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Clinical and laboratory manifestations of the new coronavirus (COVID-19) in pregnant women and analysis of the possible risk of vertical intrauterine transmission: a systematic review

Manifestações clínicas e laboratoriais do novo coronavírus (COVID-19) em gestantes e análise do possível risco de transmissão vertical intrauterina: uma revisão sistemática

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ABSTRACT: The pandemic numbers of the new coronavirus have surpassed the other members of the *Coronaviridae* family, accumulating until today, more than 24 million cases of the disease. The knowledge acquired by previous outbreaks suggests that pregnant women and their fetuses are more susceptible to poor prognosis. The purpose of this review is to verify the manifestations of the SARS-CoV-2 infection in pregnant women and the risk of vertical transmission. The review includes manuscripts that, together, presented data from 205 pregnant women and 76 neonates. Among the results, the symptoms presented by pregnant women were the same as non-pregnant patients. The same was true for laboratory alterations, such as lymphopenia and ground-glass opacity on computed tomography. In total, 163 cesarean sections were performed due to impaired respiratory function, with one death reported. Regarding the results of testing the new coronavirus in neonates, only one neonate met the diagnostic criteria for congenital infection by SARS-CoV-2. The other five neonates who were positive soon after birth were not correctly tested, and the risk of infection during delivery and in the first hours was not ruled out. Finally, studies are necessary to support the exact risk of vertical transmission, assessing the influence of maternal viral load and other data, such as gestational age with a possible greatest risk for SARS-CoV-2 transmission.

Keywords: Pregnant; Neonates; Coronavirus; COVID-19.

RESUMO: Os números da pandemia do novo coronavírus (COVID-19) ultrapassaram os outros membros da família *Coronaviridae* acumulando até o presente, mais de 24 milhões de casos da doença. O conhecimento adquirido pelos surtos anteriores sugere que gestantes e seus fetos são mais suscetíveis a prognósticos indesejáveis. Dessa forma, a presente revisão sistemática tem como objetivo avaliar as principais manifestações da infecção pelo vírus SARS-CoV-2 em gestantes e a possibilidade de transmissão vertical. Para isso, incluiu manuscritos que, ao todo, apresentavam dados de 205 gestantes e 76 neonatos. Entre os resultados, foi evidenciado que os sintomas apresentados pelas gestantes eram os mesmos que pacientes não grávidas, assim como as alterações laboratoriais, como linfopenia e a opacidade em vidro-fosco na tomografia computadorizada. No total, foram realizadas 163 cesáreas com a indicação de estado respiratório comprometido, com óbito de apenas uma paciente. Em relação aos resultados dos testes do novo coronavírus em neonatos, apenas um neonato, com seu estudo publicado em julho de 2020, encaixou-se nos critérios diagnósticos de infecção congênita por SARS-CoV-2. Os outros 5 neonatos que se apresentaram positivo logo após o nascimento, não apresentavam os testes corretos e o risco de infecção durante o parto nas primeiras horas não foi descartado. Dessa forma, estudos são necessários para embasar o exato risco de transmissão vertical, avaliando a influência da carga viral materna e outros dados como a idade gestacional de maior risco para a transmissão.

Palavras-chave: Gestantes; Neonatos; Coronavírus; COVID-19.

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INTRODUCTION

Emerging and reemerging pathogens are constant challenges worldwide, causing concerns for public health. The new SARS-CoV-2 - which was first discovered in December 2019 from a series of pneumonia patients linked to an unknown cause in Wuhan (China) - has spread and devastated the world. Although most human infections caused by a virus from the *Coronaviridae* family present with mild symptoms, two beta-coronaviruses, including the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infected around 10,000 individuals over the past two decades[1]. However, the new coronavirus (COVID-19) is by far the largest outbreak, accumulating millions of confirmed cases[2].

Regarding the epidemiology and clinical characteristics of COVID-19, studies associated the first cases to a seafood market in Wuhan. Initially, transmission was assumed to be from animals to humans. However, exponential increase has since been reported due to transmission via human interactions. The first symptoms are very similar to other viral infections, such as fever, cough, myalgia, fatigue, and diarrhea. However, high fever and shortness of breath are symptoms that may indicate a severe disease, requiring greater medical attention[3].

