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REVIEW ARTICLES

COVID-19 and Pregnancy. When are complications expected?

COVID-19 e Gravidez. Quando são esperadas complicações?

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is a RNA virus that cause coronavirus disease 2019 (COVID-19). The clinical spectrum SARS-COV-2 infection ranges from asymptomatic infection to critical and fatal illness. The expression of host receptor for SARS-CoV-2 cell entry in placental tissue and the identification of SARS-COV-2 in the placental tissue supports that SARS-COV-2 infection may affect pregnancy outcomes. At the moment, there is some evidence of the impact of the infection in pregnancy and fetal outcomes especially in symptomatic cases.

Objectives: The aim of this study was to review the current state of the art of SARS-COV-2 infection during pregnancy and risk of adverse maternal, pregnancy and fetal outcomes, and to assess when these outcomes are most likely to occur.

Main text: Asymptomatic COVID-19 disease in pregnancy is common. When present, symptoms and signs are similar to those in nonpregnant individuals. Infected pregnant women have a higher risk of rapid clinical deterioration and symptomatic pregnant patients appear to be at increased risk of severe disease and death. There is no evidence of an increased risk of congenital abnormalities or pregnancy loss in women with COVID-19 during pregnancy. Vertical transmission does not seem to be common. There is an association between COVID-19 in pregnancy and preterm labour, cesarean delivery, preeclampsia and stillbirth.

Conclusions: Maternal complications are expected in pregnant women with older age, obesity, preexisting comorbidities or unvaccinated. Adverse pregnancy and fetal outcomes are expected in pregnant women with symptomatic disease and when maternal infection occurs after 20 weeks of gestation.

Keywords: COVID-19; fetus; infant; infectious disease transmission; newborn; pregnancy; pregnancy outcome; SARS-CoV-2; vertical

RESUMO

Introdução: A síndrome respiratória aguda grave – coronavírus 2 (SARS-COV-2) é um vírus de RNA que causa a doença COVID-19. O espectro clínico da doença varia desde assintomática a infeção crítica e potencialmente fatal. A expressão de recetores que permitem a entrada do vírus na placenta e a identificação do vírus no tecido placentar sugere que a infeção pode afetar a gravidez. Atualmente, existe já alguma evidência do impacto da COVID-19 nos desfechos obstétricos e fetais.

Objetivos: O objetivo deste estudo foi avaliar o estado da arte relativamente à infeção por SARS-COV-2 na gravidez e o risco de desfechos maternos, obstétricos e fetais adversos e, ainda, analisar em que situações esses desfechos são mais prováveis de ocorrer.

Texto principal: A infeção assintomática na gravidez é comum. Quando presentes, os sinais e sintomas são similares aos da população geral.

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Grávidas infetadas têm maior risco de rápida deterioração clínica e grávidas infetadas sintomáticas têm maior risco de doença grave e morte. Não há evidência de risco aumentado de anomalias congénitas ou perda gestacional em grávidas com COVID-19. A transmissão vertical não parece ser comum. Existe evidência da associação entre COVID-19 na gravidez e parto pré-termo, cesariana, pré-eclampsia e morte fetal intrauterina.

Conclusões: Desfechos maternos adversos são mais prováveis de ocorrer em grávidas com infeção por SARS-COV-2 e idade avançada, comorbilidades, obesas ou não vacinadas. Desfechos obstétricos e fetais adversos são mais prováveis de ocorrer em grávidas infetadas sintomáticas, sobretudo doença grave, e quando a infeção ocorre após as 20 semanas de gestação.

Palavras-chave: COVID-19; desfecho obstétrico; feto; gravidez; neonato; SARS-COV-2; transmissão vertical

INTRODUCTION

At the end of 2019, a novel coronavirus, designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan, China.[1] SARS-CoV-2 cause coronavirus disease 2019 (COVID-19), a disease that spread quickly leading World Health Organization (WHO) to declare pandemic status on March 2020.[2] Globally, over 100 million confirmed cases of COVID-19 have been reported.[3]

Coronaviruses are enveloped positive-stranded RNA viruses. The host receptor for SARS-CoV-2 cell entry is the angiotensin-converting enzyme 2 (ACE2).[4] The clinical spectrum SARS-COV-2 infection ranges from asymptomatic infection to critical and fatal illness.

Pregnancy generally does not increase the risk for acquiring SARS-CoV-2 infection, but available data suggests that symptomatic pregnant women with COVID-19 are at increased risk of more severe illness and COVID-19 complications.[5,6] Pregnant patients with comorbidities may be at an even higher risk of severe illness.

