University of Diyala

College of medicine

Department of gynecology

Review article in

Association between COVID 19 and Pregnancy Loss

A project submitted to the council of College of Medicine / University of Diyala in Partial fulfillment of the Requirements for the Degree of bachelor in medicine and general surgery

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2022

بسم الله الرحمن الرحيم

(إِلَّا أَنْ يَشَاءَ اللَّهُ نَرْفَعُ دَرَجَاتٍ مَنْ نَشَاءُ وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ ﴿٧٦﴾)

سورة يوسف الآية (76)

الاهداء

إلى من علَّمني كيف أقف بكل ثبات فوق الأرض

أبي المحترم

إلى نبع المحبة والإيثار والكرم

أمي الموّقرة

إلى أقرب الناس إلى نفسي

أخواني وأخواتي

إلى جميع الشهداء رحمهم الله

إلى جميع من تلقَّىُ منهم النصح والدعم من الاقارب والأصدقاء

أهديكم خلاصة جهدي العملي

ألشكر والتقدير

الحمد لله ألذي هدانا وأعدنا وأمدنا والهمنا الصبر على المشاق
ووفقنا لما نحن عليه فله الحمد والشكر ابتداءاً وانتهاءاً
وارفع كلمة الشكر الى الأستاذة الدكتورة

(ازل صادق داوود)

وفقها الله فقد كانت سندا لي على طول الطريق
والى كل من مد يد العون لي من قريب أو بعيد
وقبل أن أمضي اقدم اسمى ايات الشكر والامتنان والتقدير
والمحبة
الى الذين مهدوا لي طريق العلم والمعرفة
الى جميع اساتذتي الافاضل

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Abstract

COVID-19 is a capsulated single-stranded RNA virus. Pregnancy loss, also referred to as miscarriage or spontaneous abortion In this article we reviewed literature about the possible association between COVID-19 and pregnancy loss. We found no increased risk of abortion among pregnant women with COVID-19.

Keywords: abortion, COVID-19, pregnancy loss

Introduction

In December 2019, a cluster of four cases of pneumonia of unknown etiology in Wuhan, China, were reported to the World Health Organization (WHO). Since then, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly across the world. On March 12, 2020 the WHO defined the outbreak as a pandemic. Many countries responded by restricting freedom of movement and limiting nonemergency health care to focus resources on COVID-19 care provision (1).

Corona virus infection

COVID-19 is a capsulated single-stranded RNA virus. The immunological response to COVID-19, like other viruses, relies on a working immune system . COVID-19 infection can result in mild disease, in which the virus is cleared effectively by the immune system or severe disease with high mortality rates (2). SARS-CoV-2, which is transmitted by respiratory droplets, direct contact with fomites, close person-to-person contact and possibly by aerosols generated, enters the body via the nasal passage and infects pulmonary cells via the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) and uses transmembrane serine protease 2 (TMPRSS2) for S protein priming. Cells in which ACE-2 and TMPRSS2 are likely to be most susceptible to entry by SARS-CoV-2. Infection with SARS-CoV-2 is followed by viral replication and release of the virus, causing pyroptosis of the host cell (3).

Pregnancy loss

Pregnancy loss, also referred to as miscarriage or spontaneous abortion, is generally defined as a nonviable intrauterine pregnancy up to 20 weeks gestation. Early pregnancy loss, which occurs in the first

trimester, is the most common type. The nonspecific symptoms of vaginal bleeding and uterine cramping associated with pregnancy loss can occur in normal, ectopic, and molar pregnancies, which can be a source of frustration for patients and clinical confusion for care providers (4). Early symptoms of miscarriage generally include vaginal bleeding and pain. An ultrasound can confirm the pregnancy is no longer viable.

COVID 19 and pregnancy

Pregnant women are particularly vulnerable to respiratory pathogens and severe pneumonia due to physiological and immunological changes, such as altered T lymphocyte immunity, increased oxygen consumption, decreased functional residual capacity and decreased chest compliance, which may result in higher maternal and fetal morbidity and mortality (5). Pregnant women with COVID-19 pneumonia showed a similar pattern in comparison with non-pregnant counterparts, including fever, cough, myalgia, fatigue, shortness of breathe or asymptomatic presentation. It is worth noting that there is currently no evidence that pregnant women with COVID-19 are at higher risk of severe illness. However, SARS and MERS were found to be greatly associated with severe maternal illness, spontaneous abortion and even maternal death and intrauterine fetal demise. Some pregnancy complications have occurred in pregnant women with COVID-19, such as fetal distress, premature rupture of membranes, preterm deliveries and stillbirths. Furthermore, these pregnancy complications might be closely related to the cytokine storm, lung injury and placental ischemia/ hypoxia caused by SARS-CoV-2 infections (6).

In this review, we will discuss the association between COVID-19 infection and pregnancy loss.

