

1 Introduction

When COVID-19 developed as a global pandemic, individuals who work at the healthcare system made the effort to cooperate and comprehend more about the disease, how the virus is spread and the impact it can cause on the health system around the world. Therefore, knowing the impact that might happen, this article has the objective of studying the uncertainties about the SARS-CoV-2 infection through maternal-fetal binomial. Currently, it is known that SARS-CoV-2 might represent further risks to women and their babies, besides the possible change of vertical transmission. Finally, it is essential to highlight the importance of updating the studies day by day in order to better understand the impact the virus can have on a pregnancy scenario.

COVID-19 is a respiratory tract infection caused by an emerging coronavirus, named SARSCoV-2, which was first identified in Wuhan, China, in December of 2019 (1). The wide dissemination of COVID-19 and the small spread of newspapers and knowledge about the SARS-COV-2's impact during gestation has been causing insecurity to physicians, managers and pregnant women or the ones who wish to have a baby.

The physiological state of pregnancy tends to make expectant mothers more susceptible to certain viral infections (2). In the initial studies, there were no evidences that pregnant women would be more susceptible to develop serious symptoms (3). However, after recent publications, one observed that the pregnancy and the post-partum period might be a moment with some additional risks to the moms and to the kids (4).

It is known that there is some data about a bigger occurrence of natural abortion, congenital anomalies, fetal growth restriction, premature birth, and perinatal complications when COVID-19 happens during the first, second or third trimester of the pregnancy. There are also concerns regarding the potential effect on the fetus and on the neonate, being also essential to know if it is possible to transmit SARS-COV-2 through breast milk to clear up doubts about breastfeeding with infected mothers. Thus, the present work aims to clarify doubts about the impact of SARSCoV-2 on the maternal-fetal binomial, based on a review and description of six case reports published in articles in PubMed, Scopus and Embase.

2 Objectives

This study aims to assemble a bibliographic revision regarding the impact of SARS-COV-2 in the maternal-fetal binominal.

3 Method

This study constitutes a bibliographic revision of analytic nature, developed mainly on the PubMed, Scopus and EMBASE's databases. The period in which the research was developed was from the 19th of March to the 12th of September of 2020. Keywords such as "coronavirus", "COVID-19" and "pregnancy" were used.

One used they key words "CORONAVIRUS, "COVID-19" and "PREGNANCY" on the PubMed platform. The used approaches were: free full text, clinical trial, meta-analysis, randomized controlled trial and Systematic Review.

The inclusion's criteria contemplated original articles, available completely for free online, in English, Spanish and Portuguese. The studies in which the maternal-fetal binominal were not analyzed or studies of review of cases that will be presented, were excluded.

Reports of primary cases have been identified, series of cases, randomized clinical trial and bibliographic revisions which contained the objective of describing women of numerous age groups affected by SARS-CoV-2 during the gestation or the postnatal period.

The articles' references for relevant studies were carefully selected. The obtained data included maternal results, tests of maternal diagnosis, maternal images, fetal results, perinatal results, neonatal results, tests of neonatal diagnosis and demographic data.

Data of studies reporting the incidence of these results during the gestations infected by SARSCoV-2 were considered eligible for analysis. Since it deals with a new infection which can occur during pregnancy, some data was collected from studies with a few samples, cases reports and series of cases were included as well.

Studies claiming cases of infectious pneumonia or other respiratory disorders during pregnancy caused by other viral agents were excluded, as well as studies of pediatric series in newborns and children of maternal age and pregnancy were not used.

Two authors reviewed all the summaries independently. The agreement regarding the relevance or potential inconsistencies was reached through a dual agreement, discussing with a third

reviewer, afterwards. Copies of complete texts of the applicable articles were obtained, and the same reviewers extracted relevant data about the characteristics of the study and the result of pregnancy, in an independent approach.

4 Results

The electronic search on the PubMed platform resulted in the identification of 35 articles using special approaches, 56 articles that were based on electronic research and other databases such as Scopus and EMBASE's were also found. The articles' abstracts were previously read and subsequently one made a more objective selection on the main topics of this article. According to the most in-depth analyses of the content, 5 articles were discussed separately, in which there are reports or series of cases where COVID-19 was examined in the binominal maternal-fetal.

All of these 5 studies were mainly related to the impact of the new coronavirus during pregnancy and the repercussions on newborns. The characteristics of these studies were summarized in table number 1. The other articles used as a basis for the discussion discuss the impact of SARS CoV 2 on human reproduction in its entirety.

