Complications and outcomes of SARS-CoV-2 in pregnancy

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Complications and outcomes of SARS-CoV-2 in Pregnancy: Where and What is the Evidence?

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Complications and outcomes of SARS-CoV-2 in Pregnancy: Where and What is the Evidence?

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Complications and outcomes of SARS-CoV-2 in Pregnancy: Where and What is the Evidence?

Abstract

Objectives

Add to the evidence on SARS-CoV-2 in pregnancy, to better inform decision making and optimize patient outcomes.

Methods

Systematic review on March 25, 2020 and a repeat PUBMed search on April 10, 2020 including pregnant patients with SARS-CoV-2 infection at any time during their pregnancy.

Results

We reviewed a total of 155 pregnancies and 118 perinatal outcomes. Evidence proposes similar rate of severe cases in pregnant women and the general population. The frequency of cesarean deliveries is high, against guidelines recommendations.

Conclusion

Limited data on COVID-19, associated with a wide variation in the methodology makes accurate data interpretation difficult.

Keywords: SARS-CoV-2; pregnancy; vertical transmission; perinatal

Funding details

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Disclosure statement

The authors report no conflict of interest.

Introduction

The emergence of a novel coronavirus (SARS-CoV-2) and the potentially life threatening respiratory disease it can produce (COVID-19)[1] has had the world on high alert since December 2019. SARS-CoV-2 infection begun as an epidemic in Wuhan, China but was declared a global pandemic by the World Health Organization (WHO) by March 11, 2020[2] due to its exponential spread and increase of cases worldwide. As of April 10, 2020 over 1.5 million cases have been documented with over 90,000 deaths internationally[3]. This situation generated a global health care crisis with pressing need for up to date scientific evidence.

Pregnancy is associated with various maternal physiological adaptations in the immune (immunosuppression) and cardiorespiratory (e.g., physiologic anemia, diaphragm elevation) systems that make this cohort of patients susceptible to theoretically poor outcomes of viral respiratory infections[4,5]. This was well documented by the high mortality of the Spanish flu pandemic in 1918 (37%), Severe Acute Respiratory Syndrome (SARS-25·8%) and Middle Eastern Respiratory Syndrome (MERS-28·6%); although no maternal deaths related to COVID-19 have been reported in the literature at this time, it has been suggested that it may follow a similar pattern to SARS and MERS. A recent systematic review by Di Mascio et al[4] has reported the following obstetrical outcomes in patients affected by SARS-CoV-2: preterm birth, pre-eclampsia, preterm-premature rupture of membranes (PPROM), and cesarean section.

There presently are limited data on the clinical course, maternal and perinatal outcomes of SARS-CoV-2 infection in pregnancy. Additionally, there is a wide variation in the methodology and data reporting in recently published cases, making accurate data interpretation difficult. The present study is a comprehensive systematic review that provides a summary of reported outcomes and critical appraisal of the rapidly evolving literature on SARS-CoV-2 infection in pregnancy. This systematic review will add to the growing body of evidence on the topic to better inform decision making and optimize patient outcomes.

Methods

Search strategy and selection criteria

A comprehensive search of several databases from January 2019 to March 25, 2020 was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and ClinicalTrials.Gov. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for COVID-19 and SARS-CoV-2 infection in pregnancy. The actual strategy listing all search terms used and how they are combined is available in the Appendix.

Due to the rapidly evolving nature of the evidence, a repeat search of the PubMED database was conducted on April 10, 2020 to include newly published relevant studies. Studies evaluating pregnant patients with COVID-19/SARS-CoV-2 infection at any time during their pregnancy were included. Exclusion criteria were studies of COVID-19/ SARS-CoV-2 infection in non-pregnant patients and review articles. Neither language nor sample sizes were a criterion for exclusion; case reports and case series were included due to paucity of data. Screening of abstracts retrieved from the initial

literature search was performed independently by two reviewers (AT and AE). Minor discrepancies were resolved after reviewing the full text of database articles with the input of a third reviewer (EI). All reviewers agreed on the papers included in this study.

