# Fetus as a patient in pregnant women with COVID-19

## Feto como paciente en gestantes con COVID-19

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**SUMMARY**

**Introduction:** *Fetus and placenta are an immunologically privileged unit, whose physiological changes during pregnancy intervenes in the behavior against SARS-CoV- 2, describing a theoretical potential teratogenic damage due to receptors ACE-2 expression, necessary for SARS-CoV-2 intracellular transport in the epiblast, vital in organogenesis, as well as the current pharmacological therapy teratogenic effects, abortions, and fetal demise. Early Chinese reports pointed to the unlikely vertical transmission, however, the diagnostic test's low sensibility with the serological detection in fetal and neonatal blood samples of IgM Anti- E SARS-CoV-2 and IL-6 caused great controversy.* **Purpose of the study:** *To resume current data about fetal risks (real or potential) from a viral agent, pharmacological therapy, or placental damage from a worldwide literature data review.* **Methods:** *Articles in all languages about the SARS-CoV-2 infection in pregnant women and fetuses as a patient searched from LILACS, PUBMED, and Google Scholar from March 2020 to February 2021 were review.* **Conclusion:** *A year later, it is seen that the placental damage is maternal and fetal vascular bad perfusion, like preeclampsia and chorioamnionitis, endothelitis, thrombosis, and inflammation, reconsidering fetal surveillance in COVID-19 pregnant women.*

**Keywords:** *Fetus, placenta, COVID- 19.*

**RESUMEN**

**Introducción:** *El feto y la placenta son una unidad inmunológicamente privilegiada, cuyos cambios fisiológicos durante el embarazo intervienen en el comportamiento frente al SARS-CoV-2, describiendo un daño teratogénico potencial teratogénico debido a la expresión de los receptores ACE-2, necesaria para el transporte intracelular del SARS-CoV-2 en el epiblasto, vital en la organogénesis, así como la*

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*terapia farmacológica actual, efectos teratogénicos, abortos y muerte fetal. Los primeros informes chinos apuntaron a la transmisión vertical poco probable, sin embargo, las pruebas de diagnóstico de baja sensibilidad con la detección serológica en muestras de sangre fetal y neonatal de IgM Anti-E SARS-CoV-2 e IL-6 causaron gran controversia.* **Objetivo:** *Resumir los riesgos fetales (reales o potenciales) por causa del agente viral, la terapia farmacológica o el daño placentario a partir de una revisión de datos de la literatura mundial.* **Métodos:** *Fueron seleccionados artículos en todos los idiomas sobre la infección por SARS-CoV-2 en mujeres embarazadas y fetos como paciente, en una revisión de base de datos LILACS, PUBMED y Google Scholar de marzo de 2020 a febrero de 2021.* **Conclusión:** *Un año después, se reporta que el daño placentario es mala perfusión vascular materna y fetal, como preeclampsia y corioamnionitis, endotelitis, trombosis e inflamación, reconsiderando la vigilancia fetal en gestantes COVID-19.*

**Palabras clave:** *Feto, placenta, COVID-19.*

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), a new zoonosis which etiologic agent, the coronavirus type 2, causal of the severe acute respiratory syndrome (SARS-CoV-2), represents an emergency in the global public health declared pandemic on 11 March 2020. Since its first description at the end of 2019, the SARS-CoV-2 has globally spread. In the mid - May 2020, more than 4.5 million people had been globally infected with over 300000 deaths (1). Is more than clear that the SARS-CoV-2 has relatively infected both men and women in almost the same proportion (2). However, numerous women during the pregnancy have been infected with SARS-CoV-2 and from the beginning of the pandemic to the present, the knowledge regarding possible effects of the virus and the pharmacologic therapy used on pregnancy have changed, as well as the knowledge regarding the "respiratory" behavior of this virus which has taken by surprise all the health providers because its particular behavior, where not only the lungs are a target organ, causing series of extrapulmonary manifestations such as cardiac, renal, hepatic, digestive, and neurological disorders, apart from the classical respiratory symptoms, inferring that the placenta and the fetus are not an exception (3).

