

COVID-19 and its relation to pregnancy and neonates: a systematic review

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Abstract

Objectives: this study systematically reviewed the literature in order to better understand the association among COVID-19, pregnancy and neonates.

Methods: MEDLINE, EMBASE, Web of Science, BVS and SCOPUS were assessed, considering the terms: (covid 19 OR covid-19 OR novel coronavirus OR 2019 novel coronavirus OR 2019-nCoV OR sarscov 2 OR sars-cov-2 OR sarscov2 OR sars cov-2) AND (pregnancy OR pregnant OR pregnant women OR gestation OR gestational) AND (infant OR fetal OR neonatal). Thirty full-text were included (408 pregnant women, 11 non-pregnant women and 279 neonates).

Results: fever (45.83%) and cough (31.61%) were the main symptoms of COVID-19 during the pregnancy. Low levels of lymphocytes (32.10%), elevated levels of C-reactive protein (32.35%); leukocytosis (29.41%); neutrophil (5.88%); and radiographic alterations on chest CT, x-ray or ultrasound (45.84%) were the main laboratorial findings. Cesarean delivery and preterm were registered in 239 and 49 cases, respectively. Ten neonates tested positive for SARS-CoV-2.

Conclusion: when COVID-19 pneumonia affects women during pregnancy, the symptoms are similar to those experienced by non-pregnant women. In addition, there is still no plausible evidence suggesting vertical transmission of SARS-CoV-2 virus from mother to child.

Key words COVID-19, SARS-CoV-2, Pregnancy, Childbirth, Newborn



Introduction

Currently known as COVID-19, SARS-CoV-2 virus (Severe Acute Respiratory Syndrome-related coronavirus 2) is a public health emergency of international concern. It has been suggested that previous complications may be risk factors for adverse outcomes related to COVID-19 such as cardiovascular disease, diabetes, hypertension, and chronic obstructive pulmonary disease.¹⁻³

Regarding symptomatology, similarities of clinical features between 2019-nCoV and previous beta coronavirus infections has been found. Most patients present fever, dry cough, dyspnea, and bilateral patchy pattern and/or ground-glass opacities on chest computerized tomography (CT) scans.¹ Nonetheless, the report from Huang *et al.*¹ mainly focused on non-pregnant women. Contrasting data are found on maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia.

Prior December 2019, others six coronaviruses were known to infect people: 229E, OC43, NL63, HKU1, SARS-CoV, and MERS-CoV (Middle East Respiratory Syndrome coronavirus). Among these, 229E, OC43, NL63, and HKU1 can be vertically transmitted from mothers to neonates through the placenta,^{4,5} whilst there is no evidence of vertical transmission of SARS-CoV and MERS-CoV.^{5,6} Nevertheless, an epidemiological research presented that 2019-nCoV was more contagious than SARS-CoV, although, its nucleotide sequences were very similar (82% homologous with SARS-CoV).⁷

Moreover, it has been stated that COVID-19 infections in pregnant women generally result in mild or moderate symptoms, and many infected pregnant women do not present any symptoms,^{8,9} which may also lead to a high risk of neonatal infection during labor. However, the clinical characteristics and potential vertical transmission of COVID-19 pneumonia in pregnant women is still new and has not been entirely clarified.^{8,10} Therefore, it is important to report the most frequent symptoms of this disease in pregnant women and neonates, as well as to understand the risk of infection that labor imposes to the neonates' health. Based on this rationale, this study aimed to systematically review the available literature in order to better understand the association among COVID-19, pregnancy and neonates.

Methods

This systematic review was conducted without patient involvement. Patients were not involved in

any way during the review of the available literature, nor during the writing or editing of this document for readability or accuracy.

The search strategy followed the indications of the National Health Service Center for Reviews and Dissemination and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Also, this systematic review was registered in International Prospective Register of Systematic Reviews (PROSPERO) with protocol CRD42020177354 (<https://www.crd.york.ac.uk/prospero>).

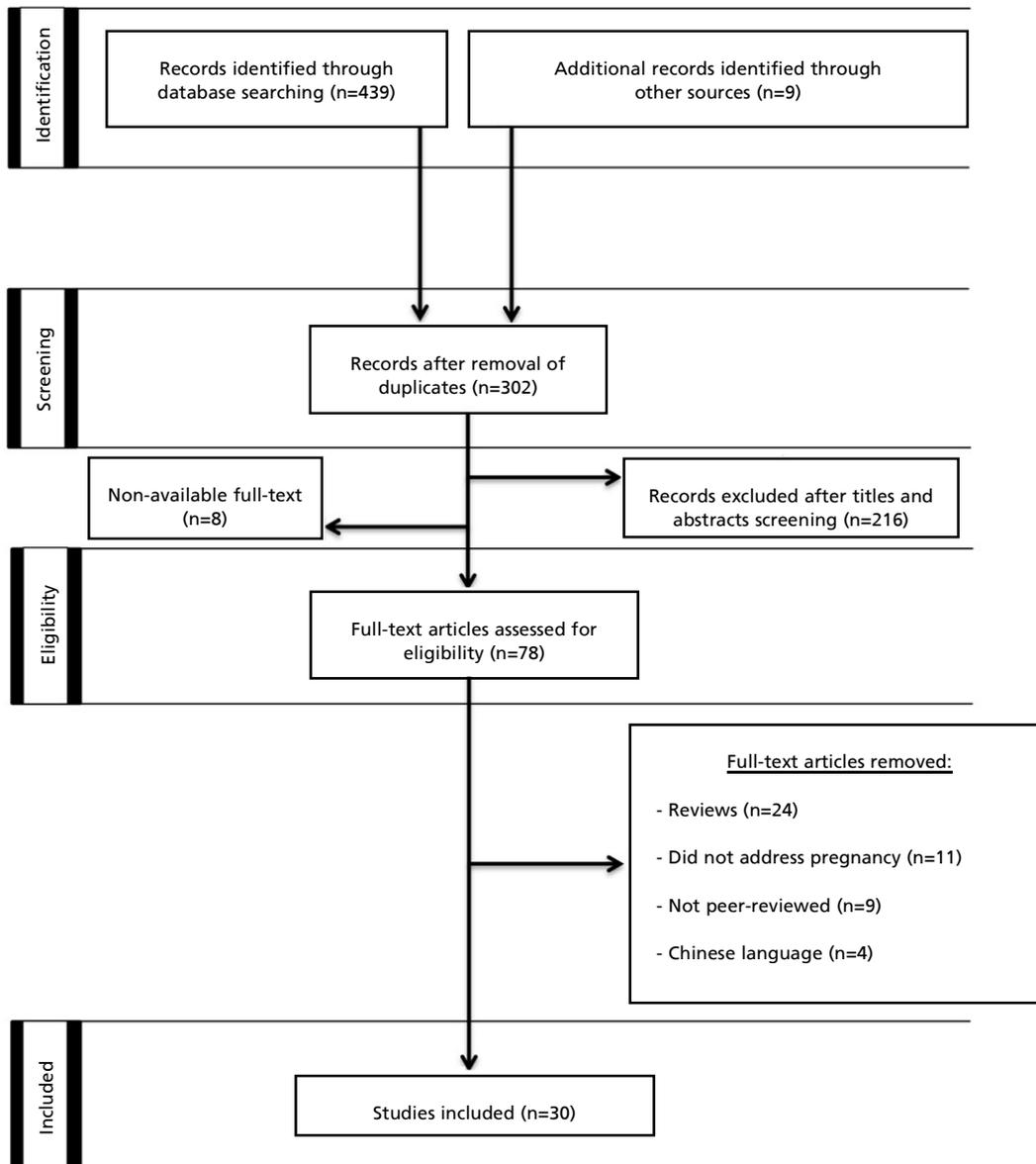
A systematic revision of relevant studies published in the literature was conducted on May 22nd, 2020, considering the period between December 1st, 2019 to May 22nd, 2020. The following database were explored: MEDLINE database (Entrez PubMed, www.ncbi.nlm.nih.gov), EMBASE, Web of Science, BVS/LILACS and SCOPUS, considering the main MeSH (Medical Subject Headings) terms: (covid 19 OR covid-19 OR novel coronavirus OR 2019 novel coronavirus OR 2019-nCoV OR sarscov 2 OR sars-cov-2 OR sarscov2 OR sars cov-2) AND (pregnancy OR pregnant OR pregnant women OR gestation OR gestational) AND (infant OR fetal OR neonatal). To identify relevant article, titles and abstracts of retrieved papers were exported to Endnote Web where duplicates were identified and removed by two reviewers (GAFJ and VM). It is important to highlight that, in order to identify missing studies, we also hand searched the reference lists of the studies included.