The knowledge acquired by previous outbreaks of SARS-CoV and MERS-CoV suggests that pregnant women and their fetuses are particularly susceptible to undesirable prognoses, and some studies have proven that the chance of death can increase by up to 35%[4]. Physiological changes in the woman's body during pregnancy predispose them to a state of vulnerability against viral infections and severe course of pneumonia, with subsequent increase in maternal and fetal mortality[5]. Thus, anatomical changes - such as increased chest diameter that decreases hypoxia tolerance and changes in the mediating cells of the inflammatory system - may be responsible for increasing vulnerability, allowing pathogens to enter cells. Considering that the fetus and future neonate have an immune system in formation and adaptation, attention is necessary as they are extremely susceptible to infections[6].

Studies have demonstrated associations between maternal viral infections and negative fetal outcomes, such as preterm delivery, neurological and cardiovascular malformation, and even chorioamnionitis. Hence, pregnant women and their newborns should be carefully assessed as a potential risk group that requires special attention in relation to prevention, diagnosis, and management during the COVID-19 pandemic[7]. Moreover, according to the *Centers for Disease Control and Prevention* (CDC), information about the effects of COVID-19 in pregnancy is still limited. Therefore, the knowledge about symptoms severity and associated complications, such as the possible risk of intrauterine transmission must be clarified[8]. Consequently, this systematic literature review was conducted in order to demonstrate the clinical and laboratory manifestations of SARS-CoV-2 infection in pregnant women and to evaluate the possible risk of intrauterine vertical transmission.

METHODS

In this study, protocols for systematic reviews were adopted (i.e., *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*; PRISMA)[9]. The search for articles was performed in PubMed, Embase and LILACS platforms on August 10, 2020. The *string* used while searching for articles contained relevant combinations of keywords obtained from the Medical subject heading (MeSH terms), namely: "COVID-19" OR "coronavirus" OR "SARS" AND "pregnancy" OR "pregnant" OR "neonate" OR "vertical" OR "placental" OR "breastfeeding" OR "intrauterine".

The abstracts were analyzed according to the following inclusion criteria: observational studies, case reports, or randomized clinical trials published in 2020 in English or Portuguese; moreover, full text availability, studies reporting on pregnant women who had confirmed diagnosis of COVID-19 exclusively by the real-time reverse-transcription polymerase chain reaction (RT-PCR) of SARS-CoV-2 and their neonates (to assess a possible risk of vertical transmission) were part of the inclusion criteria. Duplicate entries, abstract-only texts, opinion articles and studies that did not present a confirmatory diagnosis of COVID-19 in both pregnant women and their newborns were excluded from this review. Incomplete studies and those not performed in humans were excluded.

Figure 1 details the procedures for searching and selecting manuscripts according to PRISMA recommendations. Out of the 35 documents recovered, 20 were deemed potentially relevant after reading the abstracts (18 from PubMed and 2 from Embase). Fifteen non-clinical studies were excluded, 2 were excluded because the target population was not covered, 2 were not available in full-texts and another 5 had to be excluded for not reporting confirmed diagnosis of COVID-19 in pregnant women. Next, considering the articles that met the inclusion and exclusion criteria (n=11)[10-20], a manual search was performed in the references of the articles, which resulted in the inclusion of one document[21], thus resulting in 12 studies included in this review. We sought to ensure the quality of the articles included through the choice of high-quality repositories of the medical literature (e.g., PubMed, Embase, and LILACS). Although no specific tool was used to analyze risks of bias, authors' notes regarding limitations/biases presented in their studies were considered in each publication.