Data analysis

The authors designed a standardized table for data abstraction from eligible articles. The following data were collected: author and date of publication, number of pregnant patients, gestational age at infection, days from presentation to delivery, obstetric comorbidities, mode of delivery, presenting symptoms, ICU admissions, diagnostic methods, laboratory alterations and medical interventions. From the neonates we recorded number of children born, gestational date at delivery, comorbidities, and outcomes, including SARS-CoV-2 infection diagnosis and NICU admission. The data is presented in a descriptive fashion as number of cases and percentages.

Results

The initial electronic literature search yielded 84 results, 73 of which did not meet our eligibility criteria and were therefore excluded: 20 review articles, 15 links to Clinicaltrials.gov of ongoing registries and trials on COVID-19/SARS-CoV-2 infection, 25 studies unrelated to pregnancy, 10 expert opinions, 2 studies with overlapping patient cohorts and endpoints as other relevant studies, and 1 case report with no access to the full text article. Subsequently, 5 additional manuscripts were retrieved from the repeat database search. Finally, 16 studies were included in this review (Figure 1) with 155 pregnant patients; perinatal outcomes were described in 118 cases born to 116 mothers. At the time of publication of the included studies, 33 (33/155; 21·3%) pregnancies were still ongoing with no perinatal data available, Zhang L et al[6] provided data on 10 of 16 deliveries, Li N[7] and Zhu H[8] included one set of twins each. Collected data is summarized in Table 1.

Maternal age ranged from 20 to 45 years with a mean of 29. The majority (150/155; 96.8%) of patients acquired the infection during the third trimester, 3.2% (5/155) in the second trimester and none were reported in the first trimester. Maternal comorbidities (pre-eclampsia- 4/122; 3.3%, gestational hypertension- 5/122; 4.1%and gestational diabetes- 10/122; 8,2%) were seldom reported; 87.7% (136/155) of patients had a low risk pregnancy until the time of publication, 33 of these were still ongoing and were excluded from the cohort when looking at maternal comorbidities.

The most common presenting symptoms of maternal SARS-CoV-2 infection were fever (80/139; 57.6%), followed by cough (44/139; 31.7%), dyspnea or shortness of breath (19/139; 13.7%), and gastrointestinal alterations (8/139; 5.8%); 20.9% (29/139) of patients were asymptomatic. Zhang L et al[6] did not report the presenting symptoms of 16 patients, which were excluded from this analysis.

SARS-CoV-2 infection was diagnosed using reverse transcriptase polymerase chain reaction (RT-PCR) SARS-CoV-2 test in all but 2 patients, who were deemed false-negatives after classic CT alterations were noted in conjunction with clinical presentations. CT evidence of viral pneumonia was also documented in 53.5% (82/155) of cases; with changes such as “patchy lung consolidation” with ground glasslike opacities around the border and dominant sub pleural distribution [9-11]. Amongst the 82 patients who had a CT, only one with confirmed PCR showed no alterations. The

most reported laboratory alteration was lymphopenia (32/90; 35.6%); neutrophilia was present in only 8.8% (8/90) of patients.

A total of 29 patients were considered asymptomatic. Eight of the 14 asymptomatic patients reported by Breslin N[12] developed fever during hospital admission as well as one of the two reported by Li N[7].

Disease management varied according to each institution. Antivirals (Lopinavir, Ritonavir, Oseltamivir, and Ganciclovir), antibiotics (Cefoperazone, Sulbactam, Ceftriaxone, Cefazolin, and Azithromycin), corticosteroids (Dexamethasone, Methylprednisolone), and supplemental oxygen were used on a case by case basis.

Reported intrapartum management also varied considerably; 7.8% (9/116) of mothers delivered vaginally with the use of appropriate sterilization and personal protective equipment (PPE); 92.2% (107/116) of patients delivered by cesarean section but the indications for delivery varied amongst studies. Maternal indications included preeclampsia[5,13], prior C-section[5,6,12], and low maternal oxygen saturation[9,13], The fetal indications were described as premature rupture of membranes and "fetal distress/compromise"[5,6,8,10,12,14-16].There was no clear indication for C-section in 3 studies (38 patients): Lui D et al[17] believed it was necessary to implement antiviral therapy, Li N et al[7] mentioned that it was based on their hospital guidelines, and Yu N et al[18] considered it necessary due to the potential impact of the antiviral medication for maternal treatment and/or the virus itself on the fetus. Most notable obstetric outcomes were PPROM (10/116; 8.6%) and preeclampsia (4/116; 0.8%)

Five mothers (3.2%; 5/155) required ICU admission for severe disease; two patients, from Juusela A et al[13] and Liu Y[16], were still in the ICU at the time of publication. The remaining mothers, who had successfully delivered, survived to discharge and either tested negative for the virus or had resolution of clinical symptoms and CT alterations by the end of the study.