As eligibility criteria, we considered case reports, case series and clinical researches in English, Portuguese and Spanish published in peer-reviewed journals, that have addressed epidemiological, clinical features of COVID-19 and its association with pregnancy and neonates. Duplicate publications and articles that did not correspond to the objectives of this review were excluded. Similarly, publications without a research or case report, such as: review articles; descriptive studies; opinion article; correspondence; editorials; letters; and with only children's cases were also excluded. Figure 1 shows the steps of the literature search.

Two highly experienced researchers (GAFJ and VM) were previously trained regarding to criteria that were defined in this study and after they were responsible for searching the literature, applying inclusion and exclusion criteria, selecting the studies and independently extracting the data. There was a good concordance coefficient between reviewers (Kappa index=0.91). Discordances between the authors were discussed and agreed upon with a third

Figure 1

Systematic review steps according to PRISMA 2009.



author (SHCSP).

Studies assessed in this review were classified and stored by: main author, publication year, study design, sample/participants, maternal age, consequences for pregnant women, consequences for neonates, absence/presence of vertical transmission.

The initial search identified 439 studies (181 from PubMed, 135 from EMBASE, 71 from BVS, 33 from Web of Science and 19 from SCOPUS). After, nine sources were manually inserted by analyzing the references list of previous studies. Fifty-five sources remained on screening step after duplicates exclusion.

Following screening of titles and abstracts, 216 sources were excluded due to the following reasons: reviews; author reply/ comment/ correspondence/ expert comment/ guideline/ letter to editor/ in websites; not correspond to the objectives of this review; not peer-reviewed; language. Besides that, one full-text study was not found.

Seventy-eight articles in full text were assessed. Thirty were considered with good relevance, among them: clinical research (n=1); case-control (n=1); retrospective review of cases (n=10); case series (n=4); case reports (n=14). Forty-eight were removed due to the following reasons: reviews (n=24); did not address pregnancy (n=11); not peer-reviewed (n=9); Chinese language (n=4).

Results

A total of 408 pregnant women was considered. The mean age of all pregnant women in the 30 studies included in this review was 32.46 years old. Also, among the studies included in this review, 11 non-pregnant women and 279 neonates were considered.

The main symptoms of this disease in pregnant women were fever (45.83%) accompanied or not by fatigue, cough (31.61%), myalgia (15.19%), dyspnea (11.76%), sore throat (3.92%) and diarrhea (1.96%). Other less frequent symptoms, such as shortness of breath, headache and anemia were reported (Table 1).

The most frequent laboratorial features were elevated levels of C-reactive protein (32.35%); low levels of lymphocytes (32.10%); leukocytosis (29.41%); neutrophil levels above the normal range (5.88%); radiographic alterations on chest CT or x-ray (45.34%), because of viral pneumonia that is characterized by decreased diffuse and unilateral or bilateral ground-glass opacities, patchy lung consolidation and blurred borders (Table 2).

The main findings of this study point out that, of the 279 neonates, only ten tested positive for SARS-

CoV-2, indicating a low risk of vertical transmission of the disease (Table 3). Delivery outcomes, characteristics of infants at birth and evidence of vertical transmission are also displayed in Table 3.

Discussion

Due to their immunosuppressed state and physiological and adaptive changes, pregnant women are more susceptible to pneumonia and other respiratory pathogens. Nonetheless, our results highlighted that fever and cough were the main clinical features of COVID-19 during pregnancy, but asymptomatic cases are common. Several studies reported false negative diagnosis by RT-PCR, whilst chest CT and x-rays analyses seem to be a fast and highly reliable diagnostic method. Also, vertical transmission from mother to neonates seems unlikely, yet, the available data addressing this topic is still scarce. Overall, data are limited in relation to the association of the outcomes, since population-based clinical studies are still scarce and most studies have low strength of scientific evidence.

Chen *et al.*¹⁰ reported that the main symptoms of SARS-CoV-2 infection in pregnant women are fever and cough, with lower frequency for myalgia, malaise, sore throat, shortness of breath and diarrhea. Laboratorial findings also report that lymphopenia and increased ALT and AST levels are frequent. These findings are in accordance with the findings of this systematic review, where fever (45.83%) and cough (31.61%) were the most frequent symptoms among the 408 pregnant women analyzed in this review, followed by myalgia (15.19%), dyspnea (11.76%), sore throat (3.92%) and diarrhea (1.96%).^{5,8-36} Laboratorial tests reported decreased levels of lymphocytes (32.10%) and increased levels of C-reactive protein (32.35%) as frequent conditions, followed by leukocytosis (29.41%) and increased neutrophil ratio (5.88%).

Medonza *et al.*³⁷ reported that preeclampsia-like syndrome is one symptom of COVID-19, but its cause is different from obstetric preeclampsia and therefore not connected with placental failure. In addition, preeclampsia-like syndrome can resolve spontaneously following recovery from severe pneumonia and may not be an obstetric indication for delivery.

Other main findings seen in the reviewed studies was alterations on chest CT.^{5,9,12,13,15,20,21,23-25,30,31,33-35} More than 45% of patients included in this review presented alterations upon chest CT, x-ray or ultrasound. These findings, along with the study of Liu *et al.*²⁷ suggest that CT images seem to

Table 1

Description of pregnant women's clinical characteristics in the selected studies.

Author (year)	Study design	Participants	Location	Clinical features of pregnant women
Alonso Diaz <i>et al.</i> , ¹¹ (2020)	Case report	1 pregnant woman; 1 neonate	Spain	- Fever; - Cough; - Dyspnea
Alzamora <i>et al.</i> , ¹² (2020)	Case report	1 pregnant woman; 1 neonate	Peru	- Fever; - Fatigue; - Dyspnea; - Indisposição
Breslin <i>et al.</i> , ¹³ (2020)	Case series	29 pregnant women with symptomatic admitted; 14 pregnant women asymptomatic admitted	USA	- Febre (n=14); - Cough (n=19); - Myalgia or fatigue (n=11); - Dyspnea (n=7); - Chest pain (n=5); - Headache (n=8)
Breslin <i>et al.</i> , ¹⁴ (2020)	Case series	7 pregnant women	USA	- Fever (n=2); - Cough (n=3); - Myalgias (n=3); - Chest pain (n=2); - Headache (n=2)
Buonsenso <i>et al.</i> , ¹⁵ (2020)	Case series	4 pregnant women; 2 neonates	Italy	- Fever (n=3); - Cough (n=4); - Dyspnea (n=1); - Ageusia/anosmia (n=1)

continue

ICU= Intensive Care Unit; MODS= Multiple Organ Dysfunction Syndrome; ARDS= Acute Respiratory Distress Syndrome.