The impact of COVID-19 on maternal, pregnancy and fetal outcomes is under investigation. The expression of ACE2 in placental tissue and the identification of SARS-COV-2 in the placental tissue and membranes supports that SARS-COV-2 infection may affect pregnancy outcomes and may be vertically transmitted.[7,8] The physiologic and immunologic changes during pregnancy may result in systemic effects that could predispose infected pregnant women to develop obstetric complications. It has been suggested that pro-inflammatory immune responses to SARS-COV-2 by maternal, fetal and placenta tissue, with an unbalance Treg/Th17 immune response, create a pro-inflammatory intrauterine environment.[9] Fetal vascular malperfusion, fetal vascular thrombosis, maternal vascular malperfusion and generalized inflammation have been described in placental pathologies of COVID-19 patients.[10]

To define the best surveillance protocol in women infected by SARS-COV-2 during pregnancy more large-scale studies are needed to assess the impact of COVID-19 on obstetric and perinatal outcomes.

OBJECTIVES

The aim of this study was to review the current state of the art of SARS-COV-2 infection during pregnancy and risk of adverse maternal, pregnancy and fetal outcomes. Additionally, to assess when these adverse outcomes are most likely to occur.

CLINICAL FINDINGS

Asymptomatic COVID-19 disease in pregnancy is common. Some literature suggests that pregnant people were more likely to be asymptomatic than nonpregnant people of reproductive age with COVID-19.[11] When present, symptoms and signs are similar to those in nonpregnant individuals. In a report from the Centers for Disease Control and Prevention (CDC) that included over 23 000 pregnant persons with symptomatic SARS-CoV-2 infection, the most common symptoms were cough, headache, muscle aches and fever.[6] These symptoms were similar to those of nonpregnant reproductive-aged females with symptomatic SARS-CoV-2 infection. However, some of these clinical manifestations overlap with symptoms of normal pregnancy, like fatigue, nasal congestion, nausea, vomiting, which should be taken into account when evaluating pregnant women with these complaints.

Several risk factors for symptomatic disease in pregnant women have been described, namely obesity, hypertension, underlying respiratory disorder, black race and Asian ethnicity.[12]

Laboratory and imaging findings in pregnant women with SARS-COV-2 infection are generally similar to those in nonpregnant persons. The most frequent findings are raised C-reactive protein levels (49%), lymphopenia (33%), leukocytosis (26%), elevated procalcitonin level (23%), abnormal liver chemistries (15.4%) and thrombocytopenia (6.6%).[12] However, some caution should be taken in interpreting these findings, since some are physiological in pregnancy (slight elevation of C-reactive protein levels and leukocytes) and others can be found in specific complications of pregnancy (abnormal liver chemistries and thrombocytopenia in preeclampsia). The presence of respiratory

symptoms and hypertension can help in the differential diagnosis.

Regarding the histopathological findings of the placenta in women with COVID-19 during pregnancy, most studies refer fetal vascular malperfusion, villitis and placental infarction.[13] However, these findings are not specific to SARS-CoV-2 infection and may be found in other clinical contexts. So, there is no standard definition of placental SARS-CoV-2 infection and no definite COVID-19-specific placenta changes.[14]

MATERNAL OUTCOMES

Pregnancy does not increase susceptibility to SARS-CoV-2 infection but appears to worsen the clinical course of COVID-19. Infected pregnant women have a higher risk of rapid clinical deterioration and symptomatic pregnant patients appear to be at increased risk of severe disease and death, compared with nonpregnant females of the same age.[6,12] Despite the limitations, CDC reported a study that included over 23 000 pregnant persons and over 386 000 nonpregnant females of reproductive age with symptomatic SARS-CoV-2 infection. In this study pregnant women had a higher risk of intensive care unit admission, invasive ventilation, extra corporeal membrane oxygenation and death.[12] These facts led the CDC to include pregnancy as an "increased risk" category for severe COVID-19. Risk factors for severe disease or death in pregnancy are: age (35 years or older), obesity , preexisting medical comorbidities (hypertension, diabetes) or unvaccinated.[15,16]

PREGNANCY OUTCOMES

Miscarriage

There was no significantly increased risk of pregnancy loss for women with SARS-CoV-2 infection in first trimester pregnancy.[17] Studies that compared the rate of pregnancy loss during the pandemic and pre-pandemic period did not find statistically significant differences.[18,19]

Preterm Labor

Patients with severe or critical COVID-19, and underlying comorbidities, are at risk for perinatal complications including preterm birth.[20] Large cohort studies of pregnant patients with COVID-19 reported higher preterm delivery rates compared to patients without COVID-19 and compared to United States of America (USA) national rate.[21,22] Some of these preterm deliveries are iatrogenic however many studies do not make this distinction.