The search on the PUBMED's database resulted on the identification of 68 articles. Other 37 articles based on electronic research and other bases were also found. According to the objective analysis of the articles' content, 5 studies were discussed separately, in which there are reports or series of cases that examined COVID-19 in the maternal-fetal binominal. However, some articles that were not described, were used as support to the discussion to comprehend some aspects of the infection that impact the human reproduction in general.

5 Discussion

Initially, the researches regarding SARS-CoV 2's presence in semen samples were negative (5). However, a study that was done to 38 patients, positive to COVID-19, detected the presence of the virus in 6 patients' semen. In this cross-sectional study, it was clarified that SARS-CoV-2 might be present in the patients' semen, and it can also be detected in the semen of those patients who are going through recovery. The reason for that might be the imperfections in the blood, deferent and epididymis barriers, especially if there is systemically local inflammation. (6)

The main symptoms of this disease are related to the respiratory tract, such as cough, sore throat, breathing difficulty, fever and some atypical found on the pulmonary image examination. In some dramatic cases, one might develop respiratory distress syndrome (7).

During a study, a survey was made with 9 pregnant women, in comparison with another group of 9 expectant women already described on the literature. Both studies report that the clinical characteristics of the pregnant women with pneumonia due to COVID-19 were similar to those adult patients who were not pregnant and developed pneumonia because of COVID-19 (2).

A recent study, although limited, reports the occurrence of a case's trans-placental transmission of SARS CoV 2. The virus' presence was responsible for, besides maternal viraemia, placental infection and neonatal viraemia after the placenta's infection, detected through nasopharyngeal and rectal swab test in the baby, within 1 hour of life and repeated at days 3 and 18 of life. The amniotic fluid, collected before the membranes' rupture also tested positive for the genes E e S of SARS CoV 2. The viral load found in the placental tissue was much higher than in the amniotic fluid and in the maternal blood or neonatal. Regarding the histological examination, the placenta had diffuse rates of perversus fibrosis with infarction and serious villitis. (8)

The research on breast milk samples from mothers after the first lactation was tested negative to SARS-CoV-2. Considering the benefits of breastfeeding and the insignificant role of maternal milk in the transmission of other respiratory viruses, the puerperal women can breastfeed if allowed by clinical conditions (1).

Liu and associates (9) reviewed the clinical data and examinations of 15 pregnant women with non-serious pneumonia by COVID-19 at the admission moment at the hospital (Table 1). The maternal age range varied from 23 to 40 years old and the gestational age from 12 to 38 weeks. Among the pregnant women, 13 had a fever and 9 had a cough. After the treatment, 14 out of the 15 pregnant women had RT-PCR to SARS-CoV-2, with total remission of symptoms. The most common findings on the chest CT (computed tomography) scan have been ground-glass opacities. At the end of the study, 10 pregnant women had C-sections and one had vaginal delivery. There were neither asphyxia nor death cases. The Apgar scores at the 1st and 5th minute were normal during all neonates. It was not possible to find by SARS-CoV-2 on the neonates; in this study, the pregnancy and the birth seemed not to worsen the severity of the pneumonia due to COVID-19.

Chen and associate's (10) study present 9 patients with COVID-19, between 26 and 40 years old (Table 1). The gestational age at the admission varied between 36 and 39 weeks and 4 days. None of the patients had subjacent comorbid conditions. 1 patient, however, developed gestational hypertension at the 27th week, while another one developed pre-eclampsia with 31

weeks of gestation. Furthermore, 1 patient had influenza virus infection during admission at the hospital.

None of the 9 patients developed serious pneumonia or died due to COVID-19. The complications that appeared after the beginning of infection by COVID-19 included fetal suffering (with two patients) and the premature rupture of the membrane (two patients). All of them had breathing machinery support done by nasal prongs and medical treatment, as well.

The 9 babies were born through C-section, due to the uncertainty about the risk of transmission through intrapartum from mother to kid by vaginal birth, with Apgar score at the 1st minute was 8-9 and 9-10 at the 5th minute. There was no fetal death, asphyxia or neonatal death described. 4 patients had preterm labor, but the causes were not related to pneumonia because of COVID-19. 2 out of the 4 newborn premature babies with 36 gestational weeks weighed <2500g when they were born. A newborn weighed 1880g. This growth restriction of the fetal intrauterine is more probable to be a symptom related to pre-eclampsia's, which was developed during the pregnancy. A newborn weighed 2460g. Another newborn had a high improvement in cardiac enzymes at the day of birth, but without clinical symptoms.