Perinatal outcome was described in 118 neonates born to116 patients (116/155; 74.8%). Gestational age at delivery was > 36 weeks in 77 neonates (77/118; 65.3%), between 32-36 weeks in 19 neonates (19/118; 16.1%), and < 32 weeks in one neonate (1/118; 0.8%); this information was not available for 21 neonates (21/118; 17.8%) described in two studies [12,14].
NICU admission was required in 24 neonates (24/118; 20.3%), although this may have be overestimated since the report by Chen R et al[14] admitted all babies born to SARS-CoV-2 positive mothers regardless of neonatal symptoms and signs. Low birth weight was reported in 14 (14/118; 11.8%) neonates and 5 (5/118; 4.2%) developed pneumonia. Perinatal outcomes were favorable in all but 2 cases: one stillbirth and a neonatal death. The stillbirth occurred at 34 weeks gestation by a mother with severe SARS-CoV-2 infection who deteriorated and needed ICU admission, with multiple organ dysfunction and acute respiratory distress syndrome requiring Extracorporeal Membrane Oxygenation[15]; the only neonatal death was a neonate born at 34 5/7 days gestation that developed shortness of breath 30 minutes after birth and subsequently died, 8 days later, from "refractory shock and multi-organ failure"[14].
Placenta, amniotic fluid, umbilical cord blood, breastmilk, gastric juice, urine, and feces were all screened for SARS-CoV-2 in different studies[5,10,15,16,19] and were reported as negative, suggesting a possible lack of vertical transmission. One of the 95

neonates who underwent SARS-CoV-2 PCR tested positive, 36 hours after birth with isolation from the mother[18]. Additionally, one patient who tested negative for SARS-CoV-2 PCR had positive SARS CoV-2 IgM and IgG[20]. Hence, the possibility of vertical transmission is inconclusive at this point.

Discussion

Since the initial description in Wuhan, China; and the following global spread, experts have raised concerns about the potential effects of SARS-CoV-2 in pregnant women[21-23]. This present systematic review describes the clinical course and outcomes of 155 pregnant women with SARS-CoV-2, 20.9% of which were initially asymptomatic. The most common presenting clinical and laboratory findings were fever (80/139; 57.6%) and lymphopenia (32/90; 35.6%). One patient (out of 82 screened) had a negative 'chest CT' despite a positive RT-PCR. The majority of patients delivered by cesarean section, but the indications varied considerably. Unfavourable neonatal outcomes were reported in only two cases (2/118; 1.7%), one stillbirth and a neonatal death and there was minimal evidence of vertical transmission (although SARS-CoV-2 PCR was positive in one neonate 36 hours after birth and another had evidence of SARS CoV-2 IgM and IgG 2 hours after birth).

Maternal physiological changes in the respiratory system predispose pregnant women to severe respiratory infections. This patient cohort is typically less tolerant to hypoxia due to decreased chest wall compliance associated with a slight decrease in airway resistance[24]. In addition, immunological adaptations including alterations in inflammation and cell-mediated immunity are necessary to sustain pregnancy. Maternal immunological state actively adapts throughout gestation in three stages: an initial pro-inflammatory state that allows embryo implantation and placentation, then a shift to an anti-inflammatory state in the second trimester to allow fetal growth and inhibit induction of labour and, finally, a second pro-inflammatory state takes place in the third trimester to aid in delivery. Each stage is a fine balance that can be- disturbed by viral infections, leading to complications[25].

Recent evidence suggests that severe cases of SARS-CoV-2 are associated with the occurrence of a cytokine-storm, an overproduction of pro-inflammatory cytokines and chemokines that leads to extensive lung damage and acute respiratory distress syndrome.[26] If infection is associated with one of the pro-inflammatory periods of pregnancy, the cytokine-storm caused by SARS-CoV-2 may induce a more severe and harmful inflammatory state. In addition, negative outcomes have been described in association with the presence of excess cytokines in pregnant patients: pregnancy loss and preterm delivery have been correlated to high concentrations of systemic cytokines in women with malaria[27]and maternal immune activation with increase in IL-17 levels has been shown to induce an autism-like phenotype and abnormalities in brain development[28].