The members of the coronavirus family are known for being responsible for severe complications during the pregnancy such as abortions, restricted fetal growth, and congenital anomalies (4). Only some scarce studies have reported relatively high adverse perinatal results in pregnant women affected by SARS-CoV-2 in the late stages of the pregnancy (4). The role of the human placenta, which has an immunologic barrier against the entrance of pathogens, besides maintaining the immunological tolerance to the fetal cells, is theoretically proposed as a fetal and neonatal protection mechanism against the SARS-CoV-2 (5). Considering the possible adverse effect of the SARS-CoV-2 as a causal agent, the risks of the anti- COVID-19 pharmacotherapy and the possible placental damage over the fetus as a patient in the pregnant women during the different trimesters are reviewed, based on the evolution of the theories and evidence during this year of pandemic, in order as a purpose of the study to provide current data about fetal risks (real or potential) from a viral agent, pharmacological therapy or placental damage from a worldwide literature data review from LILACS, PUBMED and Google Scholar from March 2020 to February 2021 including articles in all languages, case reports, updates, and protocols of major health organizations.

### Adverse effect by etiological agent

In analogy with the severe acute respiratory syndrome (SARS, by its acronym in English) and the Middle East respiratory syndrome (MERS), during the beginning of the pandemic, it was considered that the infection by SARS-CoV-2 during the conception of the early pregnancy represented a higher risk of presenting neurological development defects in the fetus (6), the scientific evidence shows that the causal agent of COVID-19, the SARS-CoV-2, could pass both placental barriers (viral IgM detected in newborns hours after the birth) (7) and the hemato-encephalic barrier (virus detected in the cerebrospinal fluid) (8).

As the virus can enter the placenta and theoretically to the nervous system, the virus was considered by itself able to provoke some adverse effects over the pathogenesis of the neural tube defects in pregnant women with COVID-19.

Also, it was proposed that the coronavirus, SARS-CoV-2, shall have teratogenic potential, using as cellular entrance the angiotensin-converting 2 enzyme (ACE2) receptor and the proteases S expressed on the developing embryo. Particularly, the ACE2 receptors and S proteases are expressed on the early gametes, zygotes, and embryos of 4 cells (9). Therefore, the direct infection transmission of the blastocyst cells by SARS-CoV-2 was considered possible but has not been confirmed so far. In the developing embryo, is crucial the health of these cells in the epiblast, as the organogenesis is derived from these cells.

Any functional alteration of the early embryonic cells by the viral infection can lead to defects or anomalies. Another teratogenic effect attributed to this new pathogen is the vascular disruption processes by hyperthermia and hypoxia within the maternal clinical symptoms. It was considered that a higher risk of developing congenital defects existed if the infection by SARS-CoV-2 occurred during the early stages of the pregnancy, is included within the national protocols the extreme surveillance before the possible occurrence of neural tube defects through the early and detailed neurosonography in the first and second quarter (6). Nevertheless, until this date it has not been associated with an increase in neural tube defects; actually, the severity of the pandemic of COVID-19 has interrupted the normal advice to the patient process, recompilation of cases, and data processing. Therefore, as there is not knowledge unknown about the COVID-19 and the complications of the neurologic development, there is an urgent need for continuous data gathering regarding the clinical cases of infection by COVID-19 in pregnancy, especially during the first quarter or beginning of the second trimester to improve our comprehension about the role of the COVID-19 over the neural tube defects (10).

## Adverse effect by pharmacologic therapy

The use of antiviral drugs for the treatment of COVID-19 in pregnant women can have adverse results as spontaneous abortion, restriction of fetal growth, structural and congenital anomalies, including neural tube defects (10).