Throughout this study, all the collected amniotic fluid samples, umbilical cord blood, neonatal throat swab and collected breast milk from 6 patients were tested negative to SARS-CoV-2. Up to the present moment, there were not evidences that the pneumonia development due to COVID-19 during the third trimester of pregnancy can lead to serious results on neonates and fetal infections that can be caused by intrauterine vertical transmission.

The first studies during the pandemic led to an intense divulgation that there were not evidences that the obstetric population had a bigger risk of developing serious symptoms because of the disease; however, this plot seems to be changed. A systematic revision's study of 108 pregnant women showed the possibility of serious maternal morbidity related to COVID-19 (11). There needs to be some greater estimation about the risk of the disease's seriousness during pregnancy and how much impact the disease has on the maternal morbimortality. Nonetheless, as the infections caused by coronavirus might entail serious pulmonary infections, the morbidity and mortality raise among expectant women is biologically reasonable because of the immunological alterations and respiratory adaptation of pregnancy.

On the Lang and associate's study (12), a primiparous woman of 34 weeks of gestation was hospitalized for being suspicious of having COVID-19, which developed into breathing difficulties (Table 1). The RT-PCR in the nasopharyngeal swab was tested positive but in

vaginal secretions, it tested negative. The patient was hospitalized and treated with oxygen. A C-section was done to a newborn with 3120 grams and the Apgar score was 9 in the 1st minute and 10 in the 5th minute. This report's limitations include the unique case that no PCR test of amniotic fluid or placentas have been done.

Two hours after the birth, the newborn presented elevated levels of antibodies IgG to SARSCoV 2 and abnormal results on the cytokine tests. Five RT-PCR tests were performed on nasopharyngeal swabs from newborns that were negative.

The elevated level of antibodies IgM found on the newborn suggests that the infection occurred in the uterus, since the antibodies IgM are not transferred to the fetus through the placenta. What could explain this fact is that the baby was exposed for 23 days, since the moment of the diagnosis of the mom to COVID-19 until the birth. The laboratorial results showed inflammation and liver damage, which indirectly support the possibility of vertical transmission. Although the infection at the birth moment cannot be dismissed, the antibodies IgM generally do not appear until 3 to 7 days after the infection. The antibodies IgG can pass through the placenta and appear after the IgM. Therefore, the high level of IgG can reflect maternal infection or infantile.

Rasha Khory and associates' study (13) tested 241 pregnant women who were positive for COVID-19, with an average of 32 years old (Table 1). Among them, 64 were in the criteria of non-serious COVID-19, 63 had a serious case and 12 got to the critic stage when they were hospitalized for the birth. The alterations that were found in the laboratorial sum and vital signs were consistent to those of non-pregnant women, as well as the raise of fever cases, decrease in the oxygen saturation, high liver function tests, high C reactive protein, low procalcitonin and thrombocytopenia. The only variable that was associated to the seriousness of the COVID-19 disease was the BMI being at a higher number than 30 during the research.

In this study, the existing tendency and statistically significant tendency between groups of greater severity for COVID-19 and increased risk of prematurity was observed. Among the 12 women with the critical COVID-19, 5 had a full-term birth, 7 were born premature with less than 37 weeks of gestation and 3 were born premature with less than 34 weeks of gestation. Overall, the rate of single premature births in this cohort was 14.6%.

The most common complications of newborns were due to prematurity or low birth weight. Of the 245 live births, 30% received some form of resuscitation in addition to the standard

measures in the delivery room and 25.7% were admitted to the NICU. Most NBs were hospitalized for less than 2 days.

Among the pregnant women, two had intrauterine fetal death at the hospitalization moment. One of them, with 38 weeks of gestation, had decreased fetal movement, symptoms of COVID-19 and consistent image examinations which tested pneumonia due to COVID-19. The usage of an oxygen support was not necessary and she gave a vaginal birth to a male stillborn fetus. The patient refused the autopsy, pathology, genetics and tests of SARS-CoV-2 in the fetus. The placenta's pathology was normal. The second stillborn had 29 weeks of gestation in a context of fetal growth restriction (less than the first one) and hemolysis, high rate of liver enzymes and HELLP syndrome with serious COVID-19 pneumonia.

The severity's effects regarding COVID-19 in pregnant women were evident in this study, because there is a bigger number of C-sections with women with serious and critic COVID-19 cases and also a higher rate of premature births amongst women with a critic stage of COVID-19. The known respiratory complications which are associated to the infection with serious and critic cases led them to a higher number of maternal ICU, hospitalizations and C-sections and premature ones.