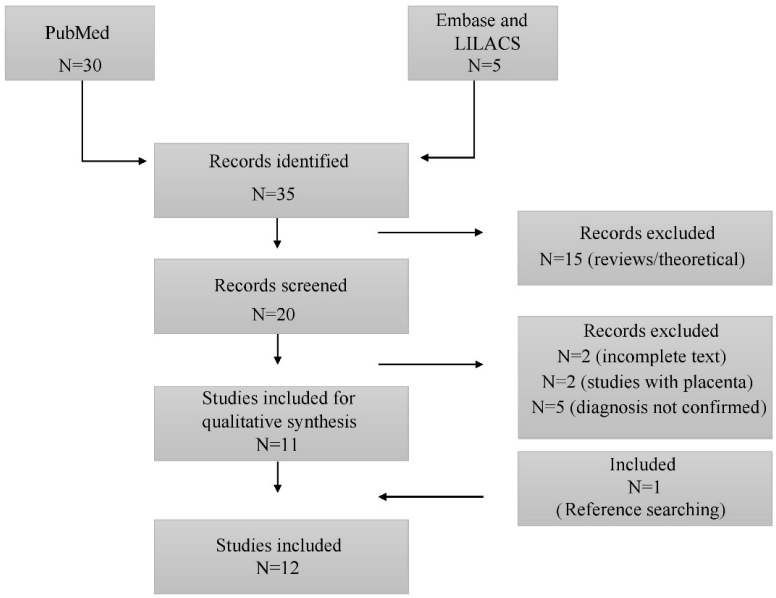

Figure 1. Flow diagram for selecting studies according to PRISMA guidelines

RESULTS

According to the search strategy adopted, 12 studies in accordance with the inclusion/exclusion criteria were identified; out of them, 8 were observational or retrospective studies with fairly large samples[11-14,16,17,19,20] and 4 were case studies[10,15,18,21]. In addition, all investigations were published between February 6 and July 14, 2020, coming mostly from China (n=10), but also from France (n=1), Peru (n=1) and Iran (n=1).

Maternal data are presented in Table 1. Data were organized according to the age of patients, gestational age, history of chronic diseases, reported symptoms, laboratory and tomographic alterations, type of delivery, reasons given for cesarean section, and maternal deaths. Table 2 contains data from the neonates tested for COVID-19, including the type of test performed, its results, and number of neonatal deaths.

Maternal results

The present systematic review reports data from 205 pregnant women with a confirmatory diagnosis of COVID-19 exclusively via RT-PCR. According to Table 1, the age of the patients ranged from 23 to 41 years old, and the gestational age at the time of the diagnosis varied between 5 to 41 weeks, while most of them occurred in the third gestational trimester. Few studies addressed the health history, chronic diseases, and other comorbidities of the patients before the infection by the novel coronavirus, yet thalassemia[13], gestational diabetes[13,16], valve surgery[13], history of placenta previa[13], hypothyroidism[17], polycystic ovary syndrome[17], uterine sinechia[17], diabetes mellitus[10], and systemic arterial hypertension[16] were reported in some investigations.

Regarding the symptoms reported and identified by physical examination, fever was the most frequent (n=105; 51%), followed by cough (n=63; 30%), fatigue (n=22; 11%), dyspnea (n=15; 7%), sore throat (n=15; 7%), myalgia (n=13; 6%), and diarrhea (n=10; 5%). Nasal congestion was present in only one patient and 27 were asymptomatic. Increased C-reactive protein (n=88; 43%), lymphopenia (n=85; 41%), altered AST/ALT transaminases (n=10; 5%), high D-dimer (n=8; 4%), and procalcitonin (n=5; 2%) were the most frequent laboratory findings. Only one patient presented with high ferritin values. In terms of radiological results, the most frequent finding was ground-glass opacity, present in two of the four case studies15,18 and in 93% (n=104) of pregnant women in the only quantitative study detailing this alteration16. COVID-19 infection, compromised respiratory status, preeclampsia, fetal distress, and premature rupture of membranes were the reasons given for cesarean sections performed (n=163; 79%). In addition, there were 20 vaginal deliveries and 22 ongoing pregnancies. No neonatal death was reported, but a case of maternal death was documented in a single report[18].