Table 1 continuation

Description of pregnant women's clinical characteristics in the selected studies.

Author (year)	Study design	Participants	Location	Clinical features of pregnant women
Chen <i>et al.</i> , ¹⁰ (2020)	Retrospective case review	9 pregnant women; 9 neonates	China	<ul style="list-style-type: none"> - Fever (n=7); - Postpartum fever (n=6); - Myalgia (n=3); - Malaise (n=2); - Cough (n=4); - Dyspnea (n=1); - Sore throat (n=2); - Diarrhea (n=1); - Influenza (n=1)
Chen <i>et al.</i> , ¹⁶ (2020)	Case series	17 parturients; 17 neonates	China	<ul style="list-style-type: none"> - Anemia (n=5); - Gestational hypertension (n=1); - Gestational diabetes (n=2); - Mild fever without chills (n=4); - Cough (n=4); - Fatigue (n=1); - Chest distress (n=2); - Dyspnea (n=1); - Diarrhea (n=1)
Chen <i>et al.</i> , ¹⁷ (2020)	Case series	4 pregnant women 4 neonates	China	<ul style="list-style-type: none"> - Fever (n=3); - Cough (n=2); - Myalgia or fatigue (n=2); - Headache (n=2); - Reduced fetal movement (n=1); - Dyspnea (n=1); - Severe dyspnea after delivery (n=1)

continue

ICU= Intensive Care Unit; MODS= Multiple Organ Dysfunction Syndrome; ARDS= Acute Respiratory Distress Syndrome.

Table 1

continuation

Description of pregnant women's clinical characteristics in the selected studies.

Author (year)	Study design	Participants	Location	Clinical features of pregnant women
Fan <i>et al.</i> , ¹⁸ (2020)	Case series	2 pregnant physicians; 2 neonates	China	- Mild fever (n=2); - Rash (n=1); - Nasal congestion (n=2); - Sore throat (n=1)
Ferrazzi <i>et al.</i> , ⁸ (2020)	Retrospective case review	42 pregnant women; 42 neonates	Italy	- Fever (n=20); - Cough (n=18); - Dyspnea (n=8); - Myalgia (n=7); - Diarrhea (n=2)
Gidlöf <i>et al.</i> , ¹⁹ (2020)	Case report	1 pregnant woman; 2 neonates	Sweden	- Pregnant women with high BMI; preeclampsia and gestational diabetes mellitus - (clinical features complicated by COVID-19); - Headache; - Sore throat; - Malaise; - Hypertension
González Romero <i>et al.</i> , ²⁰ (2020)	Case report	1 pregnant woman; 1 neonate	Spain	- Fever; - Cough; - Sore throat
Hantoushzadeh <i>et al.</i> , ²¹ (2020)	Retrospective case review	9 pregnant women; 7 neonates	Iran	- Fever (n=9); - Cough (n=9); - Dyspnea (n=6); - Sore throat (n=1); - Deaths (n=7)

continue

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Table 1 continuation

Description of pregnant women's clinical characteristics in the selected studies.

Author (year)	Study design	Participants	Location	Clinical features of pregnant women
Iqbal <i>et al.</i> , ²² (2020)	Case report	1 pregnant woman; 1 neonate	USA	- Fever; - Chills; - Dry cough; - Myalgia
Kalafat <i>et al.</i> , ²³ (2020)	Case report	1 pregnant woman; 1 neonate	Turkey	- Cough; - Dyspnea; - Swollen left leg
Li <i>et al.</i> , ²⁴ (2020)	Case-control	<p>Case groups:</p> <ul style="list-style-type: none"> - Confirmed cases who were tested positive for SARS-CoV-2 (n=16); - Suspected cases with typical chest CT imaging but negative in RT-PCR tests (n=18); <p>Control groups:</p> <ul style="list-style-type: none"> - Women admitted during January 24 – February 29, 2020 (n=120); - Women admitted during January 24 – February 11, 2019 (n=121); <p>Neonates:</p> <ul style="list-style-type: none"> - Confirmed case group (n=17); - Suspected case group (n=19); - Control 2020 (n=121); - Control 2019 (n=121) 	China	<p>Fever on admission:</p> <ul style="list-style-type: none"> - Confirmed case group (n=4); - Suspected case group (n=1); <p>Cough:</p> <ul style="list-style-type: none"> - Confirmed case group (n=0); - Suspected case group (n=1); <p>Sore throat:</p> <ul style="list-style-type: none"> - Confirmed case group (n=0); - Suspected case group (n=1); <p>Dyspnea:</p> <ul style="list-style-type: none"> - Confirmed case group (n=0); - Suspected case group (n=1)

continue

ICU= Intensive Care Unit; MODS= Multiple Organ Dysfunction Syndrome; ARDS= Acute Respiratory Distress Syndrome.

Table 1

continuation

Description of pregnant women's clinical characteristics in the selected studies.

Author (year)	Study design	Participants	Location	Clinical features of pregnant women
Li <i>et al.</i> , ²⁵ (2020)	Case report	1 pregnant woman; 1 neonate	China	- Dry cough and fever (37.2°C); - Chest auscultation slightly thicker in the right lung
Liu <i>et al.</i> , ²⁶ (2020)	Retrospective case review	15 pregnant women; 11 neonates	China	- Fever (n=13); - Cough (n=9); - Fatigue (n=4); - Muscle pain (n=3); - Dyspnea (n=1); - Sore throat (n=1); - Diarrhea (n=1); - Postpartum fever (n=1)
Liu <i>et al.</i> , ²⁷ (2020)	Clinical research	41 pregnant women*; 11 non-pregnant adults * 16 pregnant women were SARS-CoV-2 positive; 17 laboratorial-negative but with typical CT features of COVID-19 pneumonia; and the other 8 did not undergo SARS-CoV-2 test	China	- Initial onset of fever in either laboratorial-confirmed (n=7/16) or clinically-diagnosed (n=9/25) pregnant women; - Cough (n=6/16 and 9/25); - Shortness of breath (n=2/16 and 3/25); - Fatigue (n=3/16 and 2/25); - Loss of appetite (n=2/16 and 1/25); - Postpartum fever (n=5/16 and 9/25)
Liu <i>et al.</i> , ²⁸ (2020)	Retrospective case review	13 pregnant women; 13 neonates	China	- Fever, range 37.3–39.0°C, mostly accompanied with fatigue (n=10); - Dyspnea (n=3); - ICU admitted with MODS including ARDS, requiring intubation and mechanical ventilation, acute hepatic failure, acute renal failure and septic shock (n=1)

continue

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Table 1 **continuation**

Description of pregnant women's clinical characteristics in the selected studies.