A recent systematic review by Di Mascio et al[4] described the outcomes of combined coronavirus spectrum (SARS, MERS and SARS-CoV-2) in pregnant women. The rates of miscarriage (39.1%; 95% CI 20.2-59.8), preterm birth (24.3%; 95% CI 12.5-38.6 for <37 weeks gestation and 21.8%; 95%CI 12.5 -32.9 for <34 weeks gestation), preeclampsia (16.2% 95% CI 4.2-34.1), and cesarean section (83.9%; 95% CI 73.8-91.9) were much higher in pregnant women with coronavirus infections although these

findings could not be reliably attributed to the virus infections alone. In addition, there was no evidence of vertical transmission with any coronavirus, but perinatal death was 10% and up to 50% of newborns required NICU admission. However, this data seems to change when evaluating SARS-CoV-2 independently so comparison between the different viral strains must be done with caution.
A systematic review of 108 pregnant women with SARS-CoV-2 and 50 deliveries was performed by Zaigham M. et al[29]. They found maternal fever to be most presented symptom at admission (68%), reported lymphocytopenia in 59% of cases, 3% of maternal ICU admission, and no maternal death. One case is referred as possible vertical transmission with a positive SARS-CoV-2 PCR on the neonate throat swab. The present review found similar patterns in presenting symptoms, laboratory alterations, and maternal ICU admission, now in a larger cohort. A new case of neonate with positive SARS-CoV-2 serology (IgM/IgG) and negative PCR on nasopharyngeal swabs adds to the questions surrounding possible vertical transmission and warrants more research on the matter. Additionally, Wang W et al[30] investigated the bio distribution of SARS-CoV-2 among different tissues in patients with confirmed SARS-CoV-2 detection and found that bronchoalveolar lavage showed the highest positive rates of 93%, nasal swabs were positive in only 63% of cases and blood in only 1%.

The higher percentage of asymptomatic patients (14/43; 32.5%) reported by Breslin N et al[9] in a study conducted in New York, where more broad testing indications have been adopted, indicates that the rate of asymptomatic patients likely surpasses the one encountered by this review (and this is probably the case for all SARS-CoV-2 infection). This same study drives attention to the higher number of vaginal deliveries (10/18; 55.5%) since SARS-CoV-2 infection was not considered an indication for C-section by international guidelines[31,32].

The variation in reported methodology in the included studies and in the available literature is a potential limitation of our systematic review. Missing information was detected from demographic characteristics to selected outcomes, making standardization of the data a challenge. Detecting possible overlaps between studies characterized one of our biggest obstacles since authors failed to provide sufficient information on each patient and to outline previously reported patients. This was addressed to the best of our abilities by reviewing location and patient demographic but the possibility overlapping patient cohorts cannot be reliably excluded. The available data on SARS-CoV-2 infection in pregnancy is still limited, but the strength of the present systematic review is that it included more recent studies with more pregnant women infected by the SARS-CoV-2. Therefore, this review contributes to the growing body of evidence. For a more robust data, large multicenter database studies are necessary with the adoption of high-quality methodology (Clinicaltrials.gov identifier: NCT04315870, NCT04323839).

Conclusion

Current evidence proposes a similar rate of severe cases of SARS-CoV-2 infection in pregnant women and the general population. The most common presenting symptom is fever and the number of asymptomatic patients is likely still underestimated. Even with current guidelines advising against C-section for pregnant women with SARS-CoV-2 infection, the frequency of cesarean deliveries is high in this population of patients, requiring clarification. The studies have suggested lack of clinical evidence of vertical

transmission, but a recent report has shown the presence of IgM antibodies in one newborn two hours after birth. There is need to monitor the emerging body of information and improve the level of quality of the studies to allow evidence-based decisions regarding pregnant patients.