Table 1. Maternal results

Authors, year, and origin	Number of pregnant women	Ages	Gestational age	Comorbidities	Symptoms (n)	Laboratory (n)	Radiological	Type of delivery (n)	Indication for cesarean section	Maternal deaths
Alzamora et al., 2020 Peru	1	41 years old	33 weeks	Diabetes mellitus	Fever, malaise, fatigue, and severe dyspnea	Lymphopenia, increased CRP and D-dimer	Not reported	Cesarean section	Compromised respiratory state	0
Chen et al., 2020 China	9	26-40 years old	36-40 weeks	Not reported	Fever (7), myalgia (3), cough (4), dyspnea (1), sore throat (2), diarrhea (1)	Lymphopenia (5), CRP increase (6), changes in ALT/AST (3)	Not reported	Cesarean section (9)	Preeclampsia, fetal distress, COVID-19 pneumonia	0
Hu et al., 2020 China	7	30-34 years old	Not reported	Not reported	Fever (4), cough (2), diarrhea (1)	Changes in ALT/AST (1)	Not reported	Cesarean section (6), vaginal delivery (1)	Not reported	0
Liu et al., 2020 China	15	23-40 years old	12-38 weeks	Thalassemia, gestational diabetes, valve surgery, placenta previa	Cough (9), fatigue (4), myalgia (3), dyspnea (1), diarrhea (1), sore throat (1)	Lymphopenia (12), CRP increase (10)	Ground-glass opacity	Cesarean section (10), vaginal delivery (1)	Not reported	0
Liu et al., 2020 China	19	27-34 years old	Not reported	Not reported	fever (11), cough (5), dyspnea (5), diarrhea (2)	Not reported	Ground-glass opacity	Cesarean section (18), vaginal delivery (1)	Not reported	0
Lu et al., 2020 China	18	24-34 years old	35-41 weeks	Not reported	Fever (5), cough (3), sore throat (1), fatigue (2), dyspnea (2), diarrhea (1), nasal congestion (1)	Lymphopenia (8), increased CRP (10), procalcitonin increase (5), ALT/AST changes (3)	Uni or bilateral pneumonia and ground-glass opacity	Cesarean section (17), vaginal delivery (1)	Premature rupture of membrane, preeclampsia, and fetal distress	0
Vivanti et al., 2020 France	1	23 years old	35 weeks	Not reported	Fever and cough	Lymphopenia, increased CRP, ferritin increase, and ALT/AST alteration	Not reported	Cesarean section (1)	Not reported	0
Wang et al., 2020 China	1	34 years old	40 weeks	Not reported	Fever	Lymphopenia and increased CRP	Ground-glass opacity	Cesarean section (1)	Not reported	0
Yan et al., 2020 China	116	24-41 years old	5-41 weeks	Gestational diabetes and hypertension	Fever (59), cough (33), fatigue (15), dyspnea (3), sore throat (10), myalgia (6), diarrhea (1), asymptomatic (27)	Lymphopenia (51), increased CRP (51)	Ground-glass opacity in 93% of the sample	Cesarean section (84), vaginal delivery (14)	COVID-19 pneumonia, previous cesarean sections, fetal distress, and other procedural failures	0
Yu et al., 2020 China	7	29-34 years old	37-41 weeks	Hypothyroidism, polycystic ovary syndrome, and uterine synechiae	Fever (6), cough (1), dyspnea (1), diarrhea (1)	Lymphopenia (5), increased CRP (7), increased D-dimer (7), ALT/AST changes (2)	Not reported	Cesarean section (7)	Not reported	0
Zamaniyan et al., 2020 Iran	1	22 years old	32 weeks	Not reported	Fever, cough, dyspnea, myalgia, and nausea	Lymphopenia and increased CRP	Ground-glass opacity	Cesarean section (1)	Compromised respiratory state	1
Zhu et al., 2020 China	10	25-35 years old	Not reported	Not reported	Fever (9), cough (4), sore throat (1), diarrhea (1)	Not reported	Not reported	Cesarean section (8), vaginal delivery (2)	Fetal distress	0

Note. ALT: Alanine aminotransferase; AST: Aspartate transaminase; CRP: C-reactive protein.

Neonatal outcomes

Among all neonates born from mothers with confirmed infection by the novel coronavirus, 76 were tested for the disease (Table 2). Samples were taken from the nasopharynx and oropharynx by nasal swab, and/or amniotic fluid, umbilical cord, and breast milk. In all samples, the RT-PCR method was applied, which was negative in 70 neonates.

Table 2. Neonatal outcomes

Authors, year, and origin	Newborns tested (n)	Tests	Positive for COVID-19	Neonatal deaths
Alzamora et al., 2020 Peru	1	Nasal swab	1	0
Chen et al., 2020 China	6	Nasal swab, amniotic fluid, umbilical cord, and breast milk	0	0
Hu et al., 2020 China	7	Nasal swab	1	0
Liu et al., 2020 China	Not reported	Not reported	Not reported	Not reported
Liu et al., 2020 China	19	Nasal swab, amniotic fluid, umbilical cord, and breast milk	0	0
Lu et al., 2020 China	18	Nasal swab	0	0
Vivanti et al., 2020 France	1	Nasal swab and amniotic fluid	1	0
Wang et al., 2020 China	1	Nasal swab, amniotic fluid, umbilical cord, and breast milk	1	0
Yan et al., 2020 China	10	Umbilical cord	0	0
Yu et al., 2020 China	3	Nasal swab	1	0
Zamaniyan et al., 2020 Iran	1	Nasal swab and amniotic fluid	1	0
Zhu et al., 2020 China	9	Nasal swab	0	0