Author (year)	Study design	Participants	Location	Clinical features of pregnant women
Song <i>et al.</i> , ²⁹ (2020)	Case report	1 pregnant woman; 1 neonate	China	- Fever; - Cough; - Generalized myalgia; - Decreased breath sounds; - Rales on lung auscultation
Wang <i>et al.</i> , ³⁰ (2020)	Case report	1 pregnant woman; 1 neonate	China	- Fever
Wang <i>et al.</i> , ³¹ (2020)	Case report	1 pregnant woman; 1 neonate	China	- Fever; - Little rhonchi over the left lower lung field (Lung auscultation); - Severe atypical pneumonia
Wu <i>et al.</i> , ⁹ (2020)	Retrospective case review	23 pregnant women; 21 neonates	China	- Fever (n=4); - Cough (n=6); - Nasal congestion (n=1)
Xia <i>et al.</i> , ³² (2020)	Case report	1 pregnant woman; 1 neonate	China	- Fever; - Reduced fetal movement
Yan <i>et al.</i> , ³³ (2020)	Retrospective case review	116 pregnant women; 84 neonates	China	- Fever (n=50); - Cough (n=27); - Fatigue (n=15); - Dyspnea (n=10); - Sore throat (n=8); - Myalgia (n=6); - Diarrhea (n=1)

continue

ICU= Intensive Care Unit; MODS= Multiple Organ Dysfunction Syndrome; ARDS= Acute Respiratory Distress Syndrome.

Table 1

concluded

Description of pregnant women's clinical characteristics in the selected studies.

Author (year)	Study design	Participants	Location	Clinical features of pregnant women
Yu <i>et al.</i> , ³⁴ (2020)	Retrospective case review	7 pregnant women; 7 neonates	China	<ul style="list-style-type: none"> - Uterine scarring (n=3); - Abdominal pain (n=4); - Increased fetal movement (n=1); - Cough (n=1); - Fever (n=6); - Diarrhea (n=1); - H1N1 (n=2)
Zamaniyan <i>et al.</i> , ³⁵ (2020)	Case report	1 pregnant woman; 1 neonate	Iran	<ul style="list-style-type: none"> - Fever; - Cough; - Dyspnea; - Myalgia; - Gastrointestinal symptoms; - Respiratory distress; - ARDS
Zambrano <i>et al.</i> , ³⁶ (2020)	Case report	1 pregnant woman; 1 neonate	Honduras	<ul style="list-style-type: none"> - Fever; - Cough; - Headache; - Myalgia; - Bilateral conjunctival hyperemia
Zhu <i>et al.</i> , ⁵ (2020)	Retrospective case review	9 pregnant women; 10 neonates	China	<ul style="list-style-type: none"> - Fever, associated or not with a cough (n=8); - Cholecystitis (n=1); - Diarrhea (n=1)

ICU= Intensive Care Unit; MODS= Multiple Organ Dysfunction Syndrome; ARDS= Acute Respiratory Distress Syndrome.

Table 2

Description of pregnant women's laboratorial data and radiological characteristics in selected studies.

Author (year)	Study design	Participants	Pregnant women's laboratorial data and radiological characteristics
Alonso Diaz <i>et al.</i> , ¹¹ (2020)	Case report	1 pregnant woman; 1 neonate	- Severe bilateral pneumonia
Alzamora <i>et al.</i> , ¹² (2020)	Case report	1 pregnant woman; 1 neonate	- Low levels of lymphocyte; - Elevated levels of C-reactive protein; - Low levels of platelets; - High levels of ferritin; - High levels IgG and IgM; - GGO
Buonsenso <i>et al.</i> , ¹⁵ (2020)	Case series	4 pregnant women; 2 neonates	- Lymphocytopenia (n=4); - Raised lactic dehydrogenase (n=4); - Elevated levels of C-reactive protein (n=4); - Lung involvement upon chest x-ray (n=4)
Chen <i>et al.</i> , ¹⁰ (2020)	Retrospective case review	9 pregnant women; 9 neonates	- Elevated C-reactive protein (n=6); - Elevated ALT and AST (n=3)
Chen <i>et al.</i> , ¹⁶ (2020)	Case series	17 parturients; 17 neonates	- Lymphopenia (n=5); - Elevated concentrations of C-reactive protein (n=7)
Chen <i>et al.</i> , ¹⁷ (2020)	Case report	4 neonates; 4 pregnant women	- Lymphocytes were below the normal range (lymphocyte count $<1.1 \times 10^9/L$) in all patients; - Lymphopenia (n=2; lymphocyte count $<1.0 \times 10^9/L$); - Leucocytes and platelet counts were below the normal range (n=1; WBC count $<4 \times 10^9/L$, platelet count $<100 \times 10^9/L$); - Anemia (n=1; hemoglobin 83 g/L); - Significant increase of the level of C-response protein in all pregnant women; - Abnormalities in chest CT images and bilateral involvement were detected among all pregnant women

continue

ALT= alanine transaminase; AST= aspartate transaminase; CT= Computerized Tomography; GGO= Ground-Glass Opacities.

Table 2

continuation

Description of pregnant women's laboratorial data and radiological characteristics in selected studies.

Author (year)	Study design	Participants	Pregnant women's laboratorial data and radiological characteristics
Fan <i>et al.</i> , ¹⁸ (2020)	Case series	2 pregnant physicians; 2 neonates	- Lymphopenia (n=2)
Ferrazzi <i>et al.</i> , ¹² (2020)	Retrospective case review	42 pregnant women; 42 neonates	- High leukocyte count (n=16); - Lymphopenia (n=6); - Elevated C-reactive protein (n=17); - Elevated ALT or AST (n=5)
Gidlöf <i>et al.</i> , ¹⁹ (2020)	Case report	1 pregnant woman; 2 neonates	- Proteinuria; - Chest CT ruled out pulmonary embolism, but with typical signs of COVID-19 pneumonia
González Romero <i>et al.</i> , ²⁰ (2020)	Case report	1 pregnant woman; 1 neonate	- Low levels of lymphocyte; - Elevated C-reactive protein; - Elevated ALT and AST; - Elevated D-dimer; - Alterations upon chest x-ray
Hantoushzadeh <i>et al.</i> , ²¹ (2020)	Case report	9 pregnant women; 7 neonates	- Low levels of leukocyte (n=5); - Low level of lymphocyte (n=8); - Elevated levels of C-reactive protein (n=9); - Elevated levels of ALT and AST (n=6); - Low levels of platelets (n=2); - GGO (n=9)

continue

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Table 2

continuation

Description of pregnant women's laboratorial data and radiological characteristics in selected studies.

Author (year)	Study design	Participants	Pregnant women's laboratorial data and radiological characteristics
Iqbal <i>et al.</i> , ²² (2020)	Case report	1 pregnant woman; 1 neonate	<ul style="list-style-type: none"> - Lymphopenia; - Above normal D-dimer; - Elevated C-reactive protein levels; - Absolute neutrophil count above the normal range; - Erythrocyte sedimentation rate above the normal range; - Chest x-rays showed reticular interstitial opacities
Kalafat <i>et al.</i> , ²³ (2020)	Case report	1 pregnant woman; 1 neonate	<ul style="list-style-type: none"> - Lung ultrasound was consistent with viral pneumonia, with diffuse, thick B-lines; bilaterally, with predominantly basal posterior lung involvement; - Chest CT angiography: lung involvement typical for COVID-19 infection, with bilateral, peripheral GGO in the basal, posterior segments of her lungs and a crazy-paving appearance
Li <i>et al.</i> , ²⁴ (2020)	Case-control	<p>Case groups:</p> <ul style="list-style-type: none"> - Confirmed cases who were tested positive for SARS-CoV-2 (n=16); - Suspected cases with typical chest CT imaging but negative in RT-PCR tests (n=18); <p>Control groups:</p> <ul style="list-style-type: none"> - Women admitted during January 24 – February 29, 2020 (n=120); - Women admitted during January 24 – February 11, 2019 (n=121); <p>Neonates:</p> <ul style="list-style-type: none"> - Confirmed case group (n=17); - Suspected case group (n=19); - Control 2020 (n=121); - Control 2019 (n=121) 	<ul style="list-style-type: none"> - Case groups: slightly lower counts of WBC, neutrophils, C-reactive protein and ALT admission; - Pneumonia in one lung in CT imaging: <ul style="list-style-type: none"> - Confirmed case group (n=8); - Suspected case group (n=10); - Pneumonia in two lungs in CT imaging: <ul style="list-style-type: none"> - Confirmed case group (n=7); - Suspected case group (n=7)

continue

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Table 2

continuation

Description of pregnant women's laboratorial data and radiological characteristics in selected studies.