Appendix 1- Detailed search strategy

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials February 2020, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 19, 2020, Embase 1974 to 2020 March 24, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 24, 2020

Search Strategy:

#	Searches	Results
1	((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV or HCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and wuhan) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,hw,kw.	4640
2	Fetal Diseases/	37947
3	fetus disease/	13101
4	exp Fetus/	346783
5	exp Pregnancy/	1558125
6	exp Pregnancy Complications/	551825
7	exp Prenatal Care/	176224
8	exp Obstetric Surgical Procedures/	289204
9	exp Pregnancy Outcome/	133368
10	(abortion* or antenatal* or birth or births or "Cesarean Section*" or "child bearing" or "child birth*" or childbearing or childbirth* or "c-section*" or delivery or embryopath* or episiotom* or fetal or fetopath* or Fetoscop* or fetus or fetus* or foetal or foetopath* or foetus* or gestation* or "in utero" or labor or obstetric* or parturition* or placenta* or postcesarean* or "postc-section*" or postpartal* or postpartum or pregnan* or prenatal* or prepartal* or prepartum or pseudopregnan* or "umbilical cord*").ti,ab,hw,kw.	4365582
11	or/2-10	4410318
12	1 and 11	131
13	limit 12 to yr="2019 -Current"	85
14	remove duplicates from 13	59

Scopus

1	TITLE-ABS-KEY((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV or HCoV) W/4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and wuhan) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or

Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2")

2 TITLE-ABS-KEY(abortion* or antenatal* or birth or births or "Cesarean Section*" or "child bearing" or "child birth*" or childbearing or childbirth* or "c-section*" or delivery or embryopath* or episiotom* or fetal or fetopath* or Fetoscop* or fetus or fetus* or foetal or foetopath* or foetus* or gestation* or "in utero" or labor or obstetric* or parturition* or placenta* or postcesarean* or "postc-section*" or postpartal* or postpartum or pregnan* or prenatal* or prepartal* or prepartum or pseudopregnan* or "umbilical cord*")

3 1 and 2

4 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)

5 3 and not 4

ClinicalTrials.gov

Disease or Conditon
"2019 novel coronavirus" OR "2019-nCoV" OR Coronavirus OR "COVID 19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2"

Other Terms
abortion* OR antenatal* OR birth OR births OR "Cesarean Section*" OR "child bearing" OR "child birth*" OR childbearing OR childbirth* OR "c-section*" OR delivery OR embryopath* OR episiotom* OR fetal OR fetopath* OR Fetoscop* OR fetus OR fetus*

foetal OR foetopath* OR foetus* OR gestation* OR "in utero" OR labor OR obstetric* OR parturition* OR placenta* OR postcesarean* OR "postc-section*" OR postpartal* OR postpartum OR pregnan* OR prenatal* OR prepartal* OR prepartum OR pseudopregnan*

"umbilical cord*"

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Complications and outcomes of SARS-CoV-2 in Pregnancy: Where and What is the Evidence?

Abstract

Objectives

Add to the evidence on SARS-CoV-2 in pregnancy, to better inform decision making and optimize patient outcomes.

Methods

Systematic review on March 25, 2020 and a repeat PUBMed search on April 10, 2020 including pregnant patients with SARS-CoV-2 infection at any time during their pregnancy.

Results

We reviewed a total of 155 pregnancies and 118 perinatal outcomes. Evidence proposes similar rate of severe cases in pregnant women and the general population. The frequency of cesarean deliveries is high, against guidelines recommendations.

Conclusion

Limited data on COVID-19, associated with a wide variation in the methodology makes accurate data interpretation difficult.

Keywords: SARS-CoV-2; pregnancy; vertical transmission; perinatal

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Disclosure statement

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Introduction

The emergence of a novel coronavirus (SARS-CoV-2) and the potentially life threatening respiratory disease it can produce (COVID-19)[1] has had the world on high alert since December 2019. SARS-CoV-2 infection begun as an epidemic in Wuhan, China but was declared a global pandemic by the World Health Organization (WHO) by March 11, 2020[2] due to its exponential spread and increase of cases worldwide. As of April 10, 2020 over 1.5 million cases have been documented with over 90,000 deaths internationally[3]. This situation generated a global health care crisis with pressing need for up to date scientific evidence.