Regarding the positive tests for the novel coronavirus, Yu et al.[17] found 1 out of 3 neonates tested who showed a positive result in the nasal swab sample, but this test was performed 36 hours following delivery, after the onset of mild symptoms and shortness of breath; two weeks later, the neonate was discharged when obtained two consecutive negative tests. Alzamor et al.[10] also reported a neonate with positive nasal swab test 16 hours after delivery, followed by another test repeated in 48 hours which also confirmed the infection, even though the patient was in isolation from the first hour, evolving with severe shortness of breath and need for ventilatory support. Hu et al.[12] described another newborn with a positive swab sample, but without detailing further testing. Wang et al.[15] documented a positive case from a nasal swab performed 36 hours postpartum, yet with negative samples when taken from amniotic fluid, umbilical cord, and breast milk.

The newborn described in the case report from Zamaniyan et al.[18] had tested positive for COVID-19 via amniotic fluid collected at the time of the cesarean section; however, authors did not collect blood samples from the newborn, solely obtaining a positive nasal swab test 24 hours after birth. It is worth mentioning that all the studies cited so far did not rule out the possibility of failure in isolating mothers and neonates, as well as infection during cesarean section. Moreover, these investigations consider potential failures in the sterilization of surgical instruments, the risk of infection via health care workers who had contact with the newborns, and the possibility of false-negative results.

Perhaps a highlight among these studies was reported by Vivanti et al.[21] when describing a neonate with

positive molecular test results for SARS-CoV-2 obtained from the amniotic fluid before the rupture of the membrane. In addition, nasal swab, blood, and placenta samples were taken from the newborn shortly after birth, also confirming the presence of the new coronavirus. The authors stated that this would be the first documented case of vertical transmission SARS-CoV-2, and the study was published on July 14, 2020.

DISCUSSION

Epidemiological exposure, clinical history, laboratory results, computed tomography findings, and samples analyzed via RT-PCR are used to confirm COVID-19 diagnosis. Here, 205 pregnant women had a positive RT-PCR result for SARS-CoV-2, which was included as one of the inclusion criteria for this study. However, the fifth edition of the guide "*New coronavirus pneumonia prevention and control program*" stated that, in the most affected areas of China, suspected cases with consistent tomographic findings could be clinically diagnosed as COVID-19 because RT-PCR false-negative rates reach up to 30%[22]. In another study, published in August 2020, the sensitivity of findings from computed tomography compatible with the infection by the new coronavirus was greater than the sensitivity for RT-PCR testing (98% vs. 71% respectively)[23].

Additionally, ground-glass opacity was reported in 104 out of the 116 patients evaluated by Yan et al.[16] (included in this review), similarly to what has been found in other studies that specifically addressed these manifestations. The report "*Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China*" - published in Lancet Infectious Diseases - included 81 patients, with 93% presenting ground-glass opacity on radiological images, suggesting that this is not a characteristic seen exclusively in pregnant women[24].

Results from other members of the coronavirus family in pregnant women, such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have been reported in studies published in 2004[25] and 2019[4], respectively. Thus, the severity of these pathogens and their complications during pregnancy, such as the need for orotracheal intubation, admission to intensive care units, renal failure, and a maternal death rate of up to 35% were known[4]. However, as presented in this review, the impact of the new coronavirus on pregnant patients seems to be lighter, with only two cases reporting the need for intensive care[10,18] and one resulting in maternal death (patient admitted with an oxygen saturation of 75-85%, reaching 70% after cesarean section and unresponsive to therapies and resuscitations)[18]. These data emphasize the recommendations from an editorial stating that guidelines should be based on data acquired in the current pandemic and not solely on previous outbreaks because the clinical response, the epidemiology, and treatments may be different[26].

Fever was the most reported symptom, followed by cough, fatigue, dyspnea, sore throat, myalgia, and diarrhea. Lymphopenia and increased CRP were among the most notable laboratory alterations. In general, these symptoms are similar to those found in adult patients affected by the new coronavirus, thus not suggestive of any risk group. This is supported by two relatively large studies: the first one, by Huang et al.[27] and published in January 202, evaluating 41 patients; and the second one, by Wang et al.[28] with a sample of 138 patients. In both investigations, the symptoms mentioned above were among the most frequent and were characterized as clinical manifestations of SARS-CoV-2 infection. However, although it has been evidenced that pregnancy does not affect the symptomatology of the disease, some complications may have increased risk due to pregnancy, such as sepsis, intravascular disseminated coagulation, and acute renal injury[29].