Although no effective drug product for SARS-CoV-2 has been developed. The compassionate use of some antiviral drugs and anti-inflammatory agents developed for other infections and viral pathologies, area widely used in patients with COVID-19 at a global level. Many of these drug products have been used for COVID-19 without the submission of the proper safety and efficacy tests, as we are facing a severe pandemic. The use of hydroxychloroquine is a controversial subject, as it has been reported that this medicament causes many complications, including death. Even though chloroquine is classified as a class C drug by the Food and Drug Administration (FDA) of US for the pregnancy, this medicament now less used due to the evidence in the protocol SOLIDARIDAD of the world health organization (11), it was widely used until the last quarter of the last year for the treatment of COVID-19 at a global level.

Similarly, medicaments as favipiravir, a medicament developed for the treatment of the disease by the Influenza virus; remdesivir for the treatment of the disease by the Ebola virus; dolutegravir / lamivudina / tenofovir for the treatment of the human immunodeficiency virus (VIH), has been globally used for the treatment of COVID-19 base on its availability. In fact, the FDA of the US has granted emergency licenses and approval to some of these medicaments. As the effects of such medicaments have not been proven during pregnancy, especially during the first quarter, there is an increasing fear suggesting that the antiviral medicaments can cause adverse results in the fetus.

Favipiravir is contraindicated in women that could be, or are pregnant, due to its association with defects at birth (12); however, this medicament is now being widely used for treating COVID-19 in about 40 countries with the aid of the Japanese government, and in several developing countries including Bangladesh, as a test drug received from its source. The drug product has not been recommended by the FDA of the US or the Japanese Agent of Pharmaceutical Product and Medical Devices (PMDA); however, the availability of the product and the possible effects for COVID-19 has turned it into the drug of choice. Dolutegravir, effective antiretroviral therapy for the treatment of AIDS is a promising choice in the countries of low and medium-income, is also used for the treatment

of COVID-19.

Nevertheless, recent findings show that dolutegravir increases the number of neural tube defects; the prevalence of neural tube defects is 3 times higher with dolutegravir (13). Also, it has been reported an incidence structural anomaly in 9 by 1000 births if this drug product is used during pregnancy, and other described therapies include immunomodulators as tocilizumab, an interleukin 6 (IL-6) antagonist, that should not be used during pregnancy, unless completely necessary, the women of reproductive potential must use effective contraceptive methods during, and up to 3 months after the treatment (13).

Nowadays and altogether, the velocity of design and start of clinical trials for the evaluation of possible COVID-19 therapies is impressive. Even so, the evidence of the effects of the virus and the management strategy in the pregnant woman is missing, particularly in those in the early pregnancy stages. Now, in the middle of a pandemic predicted to last at least one or more years, the abstinence of pregnancy is not a practical option. Rather, it is necessary to verify the state of pregnancy of the patients with COVID-19 regarding adverse results. Also, the use of antiviral medicaments must be regulated until its potential safety and efficacy are determined through a randomized clinical trial.

**Adverse effect by placental damage**

The histological characteristics of the infected by SARS-CoV-2 placenta are not well defined until now, although some consistent histopathology anomalies have been observed. It could be said that the chronic changes related to poor maternal vascular perfusion (MVM) and poor fatal vascular perfusions (FVM), such as infarction, distal villous hypoplasia, and chorangiosis, require time to evolve and may not be manifested on acute COVID-19 infected placentas. A higher recollection of data may be needed to compare the histological manifestations of infected and non-infected by COVID-19 placentas at different infection phases to conclude the importance of the histomorphological changes related to SARS-CoV-2 in placentas.

Some suggested that the inactivation / low regulation of ACE2 occurs through the formation of the viral-ACE2 complex after the placental infection by SARS-CoV-2 which causes a decrease of the angiotensin plasmatic levels (17-23), that in return promotes the vasoconstriction and the pro- coagulopathy state, which leads to severe preeclampsia of early-onset (24). The increased IL-6 and TNF-α levels induce endothelial dysfunction, a characteristic of preeclampsia, predisposing to a maternal thromboembolic event (25).