Pregnancy is associated with various maternal physiological adaptations in the immune (immunosuppression) and cardiorespiratory (e.g., physiologic anemia, diaphragm elevation) systems that make this cohort of patients susceptible to theoretically poor outcomes of viral respiratory infections[4,5]. This was well documented by the high mortality of the Spanish flu pandemic in 1918 (37%), Severe Acute Respiratory Syndrome (SARS-25·8%) and Middle Eastern Respiratory Syndrome (MERS-28·6%); although no maternal deaths related to COVID-19 have been reported in the literature at this time, it has been suggested that it may follow a similar pattern to SARS and MERS. A recent systematic review by Di Mascio et al[4] has reported the following obstetrical outcomes in patients affected by SARS-CoV-2: preterm birth, pre-eclampsia, preterm-premature rupture of membranes (PPROM), and cesarean section.

There presently are limited data on the clinical course, maternal and perinatal outcomes of SARS-CoV-2 infection in pregnancy. Additionally, there is a wide variation in the methodology and data reporting in recently published cases, making accurate data interpretation difficult. The present study is a comprehensive systematic review that provides a summary of reported outcomes and critical appraisal of the rapidly evolving literature on SARS-CoV-2 infection in pregnancy. This systematic review will add to the growing body of evidence on the topic to better inform decision making and optimize patient outcomes.

Methods

Search strategy and selection criteria

A comprehensive search of several databases from January 2019 to March 25, 2020 was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and ClinicalTrials.Gov. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for COVID-19 and SARS-CoV-2 infection in pregnancy. The actual strategy listing all search terms used and how they are combined is available in the Appendix.

Due to the rapidly evolving nature of the evidence, a repeat search of the PubMED database was conducted on April 10, 2020 to include newly published relevant studies. Studies evaluating pregnant patients with COVID-19/SARS-CoV-2 infection at any time during their pregnancy were included. Exclusion criteria were studies of COVID-19/ SARS-CoV-2 infection in non-pregnant patients and review articles. Neither language nor sample sizes were a criterion for exclusion; case reports and case series were included due to paucity of data. Screening of abstracts retrieved from the initial

literature search was performed independently by two reviewers (AT and AE). Minor discrepancies were resolved after reviewing the full text of database articles with the input of a third reviewer (EI). All reviewers agreed on the papers included in this study.

Data analysis

The authors designed a standardized table for data abstraction from eligible articles. The following data were collected: author and date of publication, number of pregnant patients, gestational age at infection, days from presentation to delivery, obstetric comorbidities, mode of delivery, presenting symptoms, ICU admissions, diagnostic methods, laboratory alterations and medical interventions. From the neonates we recorded number of children born, gestational date at delivery, comorbidities, and outcomes, including SARS-CoV-2 infection diagnosis and NICU admission. The data is presented in a descriptive fashion as number of cases and percentages.

Results

The initial electronic literature search yielded 84 results, 73 of which did not meet our eligibility criteria and were therefore excluded: 20 review articles, 15 links to Clinicaltrials.gov of ongoing registries and trials on COVID-19/SARS-CoV-2 infection, 25 studies unrelated to pregnancy, 10 expert opinions, 2 studies with overlapping patient cohorts and endpoints as other relevant studies, and 1 case report with no access to the full text article. Subsequently, 5 additional manuscripts were retrieved from the repeat database search. Finally, 16 studies were included in this review (Figure 1) with 155 pregnant patients; perinatal outcomes were described in 118 cases born to 116 mothers. At the time of publication of the included studies, 33 (33/155; 21·3%) pregnancies were still ongoing with no perinatal data available, Zhang L et al[6] provided data on 10 of 16 deliveries, Li N[7] and Zhu H[8] included one set of twins each. Collected data is summarized in Table 1.

Maternal age ranged from 20 to 45 years with a mean of 29. The majority (150/155; 96.8%) of patients acquired the infection during the third trimester, 3.2% (5/155) in the second trimester and none were reported in the first trimester. Maternal comorbidities (pre-eclampsia- 4/122; 3.3%, gestational hypertension- 5/122; 4.1%and gestational diabetes- 10/122; 8,2%) were seldom reported; 87.7% (136/155) of patients had a low risk pregnancy until the time of publication, 33 of these were still ongoing and were excluded from the cohort when looking at maternal comorbidities.

