



BRIEF ORIGINAL

Does the maternal-fetal transmission of SARS-CoV-2 occur during pregnancy?☆



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Abstract

Background and objective: On January 7th, 2020, a new coronavirus, SARS-CoV-2, was identified, as responsible for a new human disease: COVID-19. Given its recent appearance, our current knowledge about the possible influence that this disease can exert on pregnancy is very limited. One of the unknowns to be solved is whether there is a vertical transmission of the infection during pregnancy.

Patients and methods: Using the Real-time Polymerase Chain Reaction techniques for SARS-CoV-2 nucleic acids, the possible presence of this germ in vaginal discharge and amniotic fluid was investigated in four pregnant Caucasian patients affected by mild acute symptoms of COVID-19 during the second trimester of pregnancy.

Results: There is no laboratory evidence to suggest a possible passage of SARS-CoV-2 from the infected mother to the amniotic fluid.

Conclusions: It is necessary to expand the investigation of COVID-19 cases diagnosed during pregnancy to clarify the real influence that SARS-CoV-2 has on pregnant women and their offspring, as well as those factors that modulate the disease.

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PALABRAS CLAVE

Coronavirus;
COVID-19;
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Embarazo;
Líquido amniótico;
Transmisión vertical

¿Existe transmisión materno-fetal del SARS-CoV-2 durante la gestación?

Resumen

Antecedentes y objetivo: El pasado 7 de enero de 2020 se identificó un nuevo coronavirus, el SARS-CoV-2, responsable de una nueva enfermedad en el humano: la COVID-19. Dada su reciente aparición, nuestro conocimiento actual sobre la posible influencia que esta enfermedad puede ejercer en el embarazo es muy limitado. Una de las incógnitas que hay que despejar es si existe transmisión vertical de la infección durante la gestación.

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Pacientes y métodos: Mediante técnicas de reacción en cadena de la polimerasa en tiempo real para ácidos nucleicos del SARS-CoV-2 se investigó la posible presencia de dicho germen en el flujo vaginal y el líquido amniótico de cuatro pacientes embarazadas de raza caucásica afectadas por cuadros agudos leves de COVID-19 durante el segundo trimestre de la gestación.

Resultados: No existen evidencias de laboratorio que sugieran un posible paso del SARS-CoV-2 desde la madre infectada al líquido amniótico.

Conclusiones: Es preciso ampliar la investigación de casos de COVID-19 diagnosticados durante la gestación para poder aclarar la influencia real que el SARS-CoV-2 ejerce sobre las embarazadas y su descendencia, así como aquellos factores que modulan la enfermedad.

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Introduction

On December 31st, 2019, the Wuhan Municipal Health Commission (Hubei Province, China) reported a cluster of 27 cases of pneumonia of unknown etiology with common exposure at a wholesale market. On January 7th, 2020, the novel coronavirus SARS-CoV-2 was identified as the causative agent of the outbreak. Through international consensus, the disease caused by this new virus was named COVID-19.

According to multiple observations on this new disease, it is estimated that its incubation period may range from 2 to 14 days, it mainly affects people between the ages of 30 and 79, and prolonged exposure to the virus is not necessary in order to contract it.¹ Eighty percent of cases present with mild symptoms, but up to 20% of people infected may experience more severe clinical manifestations. In the majority of these more severe cases, the patients have some type of underlying pathology.¹ The mortality rate ranges between 1% and 3%.¹

According to the data currently available, it does not appear that pregnant women are more susceptible to infection. In the event they do present with the disease, their respiratory complications are no more severe than those of the general population.²⁻⁴ In addition, in the few documented cases of COVID-19 disease in the peripartum period, no evidence has been found of intrauterine transmission of SARS-CoV-2.¹⁻⁴ Cases of neonatal SARS-CoV-2 infection have been described, with adverse effects on the newborn including respiratory distress, thrombocytopenia, abnormal liver function, and even death.^{5,6}

Although little data are available with respect to SARS-CoV-2 infection during pregnancy, previous experience with prenatal infection by other similar coronaviruses, such as SARS-CoV (Severe Acute Respiratory Syndrome) and MERS-CoV (Middle East Respiratory Syndrome), lead us to believe that mother-to-child transmission does not occur in SARS-CoV-2 during pregnancy.² With this case series, we intend to provide objective information in this regard.

Patients and methods

Using real-time polymerase chain reaction techniques for SARS-CoV-2 nucleic acids, the possible presence of this

microorganism in vaginal discharge and amniotic fluid was investigated in four pregnant Caucasian patients affected by mild acute symptoms of COVID-19. The targets for viral detection were the RdRP, S, and E genes.

All cases were pregnant women in the second trimester of pregnancy. They underwent amniocentesis for reasons other than COVID-19. At the time this invasive technique was performed, they had a confirmed active SARS-CoV-2 infection with associated mild symptoms.

Results

The main clinical data on the four cases studied are summarized in [Table 1](#).

The period of time from the first positive SARS-CoV-2 RT-PCR result in nasopharyngeal samples and the result in the cervical-vaginal and amniotic fluid samples in the four cases was five, seven, six, and twelve days, respectively.

There is no evidence to suggest possible transmission of SARS-CoV-2 from the infected mother to the amniotic fluid.

