable and has a higher risk for both the mother and the foetus.³²

A systemic review by Karimi-Zarchi et al. found no evidence that Covid-19 pneumonia during pregnancy leads to foetal infection by IUT depending on the negative results by RT-PCR of cord blood, placental blood, amniotic fluid and vaginal secretions. However, neonatal infection has been confirmed, which gives a clue that direct contact between the mothers and their neonates is the main route of infection.³³ The first reported case of Covid-19 pneumonia during pregnancy in Iraq was recently reported by Al-Kuraishy et al., confirming a negative evidence for vertical transmission.⁵ Also, Li et al. supported the negative findings of vertical transmission of SARS-CoV-2.³⁴ However, single case-report by Dong et al. confirmed the positive vertical transmission from the mother to her delivered neonatal girl by positive RT-PCR test of the neonate but amniotic, cord and placental blood were not estimated.³⁵

The low risk of vertical transmission is suggested to be due to the low expression of ACE2 at foeto-maternal tissue interface as evident by lacking of placental pathological changes during SARS-CoV-2 infections during pregnancy.³⁶ Also, low risk of vertical transmission might be explained by rapid delivery of the infected mother by CS to minimise the impact of SARS-CoV-2 infection on pregnancy outcomes.

The risk of pregnant mothers during first and second trimesters has not been evaluated in most of the published studies. The risk of different viral infections during pregnancy is trimester-dependent, as viral infections in the first and second trimester of pregnancy lead to various intrauterine and foetal effects. It has been shown that rubella infection in the first trimester leads to congenital malformations in 90% of cases, but this risk is reduced to 50% in the second trimester and becomes zero risk in the third trimester.³⁷

Regarding breastfeeding, no positive RT-PCR findings have been reported in the breast milk of the infected mother. However, the infected mothers are advised to stop feeding

till the results of RT-PCR were negative.³⁸ Concerning the type and timing of delivery, these are decided by the obstetricians, depending on the gestational age, foetal and maternal health, and specific health conditions of each pregnant woman.²⁰

Moreover, the majority of published data regarding the vertical transmission of SARS-CoV-2 infections during pregnancy depended on RT-PCR test and nasal swab that have sensitivities 63% and 29% respectively, and IgG and IgM appear within 2 weeks of SARS-CoV-2 infections which means anti-SARS-CoV-2 IgG in foetal blood does not indicate an intrauterine infection.³⁹ Also, SARS-CoV-2 viremia is present transiently only in 1% of patients with symptomatic Covid-19 pneumonia, signifying a very low possibility of this virus to be transmitted across the placenta. In addition, pathological studies of placental samples did not confirm any histopathological changes linked with SARS-CoV-2 infections.⁴⁰ Different experimental studies illustrate that low expression of placental ACE2 receptors, mainly at 6-12 weeks of gestations, limits SARS-CoV-2 transmission from mother to the foetus chiefly in the first trimester of pregnancy.⁴¹ Lamouroux et al. showed that all samples, like vaginal secretions, amniotic fluid and breast milk, of 90% of 71 pregnant women with Covid-19 were negative, suggesting a negative evidence for vertical transmission.⁴² Besides, a positive RT-PCR test for SARS-CoV-2 in neonates of Covid-19 mothers is positive in about 9% of delivered neonates. This value is not