Author (year)	Study design	Participants	Pregnant women's laboratorial data and radiological characteristics
Li <i>et al.</i> , ²⁵ (2020)	Case report	1 pregnant woman; 1 neonate	- Chest x-ray (scattered multiple patchy infiltrates in both lungs); - SARS-CoV-2 RNA remained in the woman's sputum after 3 days hospitalized
Liu <i>et al.</i> , ²⁶ (2020)	Retrospective case review	15 pregnant women; 11 neonates	- Low lymphocyte count (n=12); - Increased C-reactive protein value (n=10)
Liu <i>et al.</i> , ²⁷ (2020)	Clinical research	- 41 pregnant women*; - 11 non-pregnant adults; * 16 pregnant women were SARS-CoV-2 positive; 17 tested -negative but with typical CT features of COVID-19 pneumonia; and the other 8 did not undergo SARS-CoV-2 test	- Leukocytosis and elevated neutrophil ratio were more frequent in pregnant women (n=8/16 and 9/25); - Lymphopenia (n=9/16 and 16/25); - Decreased lymphocyte ratio (n=16/16 and 22/25); - Elevated C-reactive protein (n=13/16 and 14/25); - Pleural effusion was identified in patients in the laboratorial-confirmation (n=6/16) and clinically-diagnosed pregnant groups (n=6/25)
Wang <i>et al.</i> , ³⁰ (2020)	Case report	1 pregnant woman; 1 neonate	- Lymphopenia; - Neutrophilia; - Elevated high-sensitivity C-reactive protein level; - CT with GGO
Wang <i>et al.</i> , ³¹ (2020)	Case report	1 pregnant woman; 1 neonate	- Chest CT scan with bilateral multiple GGO

continue

ALT= alanine transaminase; AST= aspartate transaminase; CT= Computerized Tomography; GGO= Ground-Glass Opacities.

Table 2

continuation

Description of pregnant women's laboratorial data and radiological characteristics in selected studies.

Author (year)	Study design	Participants	Pregnant women's laboratorial data and radiological characteristics
Wu <i>et al.</i> , ⁹ (2020)	Retrospective case review	23 pregnant women; 21 neonates	- CT images alterations (n=23); - GGO (n=23); - Single lung lobe (n=9); - Multiples lung lobe (n=14)
Xia <i>et al.</i> , ³² (2020)	Case report	1 pregnant woman; 1 neonate	- Neutrophils 4.48 (x10 ⁹ L ⁻¹); - Lymphocytes 0.74 g L ⁻¹ ; - C-reactive protein 99.6 mg L ⁻¹
Yan <i>et al.</i> , ³³ (2020)	Retrospective case review	116 pregnant women; 84 neonates	- Low levels of leukocyte (n=96); - Low levels of lymphocytes (n=42); - Elevated levels of C-reactive protein (n=36); - GGO (n=88)
Yu <i>et al.</i> , ³⁴ (2020)	Retrospective case review	7 pregnant women; 7 neonates	- Neutrophil levels above the normal range (n=5); - Decreased lymphocytes (n=5); - Decreased platelets (n=2); - D-dimer above normal (n=7); - Liver function abnormality (n=2); - Increased ALT or AST, or both (n=2); - Regarding infection-related biomarkers, procalcitonin (measured in six patients) and erythrocyte sedimentation rate (measured in five patients) were above the normal ranges (n=4); - High concentrations of c-reactive protein(n=7); - Interleukin-6 was tested in four patients, all of whom had levels above the normal range; - <i>Legionella pneumophila</i> co-infections (n=1); - Bilateral pneumonia according to chest CT (n=6); - Unilateral pneumonia according to chest CT (n=1)

continue

ALT= alanine transaminase; AST= aspartate transaminase; CT= Computerized Tomography; GGO= Ground-Glass Opacities.

Table 2

concluded

Description of pregnant women's laboratorial data and radiological characteristics in selected studies.

Author (year)	Study design	Participants	Pregnant women's laboratorial data and radiological characteristics
Zamaniyan <i>et al.</i> , ³⁵ (2020)	Case report	1 pregnant woman; 1 neonate	<ul style="list-style-type: none"> - Low levels of leukocyte; - Low levels of lymphocytes; - Elevated levels of C-reactive protein; - Chest CT: Left-sided atelectasis in inferior zone; - Bilateral GGO
Zhu <i>et al.</i> , ⁵ (2020)	Retrospective case review	9 pregnant women; 10 neonates	- Changes typical of viral pneumonia in chest CT: decreased diffuse and bilateral GGO, patchy lung consolidation, and blurred borders; when the disease progressed, the lesions merged into strips (all patients)

Table 3

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies.

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Alonso Diaz <i>et al.</i> , ¹¹ (2020)	Case report	1 pregnant woman; 1 neonate	- Cesarean section	- Low birthweight; - Respiratory distress; - Intermittent hyperpnoea; - Oxygen desaturation; - Mild blood acidosis; - GGO	Inconclusive (Baby tested positive for SARS-CoV-2, but it had direct contact with mother)
Alzamora <i>et al.</i> , ¹² (2020)	Case report	1 pregnant woman; 1 neonate	- Cesarean section - Pre-term	-Prematurity; - Respiratory difficulty; - Cough	Likely (Baby tested positive for SARS-CoV-2 and it did not have direct contact with mother. But amniotic fluid, placenta and cord blood were not tested)
Breslin <i>et al.</i> , ¹³ (2020)	Case series	29 pregnant women with symptomatic admitted; 14 pregnant women asymptomatic admitted	- Cesarean section (n=8); - Vaginal delivery (n=10); - Pre-term (n=1)	- Prematurity (n=1); - Congenitally diagnosed multi-cystic dysplastic kidney after delivery (n=1); - Respiratory distress (n=1)	No evidence of VT (all babies tested negative by nasopharyngeal swab)
Breslin <i>et al.</i> , ¹⁴ (2020)	Case series	7 pregnant women	- Cesarean section (n=2)	- Not informed	Not informed
Buonsenso <i>et al.</i> , ¹⁵ (2020)	Case series	4 pregnant women; 2 neonates	- Cesarean section (n=2)	- No alteration informed	No evidence of VT (Babies were tested negative. Cord blood was tested negative)

continue

VT= Vertical transmission; PROM= Premature Rupture of Membranes; ICU= Intensive Care Unit; SGA= Small-for-gestational-age; PCIS= Pediatric Critical Illness Score; NRDS= Neonatal Respiratory Distress Syndrome; DIC= Disseminate Intravascular Coagulation.