The fetal inflammatory response (FIRS), as is shown by the increase of the IL-6 after the COVID-19 (26) maternal infection, can be responsible for a broad range of future adverse sequels of neurodevelopment including autism, psychosis, and neurosensorial deficits (27), like determining bacterial infections (28). However, longitudinal long–term studies are required for the validation of these associations. Apart from the transmissibility of the virus, the studies *in silico* suggest that the placental function can be modulated by the SARS-CoV-2 through different proteins of ACE2 y TMPRSS2, as those participating in the invasion and migration of trophoblast, syncytium, and implantation (29). It is to be determined how these other proteins are correlated with the placental morphology so far described in the cases of COVID-19 and the results of the pregnancy.

In conclusion, the accumulated published data about the placenta with infection by COVID-19 showed common histological characteristics that include MVM, inflammation and FVM, endothelitis, thrombosis, and inflammation. The risks of perinatal adverse results and at long – term of the COVID-19 infection include spontaneous abortion, fetal death and fetal growth restriction, preeclampsia of early-onset, FIRS, and neurosensorial development delay. A well-designed study of a prospective cohort in a higher population number with a complete placental test that adopts an approach of standardized diagnosis is required to facilitate the current comprehension of the impact of SARS-CoV-2 in the placenta and how it influences the results of the pregnancy. A causal relationship between the maternal infection by SARS-CoV-2 and the placental pathology/pregnancy results is essential to lead (and warrant) optimum maternal care in the challenging period of a global pandemic.

**Antenatal fetal surveillance**

In a pandemic context, the SARS-CoV2 / COVID-19 effect over the fetus remains uncertain, based on the scarce evidence and case reports of MERS and SARS-CoV1 coronavirus. It is not demonstrated a convincing or statistically significant relation between the infection and the increase of malformations and gestation loss in the follow up from the year 2002/ 2003 to the present. To this date, there is no evidence of vertical transmission and intra – uterus infection by COVID-19, it is hypothetically considered unlikely that congenital alterations exist because of the virus in the fetal development; nevertheless, in the actual– going pandemic, son national consensus propose a guideline for the evaluation that includes genetic ultrasound in the first trimester between the 11-13+6 weeks with doppler ultrasonography of uterine arteries assessment (6), clarify that the incidence of abortions has not a significantly higher incidence in the general population (3), leaving behind the premise of a higher risk of abortion, with no association with and increment of aneuploidy, not linked to an increase of malformations.

For the second and third trimester is proposed a maternal-fetal hemodynamic doppler profile according to the model of follow-up by fetal growth restriction ultrasound, exclusion of uteroplacental impairment and oligohydramnios; adding in the third trimester the fetal monitoring, biophysical profile, and evaluation by ultrasonography of the fetal neurodevelopment.

## CONCLUSION

It was initially described potential theoretical damage because of the expression of ECA-2 receptors needed for the intracellular transportation of the SARS-CoV-2 in the embryonic epiblast, vital for the organogenesis, resulting in a hypothetical high risk of neural tube defects as well as abortions, fetal loss influenced by the vascular disruption and hypoxia, maternal hyperthermia, desaturation and hypoxia described in the nosological clinical symptoms and the potential teratogenic damage from the described pharmacological therapy.

The vertical transmission unlikely, not impossible requires an unequivocal diagnosis of the trans-placental infection by SARS-CoV-2 the detection of viral RNA in the placenta, amniotic fluid, before the beginning of the labor, blood sample/corporal fluid / respiratory of cord / neonatal, or the demonstration of viral particles by electronic microscopy, immunohistochemistry or *in situ* hybridization method of fetal/placental tissues.

There is still no confirmation of the usefulness of serologic tests in the diagnosis of the SARS-CoV-2 infection. Is questionable the specificity of the IgM tests due to the high false positivity.

At present, it is in sight that the placental damages are severe of maternal-fetal poor perfusion type similar to preeclampsia, and similar to chorioamnionitis, with scarce reports of neural tube defects and ruling out the increase of stillbirth by the causality of the etiological agent, more likely representing a consequence of the quarantine and the difficult access to health centers.

Fetal surveillance in COVID-19 pregnant woman must consider the fact of the fetus is submitted to the potential damage by the virus *per se*, by the pharmacologic therapy, and adding the new component of endothelitis, thrombosis, and inflammation.

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