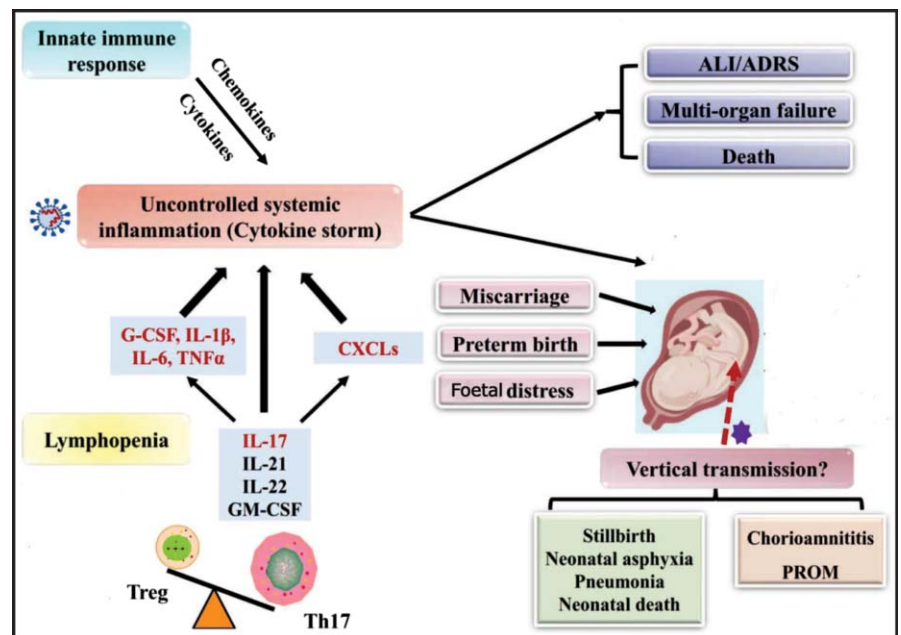


Figure-3: Immunological interactions against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy.

dependable since IgM does not cross the placenta and is subjected to different cross-reactivity, indicating that the positive result reflects perinatal rather than congenital infection.⁴³

It has been reported that immunological tolerance during pregnancy is associated with the elevation of soluble cluster of differentiation 26 (sCD26) receptors, which have anti-inflammatory effects.⁴⁴ Sclicht et al. revealed that circulating sCD26 receptors are reduced in severely-affected Covid-19 patients, as these receptors neutralise SARS-CoV-2 and reduce viral infectivity.²¹ Therefore, high circulating sCD26 receptors during pregnancy may reduce severity of SARS-CoV-2 infection and may limit vertical transmission. Therefore, there are noteworthy immunological interactions against SARS-CoV-2 infection during pregnancy (Figure-3).

Management of Covid-19 during pregnancy: The general principles in the management of Covid-19 during pregnancy include early diagnosis, isolation, oxygen therapy, empirical antibiotics for secondary bacterial infections, monitoring of uterine contraction and foetal distress as well as planning for delivery type. Frequent monitoring and consultations for detection of early and late complications, such as premature rupture of membrane and preterm delivery, should be evaluated.⁴⁵

Corticosteroids should be avoided in the management of Covid-19 during pregnancy, as they delay the clearance of SARS-CoV-2 and may increase the risk of secondary bacterial infections. However, using corticosteroid for the induction of foetal lung maturity should depend on the considerations of guideline and medical consultations.⁴⁵

At present, there are no antiviral medications approved by the Food and Drug Administration (FDA) during pregnancy, even though broad-spectrum antiviral drugs against MERS are in use against SARS-CoV-2. Nonetheless, during pandemic, the ethical use of non-licensed drug during pregnancy should be according to the Monitored Use of Unregistered Interventions (MEURI). Recently, both chloroquine and remdesivir have been evaluated to be effective in the treatment of Covid-19 during pregnancy, as they block the replication of SARS-CoV-2 and are safe during all trimesters of pregnancy. However, chloroquine has a large volume of distribution, thus a large dose of it is needed during pregnancy, which may reach up to 500mg/twice daily.⁴⁶ Chloroquine and remdesivir reduce radiological opacities and accelerate clinical and serological resolutions in the pregnant women with Covid-19. In addition, viral protease inhibitors, such as lopinavir and ritonavir, are effective in pregnant women with Covid-19, but their safety in the pregnancy has not

been tested in large population-based research. Conversely, favipiravir, arbidol, ribavirin and baricitinib are teratogenic, and, as such, are contraindicated in pregnancy.⁴⁷ moreover, low dose of aspirin and low-molecular-weight heparin are recommended in pregnant women with severe Covid-19 to prevent thrombosis and coagulopathy-induced ALI or Acute respiratory distress syndrome (ARDS).⁴⁸

Conclusions

As the Covid-19 pandemic continues to extend around the world, the challenge to find drugs and adequate management of Covid-19 cases, mainly in the pregnant women, is essential. Clinical recommendations regarding the management of pregnant women with Covid-19 should be based on clinical data from epidemic centres rather than from single limited experiences. The clinical presentation and management of pregnant women with Covid-19 is similar to that of non-pregnant women and there is no strong clinical evidence of vertical transmission. Also, only chloroquine and remdesivir have been found to be effective in the treatment of Covid-19 during pregnancy.

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