Cesarean section was indicated for 163 women and 20 underwent vaginal delivery. The causes for pursuing cesarean section included fetal distress, premature rupture of the membrane, failure in the natural delivery process, and severe preeclampsia; however, the most cited cause was a compromised respiratory state of the patient due to the new coronavirus. Although some studies had not reported the reason for cesarean sections, it is possible that this decision was made due to understandable anxiety about the potential consequences of a novel and unknown viral infection[30]. As COVID-19 does not seem to be an extremely severe maternal disease, decisions should be taken by a multidisciplinary team and must consider obstetric indications of each patient. However, it is still reasonable to assume that there is a lack of evidence that cesarean sections are fully protective, and that vaginal delivery is not fully contraindicated[29].

An international classification for case definition of SARS-CoV-2 infection in pregnant women, fetuses and neonates has been recently published. According to the authors, a neonatal congenital infection is confirmed against samples of amniotic fluid containing the virus, collected before membrane rupture, or blood samples taken in the first hours of life[31]. Thus, the six cases of neonates who tested positive for the new coronavirus among the 76 tested that were included in this review should be reviewed with caution.

The neonates described by Alzamor et al.[10], Hu et al.[12], Wang et al.[15] and Yu et al.[17]could not be classified as confirmed cases of intrauterine vertical transmission according to the international classification as nasal swab samples were taken a few hours after delivery[31]. The case reported by Zamaniyan et al.[18] presented a sample

of positive amniotic fluid, but this was collected during cesarean section, and as already presented in the results, the authors did not rule out flaws regarding isolation or other methods of infection.

The only study presented in this review that could be classified as vertical intrauterine transmission would be the one described by Vivanti et al.[21]. In this case report, the newborn was tested by samples taken from amniotic fluid before rupture of the membrane, nasal swab, blood samples, and histological analysis of the placenta. From all these tests, confirmatory results for the new coronavirus were obtained. Besides, according to the analysis and evidence of high levels of angiotensin-converting enzyme 2 receptors in the placenta, authors were able to conclude that the transmission is possible in the last weeks of pregnancy, but studies are still lacking to assess the risk of transmission in the first and second trimester of gestational age[21].

It is worth mentioning that, despite this isolated confirmed case of intrauterine vertical transmission following the international classification published by Shah et al.[31], more studies should be carried out with larger samples and comprising pregnant women in the first and second trimester of pregnancy. Moreover, detailed attention to the patient's viral load, something that has been the subject of recent a publication that demonstrated a relationship between viral load and the possibility of transmission of pathogens from the mother to the child[32].

CONCLUSION

The recently published studies do not allow to fully clarify all the complications caused by the new coronavirus in pregnant women and their newborns. However, as reported by this article, there was no difference between the clinical and laboratory manifestations of SARS-CoV-2 infection among pregnant women when compared to non-pregnant women. Findings so far seem favorable, but maternal and fetal risk should not be ruled out. In respect to the risk of vertical transmission, studies reported a still significant lack of evidence; on the other hand, the first case was reported following the recently published diagnostic standards, which could increase concerns exponentially. Until now, scholars have claimed the lack of information to prove it and, although it has been an isolated case so far, more studies are needed to support the exact risk of vertical transmission, assessing the influence of maternal viral load and other data, such as gestational ages with higher risk for transmission.

This study has some limitations. For instance, articles published in Chinese were not included, and only women with a confirmatory diagnosis of COVID-19 by RT-PCR were included. Moreover, most of the patients were diagnosed in the third gestational trimester, which impeded the understanding on the effects of the disease in the first months of pregnancy. In addition, many studies did not report essential data. Although a total of 205 pregnant women had their data here reviewed, with the majority being from China, this sample is small and with a lower relevance when compared to the rapid spread of the pandemic, which makes even more difficult to draw any definitive conclusions about the course of the new coronavirus in the studied population.

Finally, it seems clear that the best strategy available so far is to prevent maternal infection and consequently reduce neonatal exposure to the virus. Patients should be monitored according to prenatal, intrapartum, and postpartum guidelines, always ensuring the individuality of each patient by a multidisciplinary team.

Authors contributions: *Pereira O* - designed the study, searched for articles, collected data, synthesized the results, and wrote the final text. *Wendt G* - helped with the study design, methodological procedures, and final revision of the manuscript.

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