Table 3

continuation

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies.

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Chen <i>et al.</i> , ¹⁰ (2020)	Retrospective case review	9 pregnant women; 9 neonates	- Cesarean section (n=8); - Emergency cesarean section (n=1); - Gestational age at birth: 36-39 weeks + 4 days; - Fetal distress (n=2); - Preterm birth (n=4); - PROM (n=2)	- Prematurity (n=4); - Birthweight lower than 2,500 g (n=2); - Mild increase in myocardial enzymes (n=1)	Inconclusive (one baby diagnosed with SARS-CoV-2 36h after birth, even after being isolated from the mother. Nevertheless, placenta, cord blood and amniotic fluid were negative for the virus)
Chen <i>et al.</i> , ¹⁶ (2020)	Case series	17 parturients; 17 neonates	- Cesarean section (n=14); - Emergency cesarean section (n=3)	- Premature birth with normal weight (n=3)	No evidence of VT (no babies tested positive for SARS-CoV-2)
Chen <i>et al.</i> , ¹⁷ (2020)	Case report	4 neonates; 4 pregnant women	- Cesarean section in the acute phase of the disease (n=3); - Vaginal delivery (n=1); - All babies were born beyond 37 weeks' gestation and with birthweight above 3,000 g	- Negative for COVID-19 (n=3). One baby's parents did not provide consent for their baby to be tested for COVID-19; - Rashes of unknown etiology at birth (n=2); - Facial ulcerations (n=1); - Tachypnea (n=1); - Edema of the lateral thigh and low level of serum albumin (n=1)	No evidence of VT (no babies tested positive for SARS-CoV-2)

continue

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Table 3

continuation

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies.

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Fan <i>et al.</i> , ¹⁸ (2020)	Case series	2 pregnant physicians; 2 neonates	- Cesarean section (37 weeks and 36 weeks and 5 days) (n=2); - Preterm (n=1)	- Prematurity with normal weight (n=1); - Pneumonia (n=1); - Lymphopenia (n=2); - Low-grade fever (n=1); - Abdominal distension (n=1)	No evidence of VT (no babies tested positive for SARS-CoV-2. Baby's nasopharyngeal swab, and maternal serum, placenta tissue, umbilical cord blood, amniotic fluid, vaginal swabs and breast milk were tested)
Ferrazzi <i>et al.</i> , ⁸ (2020)	Retrospective case review	42 pregnant women; 42 neonates	- Elective cesarean section for conditions determined by COVID-19 (n=10); - Elective cesarean section for reasons unrelated with COVID-19 (n=8); - Vaginal delivery (n=24); - Pre-term (n=11)	- Prematurity (n=11); - Respiratory symptoms (n=1); - Gastrointestinal symptoms (n=1)	Inconclusive (3 babies tested positive for SARS-CoV-2 through throat swab tested by RT-PCR)
Gidlóf <i>et al.</i> , ¹⁹ (2020)	Case report	1 pregnant woman; 2 neonates	- Emergency cesarean section; - Pre-term	- Prematurity; - Twin 1 had a birthweight of 2,680 g. At 22 minutes after childbirth it developed breathing problems. Twin 2 had a birthweight of 2,160 g	No evidence of VT (Both twins had negative nasopharyngeal Covid-19 tests taken at 34 hours; and 4½ days of age)

continue

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Table 3

continuation

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies..

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
González Romero <i>et al.</i> , ²⁰ (2020)	Case report	1 pregnant woman; 1 neonate	- Cesarean section; - Pre-term	- Prematurity; - Low birthweight	Not informed (Baby untested for SARS-CoV-2)
Hantoushzadeh <i>et al.</i> , ²¹ (2020)	Retrospective case review	9 pregnant women; 7 neonates	- Cesarean section (n=6); - Vaginal delivery (n=1); - Pre-term (n=5)	- Prematurity (n=5); - Low birthweight (n=4); - Neonatal pneumonia (n=1); - Neonatal mortality (n=4; twin pregnancy)	No evidence of VT (One was tested positive for SARS-CoV-2 after 7 days of live through nasopharyngeal swab test)
Iqbal <i>et al.</i> , ²² (2020)	Case report	1 pregnant woman; 1 neonate	- Uncomplicated Spontaneous vaginal delivery	- Telephone follow-up after childbirth indicated there were no signs of neonatal infection	Not evidence of VT (no evidence of neonatal or intraamniotic infection)
Kalafat <i>et al.</i> , ²³ (2020)	Case report	1 pregnant woman; 1 neonate	- Reduced fetal movements; - Elective Cesarean section	- Birthweight of 2,790 g	No evidence of VT (neonatal swabs, cord blood, and placental swab RT-PCR tests were negative for SARS-CoV-2)

continue

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Table 3

continuation

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies..

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Li <i>et al.</i> , ²⁴ (2020)	Case-control	<p>Case groups:</p> <ul style="list-style-type: none"> - Confirmed cases who were tested positive for SARS-CoV-2 (n=16); - Suspected cases with typical chest CT imaging but negative in RT-PCR tests (n=18); <p>Control groups:</p> <ul style="list-style-type: none"> - Women admitted during January 24 – February 29, 2020 (n=120); - Women admitted during January 24 – February 11, 2019 (n=121); <p>Neonates:</p> <ul style="list-style-type: none"> - Confirmed case group (n=17); - Suspected case group (n=19); - Control 2020 (n=121); - Control 2019 (n=121) 	<ul style="list-style-type: none"> - Gestational weeks on admission ranged: 33 + 6 to 40 + 4; <p>Cesarean section:</p> <ul style="list-style-type: none"> - Confirmed case group (n=14); - Suspected case group (n=16); - Control 2020 (n=57); - Control 2019 (n=44); <p>Pre-term:</p> <ul style="list-style-type: none"> - Confirmed case group (n=3); - Suspected case group (n=3); - Control 2020 (n=7); - Control 2019 (n=6); <p>Fetal distress:</p> <ul style="list-style-type: none"> - Confirmed case group (n=2); - Suspected case group (n=1); - Control 2020 (n=6); - Control 2019 (n=6); <p>PROM and placental abruption:</p> <ul style="list-style-type: none"> - Confirmed case group (n=2); - Suspected case group (n=0); - Control 2020 (n=0); - Control 2019 (n=0) 	<p>Prematurity:</p> <ul style="list-style-type: none"> - Confirmed case group (n=4); - Suspected case group (n=4); - Control 2020 (n=7); - Control 2019 (n=6); <p>Low birthweight:</p> <ul style="list-style-type: none"> - Confirmed case group (n=3); - Suspected case group (n=2); - Control 2020 (n=3); - Control 2019 (n=3) 	No evidence of VT (all of them tested negative for SARS-CoV-2)

continue

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Table 3

continuation

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies.