Possible etiology of pregnancy loss in COVID-19

When assessing the effects of COVID-19 in pregnancy, it is important to distinguish studies comparing pregnant women with COVID-19 and non-pregnant women with COVID-19, from those studies comparing pregnant women with and without COVID-19. The former address the question as to whether pregnancy increases the risk of adverse outcomes in women who have the disease. The latter addresses the question as to whether contracting the disease during pregnancy increases the risk of adverse outcomes (7). The etiologic factors of the fetal loss during the first 24 weeks of gestation were classified into several systematic inflammatory events, including but not limited to the systematic inflammation involving the placenta. These etiologic factors could cause premature contraction and premature rupture of the membrane resulting in premature delivery. In addition, it is well known that early pregnancy loss is predominantly related to intrinsic embryonic inborn errors. In non-hospitalized Pregnant women with COVID-19 infection detected by serologic methods did not significantly differ in nuchal translucency thickness and double test in first-trimester screening. Furthermore, there was no significant increased risk of pregnancy loss in women with COVID-19 infection in the first trimester (8,9).

Studies related to abortion in pregnant females with COVID-19 show that most of the miscarriages due to COVID-19 in the first trimester were due to placental insufficiency. Such conditions that led to the COVID-19 related miscarriages include spontaneous miscarriage, preterm delivery, and intrauterine growth restriction (10). Acute or chronic placental insufficiency resulting in subsequent miscarriage or Intrauterine growth restriction (IUGR) was observed in 40% of maternal MERS-CoV and SARS-CoV. Recent studies have shown the deposition of perivillous fibrin

and multiple villous infarcts in the placenta of SARS-CoV-2 infected mothers. As a result, the placental infection can disturb the transportation of nutrients from mother to fetus, leading to adverse pregnancy outcomes (11).

Although stillbirth was a rare outcome overall, a COVID-19 diagnosis documented during the delivery hospitalization was associated with an increased risk for stillbirth in the United States, with a stronger association during the period of Delta variant predominance. A previous study of pregnancies complicated by SARS-CoV-2 infection identified placental histopathologic abnormalities, suggesting that placental hypoperfusion and inflammation might occur with maternal COVID-19 infection (12).

Increased risk of embryo implantation failure and miscarriage has been reported during the periconceptional period in women with COVID-19. It was speculated that the reproductive failure was due to systemic inflammation and interference with trophectoderm-endometrium molecular signaling rather than a direct action of SARS-CoV-2 at the implantation site (13).

The immunopathology of COVID-19, accompanied by high levels of IL-6, IL-8, TNF-alpha, and other cytokines. Consequently, the "cytokine storm" of COVID-19 induces a hypercoagulable state that is detrimental to normal in-utero blastocyst/fetal development (toxic endometrial microenvironment and hypoperfusion secondary to microthrombus formation), as well as an unfavorable uterine immune response to embryo implantation. Indeed, abnormalities in the maternal immune response during peri-implantation and early pregnancy, with a predominant pro-inflammatory response (Th1 and Th17), and thrombophilic conditions have been linked to recurrent implantation failure and miscarriage (14).

Studies that support the association between COVID-19 and pregnancy loss

1. *Kazemi et al.,*(2021 Aug) found that there is an increased risk of abortion in mothers who tested positive for SARS-CoV-2, which case reports and case series have identified during the pandemic. Most of these studies referred to the effect of the virus on the placenta and inflammation, resulting in fetal growth retardation and may induce abortion. However, data from the pregnant females during the pandemic who experienced abortion is limited (15).

Studies that does not support the association

1. *Hirshberg et al,* (2020 May) initially suggested that pregnant women were not at an increased risk of COVID-19-related complications as compared to the general population. Further case reports from countries such as the United States (US) and Iran produced contradictory evidence, with some reports that described women who required invasive mechanical ventilation and at an increased risk of death. Since then, further large-scale studies have added more robust evidence to these preliminary findings, though definitive answers to many of these questions are still awaited (16).
2. *Trocado et al,*(2020 Jul) conducted a meta-analysis on 95 pregnant women and found no pregnancy loss among them (17).
3. *Frieslebon et al,* (2021 Jan) found no significant increased risk of pregnancy loss in women with SARS-CoV-2 infection in the first trimester. Serological studies investigating the impact of SARS-CoV-2 on later stages of pregnancy are needed to develop clinical guidelines and recommendations for any possible restrictions for pregnant women in relation to SARS-CoV-2 (18).

4. *Joseph et al*, (2021 Apr) reviewed literature and found no significant difference between the exposure group and the control in rates of pregnancy loss (19).
5. *Jacoby et al*, (2021 Oct) found Found that pregnancy loss is reassuring because it is not significantly higher than the expected miscarriage rate without viral infection (20).

Conclusion

There is no increased risk of abortion in mothers who tested positive for SARS-CoV-2, which case reports and case series have identified during the pandemic. More extensive studies, including multiple hospitals from the same region, are needed to avoid sampling bias. Serological data to document previous SARS-CoV-2 infection would be useful to demonstrate a causal link between miscarriage and SARS-CoV-2 infection. Our study provides reassuring findings for women who intend to become pregnant during the SARS-CoV-2 pandemic or who became infected during their first trimester of pregnancy. COVID-19 appears to have a favorable maternal course at the beginning of pregnancy, consistent with what has been observed during the third trimester when the clinical characteristics of COVID-19 positive pregnant women were similar to those found in women from the general population.

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