Cesarean delivery

Pregnant women with severe or critical COVID-19 are also at risk of cesarean birth.[21] Rates of cesarean delivery were generally higher compared to women without COVID-19 and to the overall cesarean rate in the USA.[23]

Preeclampsia

Studies had suggested that SARS-CoV-2 infection during pregnancy increases the risk of developing preeclampsia, preeclampsia with severe features, eclampsia, and HELLP syndrome. In contrast to preterm birth, both asymptomatic and symptomatic patients experienced an increased risk, with a higher risk among symptomatic patients.[23]

This association could be related to endothelial dysfunction. Endothelial cells express ACE2, so these cells can be infected by SARS-COV-2 and infection can induce the activation of thrombin, intravascular inflammation and damage of the microvasculature in target organs, leading to a syndrome similar to preeclampsia and eclampsia.[24]

So, the risk of adverse pregnancy outcome is increased in symptomatic pregnant women with COVID-19, especially those with severe or critical disease. Pregnant women with asymptomatic infections appear to have similar outcomes as those without a COVID-19 diagnosis, except for an increased risk for preeclampsia.[25] An international retrospective cohort study reported that maternal infection after 20 weeks of gestation increased the risk of adverse obstetric outcomes, maternal infection after 26 weeks increased the risk of adverse neonatal outcomes, whereas earlier infection did not increase these risks.[26]

FETAL OUTCOMES

Congenital infection

The extent of vertical transmission remains under investigation. Several studies reported clinical cases of vertical transmission but only few are well-documented. In utero transmission can occur through the hematogenous route or the ascending route. However, viremia rate is low and transient in patients with COVID-19, suggesting placental seeding is not common, and ascending route seems to be rare.[27,28] Intrapartum transmission can occur by contact with vaginal secretions or by fecal contamination of the perineum in infected women.[29] Postnatal transmission can occur through breastfeeding or, more often, through direct contact with infected caregivers. Despite this, actual data suggests that the overall rate of congenital infection is less than 2%.[30] However, we should consider that maternal infection can affect the fetus and the pregnancy not only through direct placental infection but also through placental changes (ischemic or inflammatory) induced by SARS-COV-2 maternal response.

Congenital anomalies

Published studies have not found an increased risk of congenital abnormalities in the offspring of women with SARS-COV-2 infection during pregnancy.[22]

Stillbirth

Contrary to what was initially thought, recent studies suggest

an association between COVID-19 in pregnancy and stillbirth. In an analysis of over 1.2 million delivery hospitalizations with over 8000 stillbirths in the USA, *DeSisto et al.* concluded that having a COVID-19 diagnosis at the time of delivery was associated with a two-fold increased risk of stillbirth. The highest risk for stillbirth was during the Delta variant period and in women with COVID-19 and comorbidities.[31] Case series of stillbirth in women with COVID-19 during pregnancy reported fibrin deposition and trophoblast necrosis on placental pathology, however these studies have critical limitations.

CONCLUSIONS

In pregnant women with COVID-19 during pregnancy maternal complications are expect when these women have older age, obesity, preexisting medical comorbidities (hypertension, diabetes or more than one comorbidity) or unvaccinated women. These women have greater risk of severe COVID-19 disease and death.

Adverse pregnancy and fetal outcomes are expect when pregnant women with COVID-19 have symptoms, especially severe or critical disease, and when maternal infection occurs after 20 weeks of gestation, the exception is preeclampsia, both asymptomatic and symptomatic patients experienced an increased risk, with a higher risk among symptomatic patients.

Other adverse pregnancy outcomes include preterm labor and delivery, cesarean delivery and stillbirth.

The risk of severe illness and COVID-19 complications in pregnancy and the possibility of adverse pregnancy and fetal outcomes support vaccination in people planning pregnancy or in those who are pregnant or recently pregnant. Data from vaccinated pregnant women demonstrated safety and efficacy during pregnancy and lactation. In the studies carried out, vaccination was not associated with an increased risk of adverse obstetric or fetal outcomes.[32] Serious side effects (myocarditis, pericarditis, Guillain-Barré syndrome, thrombosis with thrombocytopenia syndrome) are rare and are similar in pregnant and nonpregnant women.[33] Recent studies have provided more robust evidence on the effect of vaccination on reducing maternal SARS-COV-2 infection, maternal COVID-19 severe and critical disease, perinatal death and COVID-19 hospitalization among infants up to six months of age.[34,35] So, maternal antibodies cross the placenta and are transferred into breast milk, conferring protection to the infant for at least six months. Furthermore, vaccination of pregnant women reduces serious maternal and pregnancy morbidity from infection. Currently, vaccination is recommended as early as possible in pregnancy, regardless of gestational age, and can be given simultaneously with other vaccines recommended in pregnancy (Tdpa, influenza).

Thus, since the beginning of the pandemic, much has been discovered about SARS-COV-2, COVID-19, COVID-19 in pregnancy and its impact on maternal, obstetric and fetal outcomes. However, more large-scale studies are needed to assess the impact of COVID-19 on obstetric and perinatal outcomes and to define the best surveillance protocol in women infected by SARS-COV-2 during pregnancy. Vaccination is the best method to reduce maternal and fetal complications of SARS-CoV-2 infection.

AUTHORSHIP

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