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Li <i>et al.</i> , ²⁵ (2020)	Case report	1 pregnant woman; 1 neonate	- Emergency cesarean section in the 35 th gestational week (pre-term); - No complications during delivery	- Prematurity; - Fetal heart rate monitor showed 110 beats/min that resulted in medical decision for emergency cesarean section; - baby was negative for SARS-CoV-2 immediately after he was taken from the uterus and after 2 days	No evidence of VT (Baby tested negative for SARS-CoV-2. Urine, feces, amniotic fluid, umbilical cord blood, placenta and breast milk were tested)
Liu <i>et al.</i> , ²⁶ (2020)	Retrospective case review	15 pregnant women; 11 neonates	- Cesarean section (n=10); - Vaginal delivery (n=1); - Delivery time ranged from 34 to 38 gestational weeks	Not informed	No evidence of VT (no babies tested positive for SARS-CoV-2)
Liu <i>et al.</i> , ²⁷ (2020)	Clinical research	- 41 pregnant women*; - 11 non-pregnant adults; *16 pregnant women were SARS-CoV-2 positive; 17 laboratory-negative but with typical CT features of COVID-19 pneumonia; and the other 8 did not undergo SARS-CoV-2 test	- Gestational age ranged from 22 weeks to 40 weeks + 5 days	Not informed	Not informed

continue

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Table 3

continuation

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies.

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Liu <i>et al.</i> , ²⁸ (2020)	Retrospective case review	13 pregnant women; 13 neonates	- 3 patients improved after hospitalization and got discharged with an uncomplicated ongoing pregnancy; - Cesarean section in 10 patients, being emergency cesarean section in 5 patients due to complications; - Fetal distress (n=3); - PROM (n=1); - Stillbirth (n=1); - Preterm labor between 32-36 weeks of gestation (n=6)	- Prematurity (n=6); - Death (n=1)	No evidence of VT (no babies tested positive for SARS-CoV-2)
Song <i>et al.</i> , ²⁹ (2020)	Case report	1 pregnant woman; 1 neonate	- Emergency cesarean section (36 weeks and 3 days); - Preterm	- Prematurity with normal weight (3.63 kg)	No evidence of VT (Baby did not test positive for SARS-CoV-2)
Wang <i>et al.</i> , ³⁰ (2020)	Case report	1 pregnant woman; 1 neonate	- Cesarean section (40 weeks)	- Lymphopenia; - Deranged liver function tests; - Elevated total and indirect bilirubin; - Elevated creatine kinase level	Inconclusive (Baby tested positive for SARS-CoV-2. Cord blood, placental specimens and breast milk were tested)

continue

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Table 3

continuation

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies..

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Wang <i>et al.</i> , ³¹ (2020)	Case report	1 pregnant woman; 1 neonate	- Emergency cesarean section during the 30 th gestational week; - Preterm	- No fetal movement and no variability of fetal heart rate; - Prematurity; - Low birthweight (1.83 kg); - Kept in isolation ICU for observation; - Baby had an uneventful neonatal course	No evidence of VT (Baby did not test positive for SARS-CoV-2. Amniotic fluid, placenta, umbilical cord blood, gastric juice and throat swabs were tested)
Wu <i>et al.</i> , ⁹ (2020)	Retrospective case review	23 pregnant women; 21 neonates	- Cesarean section (n=18); - Vaginal delivery (n=2)	Not informed	No evidence of VT (4 babies tested negative for SARS-CoV-2 RT-PCR. Others were not tested)
Xia <i>et al.</i> , ³² (2020)	Case report	1 pregnant woman; 1 neonate	- Emergency cesarean section (37 weeks and 2 days)	Not informed	No evidence of VT (Baby did not test positive for SARS-CoV-2)
Yan <i>et al.</i> , ³³ (2020)	Retrospective case review	116 pregnant women 84 neonates	- Cesarean section (n=85); - Vaginal delivery (n=14); - Pre-term (n=23); - Fetal distress (n=9); - Abnormal placenta (placenta previa) (n=3); - Abnormal fetal growth (n=2)	- Prematurity (n=23); - Low birthweight (n=8); - Death (n=1)	No evidence of VT (Baby did not test positive for SARS-CoV-2. Cord blood, amniotic fluid, vagina mucus and breast milk were tested)

continue

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Table 3

continuation

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies..

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Yu <i>et al.</i> , ³⁴ (2020)	Retrospective case review	7 pregnant women; 7 neonates	- Cesarean section; - Delivery time ranged from 37 weeks to 41 weeks plus 2 days	- Mild shortness of breath symptoms. - Chest x-ray revealed mild pulmonary infection (n=1)	Inconclusive (one baby diagnosed with SARS-CoV-2 36h after birth, but placenta and cord blood were negative for virus)
Zamaniyan <i>et al.</i> , ³⁵ (2020)	Case report	1 pregnant woman; 1 neonate	- Cesarean section; - Pre-term	- Prematurity; - Low birthweight; - Fever	Likely (Baby was tested positive for SARS-CoV-2 and it did not have direct contact with mother. Amniotic fluid tested positive for SARS-CoV-2)
Zambrano <i>et al.</i> , ³⁶ (2020)	Case report	1 pregnant woman; 1 neonate	- Obstetric ultrasound: fetus with a dysplastic and multicystic right kidney; - Pre-term; - Vaginal delivery	- Prematurity (32 gestational week); - Birthweight of 1,500 g	No evidence of VT (nasopharyngeal and blood samples tested by SARS-CoV-2 RT-PCR were negative)

continue

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Table 3

concluded

Description of childbirth, babies' characteristics at birth and vertical transmission in selected studies.

Author (year)	Study design	Participants	Childbirth	Characteristics of the babies at birth	Vertical transmission
Zhu <i>et al.</i> , ⁵ (2020)	Retrospective case review	9 pregnant women; 10 neonates	<ul style="list-style-type: none"> - Cesarean section (n=7); - Vaginal delivery (n=2); - Pre-term (n=6); - Intrauterine distress (n=6); - PROM (5 to 7 hours before the onset of true labor) (n=3); - Abnormal amniotic fluid (n=2); - Abnormal umbilical cord (n=2); - Abnormal placenta (placenta previa) (n=1) 	<ul style="list-style-type: none"> - Prematurity (n=6); - SGA (n=2); - Large-for-gestational-age (n=1); - PCIS score of less than 90 (n=6); - First symptom: Shortness of breath (n=6); - Fever (n=2); - Rapid heart rate (n=1); - Feeding intolerance, bloating, refusing milk, and gastric bleeding (n=4); - Abnormalities in chest x-ray: infectious (n=4), NRDS (n=2), and pneumothorax (n=1); - Thrombocytopenia complicated with abnormal liver function (n=2); - One pre-term neonate (34 weeks and 5 days) had shortness of breath and moaning. Eight days later he developed refractory shock, multiple organ failure, and DIC. He died on the 9th day; - One preterm neonate (34 weeks and 6 days) had shortness of breath and moaning. He suffered from frequent oxygenation fluctuations at 3 days of age, along with poor response and sharp drop in platelets. He was cured 15 days later 	No evidence of VT (no babies tested positive for SARS-CoV-2)

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be helpful to diagnose virus pneumonia.²⁷ In their study, some patients tested by real-time reverse transcription polymerase chain reaction assay (RT-PCR) retrieved negative results and presented alterations on chest CT images, such as patchy shadows and/or ground-glass opacities. In this case, chest CT seems to have a high accuracy to diagnose SARS-CoV-2 infections and present low levels of false negative results,^{9,10,13,15,19,23,33} unlike RT-PCR. In addition, relevant clinical examinations such as blood cell counts should be performed together with a comprehensive assessment of the patient's medical history, epidemiological exposure and symptoms in general.^{8-10,13,24,33}

It is important to highlight that, despite chest CT not being frequently conducted on pregnant women due to its level of radiation, in Liu *et al.*²⁷ the dose was adjusted to pregnant women to allow the acquirement of images that could present signals of viral infection. This adjustment was responsible for lower-resolution images, but the quality of these images was sufficient to diagnose viral pneumonia and other alterations, such as ground-glass opacities.