Another observed association in this study was between the seriousness of the disease and the BMI, type of birth and pregnancy duration. Like one can observe in the general population, pregnant women with a BMI that's higher than 30 must be considered to be a group with greater risk to serious and critic COVID-19 cases.

Throughout her study, Erika M. Lokken and associates (14) also related the connection between obesity and a higher risk of premature birth. 46 expectant women were evaluated, among them, 3 asymptomatic at the beginning of hospitalization and the other ones had a cough, fever or shiver, nasal congestion and shortness of breath (Table 1). The taste or the smell loss was felt by 13 among them. The average time for the symptoms to vanish lasted 24 days. In this study, the average age of the pregnant women was around 29 years old, 27 among them were overweight or obese and 12 had some additional comorbidity. During the study, 8 patients gave birth, with 7 of them being alive and one stillborn. In the case of the stillborn, the examination which was done after the death in the placenta showed serious villitis, but with no viral inclusions. The qualitative PCR test on placental tissue and fetal were tested negative to SARS-CoV-2 and cytomegalovirus. In one case, the seriousness of the breathing state and multiple

comorbidities, such as level II obesity, led them to have the birth procedures prematurely with 33 weeks of pregnancy.

According to these maternal and fetus evaluations, one concluded that pregnant women with health problems such as obesity, may be at higher risk of severe COVID-19 and premature birth with medical indication to improve lung function. However, this intervention is a maternal-fetal dilemma, as it benefits the mother in improving lung function but can lead to the newborn's morbidity or mortality. The rate of premature births with medical indication is an important feature that contributes to the vulnerability of pregnant women to COVID-19.

Data from Maira Takemoto and associate's study (4) held in Brazil, has shown that, up to the research's publication moment, COVID-19 caused a total of 124 deaths of expectant women in Brazil. The death rate of the Brazilian pregnant population was 12,7, which is almost 3,4 times higher than the maternal death rate because of COVID-19 in the world, until this moment. The explanation to such alarming factors is due to the obstetrical assistance in the country that is problematic and that can affect the maternal and perinatal results, such as low quality prenatal assistance, insufficient resources to manage serious and emergency care, racial disparities when accessing the maternal services, obstetric violence and the pandemic itself represents additional barriers to health care access.

6 Concluding Remarks

Initially, studies reported that the obstetric population seemed to have susceptibility, infectiousness and similar seriousness to what was observed in the non-pregnant population. However, the pandemic scenario, with an emerging disease, is dynamic and requires researches and upload at all time, therefore, it is known that COVID-19 has a potential risk of causing serious symptoms to vulnerable populations, such as the pregnant ones.

The way the host cell acts is mainly mediated by the receptor ACE2. The presence of this receptor in the placenta was always an alert sign to the risk of vertical transmission. Currently, there are reports of this possible transmission, with identification of the genes E and S of SARS-CoV 2 in placental and amniotic samples, related to neonatal neurologic symptoms. The placenta presented traces of acute and chronically serious inflammation with a systematic maternal inflammatory state caused by SARS-CoV-2. It is important to highlight that there needs to be bigger evidences in this area and clarification, however, prevention measures must always be done.

SARS-CoV 2 detection in the semen of some patients elicited new discussions regarding the impact of the disease in sexual relations. The exact mode of how the virus reaches the testicle is still unknown, but it probably relates to the inflammatory state that generates failings in the blood, deferent and epididymis barriers. Despite what has been found so far proves that this viral infection is not sexually transmitted, additional studies should be done to make sure of this conclusion.

Although there is a small number of expectant women included in the available research, the achieved results on these studies allowed comprehending that SARS-COV 2 is not found in vaginal fluid. Thus, the evidences suggest that the sexual transmission through vaginal secretion, like the intrapartum transmission, given by the contact with such secretions, does not happen.

This point needs attention, although most of the pregnant women have a good puerperium evolution. A few asymptomatic pregnant women, who got better and discharged, needed to head back to the hospital because of a severe case six days after the birth. It has to do only to the natural evolution of the disease, once most of these women interrupted the pregnancy when the case started being severe or it might be due to physiological alterations during this period.

The indication of C-section in the studies seems to be influenced by the uncertainties regarding a new virus and the pressure of the pandemic rather than the disease itself. There is no information about teratogenicity yet or the effects in the fetal development. There was little repercussion regarding the relation between newborns and SARS-CoV 2. As until now there is no scientific evidence of transmission through breast milk, it is recommended that the practice be maintained in case of infection by SARS-CoV 2, since it is done with various precautions that could reduce the risk of baby contamination.

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