The most common presenting symptoms of maternal SARS-CoV-2 infection were fever (80/139; 57.6%), followed by cough (44/139; 31.7%), dyspnea or shortness of breath (19/139; 13.7%), and gastrointestinal alterations (8/139; 5.8%); 20.9% (29/139) of patients were asymptomatic. Zhang L et al[6] did not report the presenting symptoms of 16 patients, which were excluded from this analysis.

SARS-CoV-2 infection was diagnosed using reverse transcriptase polymerase chain reaction (RT-PCR) SARS-CoV-2 test in all but 2 patients, who were deemed false-negatives after classic CT alterations were noted in conjunction with clinical presentations. CT evidence of viral pneumonia was also documented in 53.5% (82/155) of cases; with changes such as “patchy lung consolidation” with ground glasslike opacities around the border and dominant sub pleural distribution [9-11]. Amongst the

82 patients who had a CT, only one with confirmed PCR showed no alterations. The most reported laboratory alteration was lymphopenia (32/90; 35.6%); neutrophilia was present in only 8.8% (8/90) of patients.

A total of 29 patients were considered asymptomatic. Eight of the 14 asymptomatic patients reported by Breslin N[12] developed fever during hospital admission as well as one of the two reported by Li N[7].

Disease management varied according to each institution. Antivirals (Lopinavir, Ritonavir, Oseltamivir, and Ganciclovir), antibiotics (Cefoperazone, Sulbactam, Ceftriaxone, Cefazolin, and Azithromycin), corticosteroids (Dexamethasone, Methylprednisolone), and supplemental oxygen were used on a case by case basis.

Reported intrapartum management also varied considerably; 7.8% (9/116) of mothers delivered vaginally with the use of appropriate sterilization and personal protective equipment (PPE); 92.2% (107/116) of patients delivered by cesarean section but the indications for delivery varied amongst studies. Maternal indications included preeclampsia[5,13], prior C-section[5,6,12], and low maternal oxygen saturation[9,13], The fetal indications were described as premature rupture of membranes and "fetal distress/compromise"[5,6,8,10,12,14-16].There was no clear indication for C-section in 3 studies (38 patients): Lui D et al[17] believed it was necessary to implement antiviral therapy, Li N et al[7] mentioned that it was based on their hospital guidelines, and Yu N et al[18] considered it necessary due to the potential impact of the antiviral medication for maternal treatment and/or the virus itself on the fetus. Most notable obstetric outcomes were PPROM (10/116; 8.6%) and preeclampsia (4/116; 0.8%)

Five mothers (3.2%; 5/155) required ICU admission for severe disease; two patients, from Juusela A et al[13] and Liu Y[16], were still in the ICU at the time of publication. The remaining mothers, who had successfully delivered, survived to discharge and either tested negative for the virus or had resolution of clinical symptoms and CT alterations by the end of the study.

Perinatal outcome was described in 118 neonates born to116 patients (116/155; 74.8%). Gestational age at delivery was > 36 weeks in 77 neonates (77/118; 65.3%), between 32-36 weeks in 19 neonates (19/118; 16.1%), and < 32 weeks in one neonate (1/118; 0.8%); this information was not available for 21 neonates (21/118; 17.8%) described in two studies [12,14].
NICU admission was required in 24 neonates (24/118; 20.3%), although this may have be overestimated since the report by Chen R et al[14] admitted all babies born to SARS-CoV-2 positive mothers regardless of neonatal symptoms and signs. Low birth weight was reported in 14 (14/118; 11.8%) neonates and 5 (5/118; 4.2%) developed pneumonia. Perinatal outcomes were favorable in all but 2 cases: one stillbirth and a neonatal death. The stillbirth occurred at 34 weeks gestation by a mother with severe SARS-CoV-2 infection who deteriorated and needed ICU admission, with multiple organ dysfunction and acute respiratory distress syndrome requiring Extracorporeal Membrane Oxygenation[15]; the only neonatal death was a neonate born at 34 5/7 days gestation that developed shortness of breath 30 minutes after birth and subsequently died, 8 days later, from "refractory shock and multi-organ failure"[14].
Placenta, amniotic fluid, umbilical cord blood, breastmilk, gastric juice, urine, and feces were all screened for SARS-CoV-2 in different studies[5,10,15,16,19] and were

reported as negative, suggesting a possible lack of vertical transmission. One of the 95 neonates who underwent SARS-CoV-2 PCR tested positive, 36 hours after birth with isolation from the mother[18]. Additionally, one patient who tested negative for SARS-CoV-2 PCR had positive SARS CoV-2 IgM and IgG[20]. Hence, the possibility of vertical transmission is inconclusive at this point.