Clinical progress was favorable in all cases and none required hospitalization or pharmacological treatment apart from the administration of antipyretics and analgesics. Currently, between three and six weeks after the amniocentesis, the pregnant women are progressing normally, with continued positive SARS-CoV-2 PCR results in nasopharyngeal exudate in one case.

Discussion

The recent emergence of the COVID-19 disease means that our current knowledge about the possible implications during pregnancy is very limited.² The presence of angiotensin-converting enzyme-2 in placental cells has been described⁷, but according to the data available at present, there does not seem to be a greater risk of pregnancy loss, preeclampsia, or premature membrane rupture in pregnant women affected by COVID-19.^{8,9}

However, cases of premature birth associated with the disease have been described.^{2,3,9} The majority were secondary to the need to end the pregnancy early for the mother's well-being. One case of intrauterine growth retardation has also been reported. It occurred in a pregnant

Table 1 Summary of the main clinical and analytical variables in the cases studied.

	Maternal age (in years)–Gestational age (in weeks)	Reason for performing amniocentesis	Maternal blood test at the time of amniocentesis	Maternal blood test 14 days after amniocentesis	Result of the RT-PCR (SARS-CoV-2) of vaginal discharge	Result of the RT-PCR (SARS-CoV-2) in amniotic fluid
CASE 1	31 years–16 weeks	Suspected chromosomal disorder (according to screening test)	PCR +	PCR -	Negative	Negative
			Ig M – Ig G –	Ig M + Ig G +		
CASE 2	39 years–16 weeks	Suspected chromosomal disorder (according to screening test)	PCR +	PCR -	Negative	Negative
			Ig M – Ig G –	Ig M + Ig G +		
CASE 3	27 years–21 weeks	Suspected chromosomal disorder (due to fetal anomaly)	PCR +	PCR +	Negative	Negative
			Ig M + Ig G -	Ig M + Ig G +		
CASE 4	40 years–24 weeks	Suspected cytomegalovirus infection	PCR +	PCR –	Negative	Negative
			Ig M + Ig G +	Ig M + Ig G +		

woman affected by very severe systemic symptoms, which makes it difficult to determine if the pregnancy complication was secondary to the infection or to maternal deterioration itself.¹⁰

Before SARS-CoV-2, six other species of coronavirus that are able to cause infections in humans had been described: HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, MERS-CoV, and SARS-CoV. The most well-known of these coronaviruses in terms of their interaction with pregnancy are SARS and MERS. Both have significant structural similarities to SARS-CoV-2. Therefore, previous experience with these species can be considered as potentially predictive of the perinatal behavior of this novel coronavirus.²

Based on observational studies on SARS and MERS, a clear association has been able to be established between maternal coronavirus infection and onset of complications,² including severe maternal disease, intrauterine growth retardation, premature birth, spontaneous miscarriage, greater rate of neonatal hospitalization in intensive care units (ICU), and maternal and neonatal death. All of these perinatal complications seem to be secondary to postpartum infection and in contrast to what occurs in other viruses such as Zika and Ebola, the maternal-fetal transmission rate of coronaviruses is presumed to be very low. In fact, no incontrovertible cases of vertical transmission have been documented to date.^{2,3,8–10}

Various suspected cases of vertical SARS-CoV-2 transmission have been described based on nasopharyngeal isolations of the virus in the period immediately following birth as well as the presence of IgM in neonatal blood in the first hours of life.⁴ Both pieces of evidence are doubtful indicators of vertical infection for the following reasons:

1. Isolation of the virus in a neonate during the post-partum period, however soon after delivery it may be, does not allow for horizontal transmission to be ruled out.
2. Although IgM does not cross the placenta, tests to identify it have a high rate of false positives.^{3,6,8,10}

On the other hand, a negative result found using even the most sensitive techniques does not allow possibility of infection to be ruled out.^{3,6,8,10} Evidently, the best evidence of intrauterine transmission of SARS-CoV-2 would be confirmation of its presence and replication in fetal lung tissue, but this is technically inviable. Therefore, isolation of the virus in the placenta, amniotic fluid, and umbilical cord blood are considered indirect yet reliable indicators of congenital transmission, provided that these samples are extracted during the pregnancy or immediately after birth, so long as the sample has been taken in strict aseptic conditions that limit risk of contamination.

Although more than a hundred cases of COVID-19 during pregnancy have been reported in the literature to date, the majority have occurred in the third trimester, very near the birth. The main limitation of these experiences is that not all possible pathways of neonatal infection apart from the known respiratory and contact routes have been considered; these possible pathways include transplacental transmission, ascending transmission, through the birth canal, and through breastfeeding.

The main contribution of our series is the evaluation of possible vertical transmission of SARS-CoV-2 during the second trimester of pregnancy. Up until now, this aspect has been unknown, as there is no clinical justification

for performing invasive prenatal diagnosis techniques for intrauterine coronavirus infection.

Despite the fact that the sample size studied is very limited and only includes patients with mild COVID-19 symptoms, as of now there is no evidence of vertical transmission of SARS-CoV-2 in the second trimester of pregnancy. Based on our data and on previous experiences, it can be assumed that if vertical transmission of coronavirus exists, it must be infrequent. Therefore, it is not foreseeable that congenital defects associated with it may occur. In any case, the real influence of SARS-CoV-2 on pregnant women and their offspring as well as factors that modulate the disease will only be clarified with time and rigorous observation of cases.

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