All studies included in this review diagnosed patients with SAR-CoV-2 infection by using RT-PCR. However, it is important to highlight that several studies reported the possibility of a false negative result for patients who might have been infected by SARS-CoV-2.^{5,10,27,30,33,34} Previous evidence has argued that false negative results could have happened due to insufficient viral load, sampling at early or late stage of the illness, and inappropriate swabbing sites.³⁰ In Fan *et al.*¹⁸ study a pregnant patient was positive diagnosed with SARS-CoV-2 after two negative samplings, and Liu *et al.*²⁷ conducted several analyses in 25 pregnant women clinically-diagnosed but they had not received the laboratorial- confirmation.

Due to this uncertainty related to false negative results, almost all reviewed papers reported the election of a cesarean section (n = 239 women) for childbirth.^{8-21,23-26,28-36} Only 42 cases of pregnant women delivered babies vaginally were reported,^{5,8,9,13,17,21,22,26,33,36} but all newborns were negative for SARS-CoV-2.

Out of the 279 neonates, 17 were delivered by an emergency cesarean section.^{10,11,15,16,19,21,25,28,29,31,32} For these mothers, an emergency cesarean section was elected due to some complications such as pre-eclampsia,^{19,21} gestational hypertension,^{10,19} fetal bradycardia,¹⁵ fetal distress,^{5,10,16,28} PROM^{5,10,28} and decreased fetal movement and oxygen decompensation.²¹

Previous studies have reported the pregnant

women with viral pneumonia are more likely to have complications during pregnancy and can also lead to spontaneous miscarriage, preterm birth, low birth weight infants, intrauterine growth restriction and five-minute Apgar score <7 compared to healthy pregnant women.³⁸ The results of this study have evidenced a high rate of preterm births (n=49), and out of 273 neonates were delivered and six deaths were reported.

Previous studies have shown that SARS-CoV-2 can be transmitted from human-to-human through close contact of the droplets and also via aerosol.^{1,2} However, the potential for transmissibility from mother-to-fetus is still unknown. In this review, among 279 neonates evaluated by different studies, only ten showed a positive result for SARS-CoV-2, after at least 30 hours of childbirth.^{10,30,34} However, in some cases, the placenta, umbilical cord, amniotic fluid and breast milk were tested and no positive result for the presence of the virus was found.^{10,18,25,30,31,34} It is important to consider the possibility of false-negative in these cases, since RT-PCR method was adopted, which may have limitations due to the latency period of the virus, as previously mentioned.

Although, some authors believe that vaginal delivery may increase the risk of vertical transmission of COVID-19, the hypothesis that best explains the mother's non-viral transmission to her child was demonstrated by Zheng *et al.*,³⁹ who state that the angiotensin-converting enzyme 2 (ACE2) receptor of COVID-19 has very low expression in almost all cell types of the early maternal-fetal interface, suggesting that there may be no cells that are potentially susceptible to COVID-19 in the maternal-fetal interface.

Despite still being unclear and requiring future clinical studies with a larger sample size to guarantee scientific evidence, vertical transmission seems unlikely. However, protocols for the care of pregnant women and newborns should take into account that, although studies have not shown a positive test for SARS-CoV-2 in breast milk, breastfeeding may present risks of contamination due to direct physical contact.⁴⁰ Despite this, breastfeeding should be encouraged, but mothers should be properly advised on preventive protocols to avoid transmission.

Recently, the medical field has debated about the immunization of pregnant women against SARS-CoV-2, but clinical trials involving pregnant women are still scarce.⁴¹⁻⁴³ A shared decision-making between the mother, her family, and the obstetrician is essential. The discussion should focus on the risks

of infection, risk of morbidity and mortality, and the uncertainty regarding the safety of the vaccine in pregnancy and lactation. But it must be emphasized that at this point we do not have biologic reasons to believe that the currently approved vaccines are harmful to pregnant women or infants.^{41,43}

As well known, antibodies can be transmitted from mother to the fetus via placental transport.^{44,45} The transportation of antibodies, such as Immunoglobulin-G (IgG), protect the baby from virus infections after birth, and this process is known as passive immunization.^{44,45} However, in Wang *et al.*,⁴⁰ the IgG levels of infants decreased considerably in the first two months of life, suggesting that the passive immunization of IgG for SARS-CoV-2 provided limited protection for the infants, especially if the mother was infected with the virus for less than two weeks before delivery.

The key question to be answered at this point is whether there is transmissibility of antibodies from the pregnant woman who received the vaccine to the fetus. Rottenstreich *et al.*⁴⁶ indicated that immunization of pregnant women may provide maternal and neonatal protection, since they found antibodies (IgG) in umbilical cord serum. This is still unclear, so clinical trials should be conducted to understand the association of these outcomes.

Our study has some limitations. Because of the unprecedented nature of the subject due to the recent pandemic, few population-based clinical studies have been published in the literature assessing the health condition of pregnant women and newborns relating to the involvement of COVID-19. Most of the studies included in this review were case reports and retrospective case report analyzes with a small sample size. We suggest that longitudinal clinical studies with a representative sample be conducted in order to ensure a better understanding of the relationship among COVID-19, pregnancy and neonate outcomes. Also, the percentages of each symptom during pregnancy were calculated based on a ratio between the total number of cases and the studies that have reported such condition. If a paper had not reported a determined symptom, it was inferred that that condition was not present. Moreover, most of the studies published so far have evaluated patients in the 3rd trimester of pregnancy, which makes it impossible to understand the cause-and-effect relationship of the 1st and 2nd trimesters and COVID-19. Finally, future studies should answer some other questions, such as whether vaginal delivery increases the risk of vaginal transmissibility and whether uterine contractions increase the possibility of the virus ascending. As well as, the role of

women's vaccination on infants' protection.

Despite the limitations of this study, this review carried out an extensive search of the literature in different databases, with well-defined criteria and in a standardized protocol, which ensured the inclusion of studies published in high-impact journals.

Based on this review, it can be concluded:

1- COVID-19 in women during pregnancy results in symptoms similar to those experienced by non-pregnant women when affected by the same disease. There is a high rate of asymptomatic positive cases during pregnancy. When the cases are symptomatic, the disease is revealed in its mildest form. Fever and cough are the clinical signs commonly seen in pregnancy;

2- There is still no plausible evidence suggesting vertical transmission of SARS-CoV-2 virus from mother to child. However, in this review it was possible to observe that cesarean sections have been performed more frequently. High rates of premature births also have been reported;

3- As COVID-19 maternal illness does not appear to be as severe as SARS and MERS, the high rate of cesarean section is unreasonable. Obstetricians should assess case by case in order to avoid the indication of unnecessary cesarean sections;

4- Although there is no evidence of the virus in the infected woman's breast milk, breastfeeding might lead to the baby's infection due to the close contact. Nevertheless, breastfeeding should be encouraged, but mothers should be given adequate guidance on preventive protocols to avoid transmission.

Authors' contribution

Foratori-Junior GA and Mosquim V contributed with literature search, figures, study design, data collection, data analysis, data interpretation and writing of this manuscript. Machado MAAM, Oliveira TM and Sales-Peres SHC contributed with study design, data analysis, data interpretation and writing of this manuscript. All authors approved the final version of the article.

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