Discussion

Since the initial description in Wuhan, China; and the following global spread, experts have raised concerns about the potential effects of SARS-CoV-2 in pregnant women[21-23]. This present systematic review describes the clinical course and outcomes of 155 pregnant women with SARS-CoV-2, 20.9% of which were initially asymptomatic. The most common presenting clinical and laboratory findings were fever (80/139; 57.6%) and lymphopenia (32/90; 35.6%). One patient (out of 82 screened) had a negative 'chest CT' despite a positive RT-PCR. The majority of patients delivered by cesarean section, but the indications varied considerably. Unfavourable neonatal outcomes were reported in only two cases (2/118; 1.7%), one stillbirth and a neonatal death and there was minimal evidence of vertical transmission (although SARS-CoV-2 PCR was positive in one neonate 36 hours after birth and another had evidence of SARS CoV-2 IgM and IgG 2 hours after birth).

Maternal physiological changes in the respiratory system predispose pregnant women to severe respiratory infections. This patient cohort is typically less tolerant to hypoxia due to decreased chest wall compliance associated with a slight decrease in airway resistance[24]. In addition, immunological adaptations including alterations in inflammation and cell-mediated immunity are necessary to sustain pregnancy. Maternal immunological state actively adapts throughout gestation in three stages: an initial pro-inflammatory state that allows embryo implantation and placentation, then a shift to an anti-inflammatory state in the second trimester to allow fetal growth and inhibit induction of labour and, finally, a second pro-inflammatory state takes place in the third trimester to aid in delivery. Each stage is a fine balance that can be disturbed by viral infections, leading to complications[25].

Recent evidence suggests that severe cases of SARS-CoV-2 are associated with the occurrence of a cytokine-storm, an overproduction of pro-inflammatory cytokines and chemokines that leads to extensive lung damage and acute respiratory distress syndrome.[26] If infection is associated with one of the pro-inflammatory periods of pregnancy, the cytokine-storm caused by SARS-CoV-2 may induce a more severe and harmful inflammatory state. In addition, negative outcomes have been described in association with the presence of excess cytokines in pregnant patients: pregnancy loss and preterm delivery have been correlated to high concentrations of systemic cytokines in women with malaria[27]and maternal immune activation with increase in IL-17 levels has been shown to induce an autism-like phenotype and abnormalities in brain development[28].

A recent systematic review by Di Mascio et al[4] described the outcomes of combined coronavirus spectrum (SARS, MERS and SARS-CoV-2) in pregnant women. The rates of miscarriage (39.1%; 95% CI 20.2-59.8), preterm birth (24.3%; 95% CI 12.5-38.6 for <37 weeks gestation and 21.8%; 95%CI 12.5 -32.9 for <34 weeks gestation), preeclampsia (16.2% 95% CI 4.2-34.1), and cesarean section (83.9%; 95% CI 73.8-

91.9) were much higher in pregnant women with coronavirus infections although these findings could not be reliably attributed to the virus infections alone. In addition, there was no evidence of vertical transmission with any coronavirus, but perinatal death was 10% and up to 50% of newborns required NICU admission. However, this data seems to change when evaluating SARS-CoV-2 independently so comparison between the different viral strains must be done with caution.
A systematic review of 108 pregnant women with SARS-CoV-2 and 50 deliveries was performed by Zaigham M. et al[29]. They found maternal fever to be most presented symptom at admission (68%), reported lymphocytopenia in 59% of cases, 3% of maternal ICU admission, and no maternal death. One case is referred as possible vertical transmission with a positive SARS-CoV-2 PCR on the neonate throat swab. The present review found similar patterns in presenting symptoms, laboratory alterations, and maternal ICU admission, now in a larger cohort. A new case of neonate with positive SARS-CoV-2 serology (IgM/IgG) and negative PCR on nasopharyngeal swabs adds to the questions surrounding possible vertical transmission and warrants more research on the matter. Additionally, Wang W et al[30] investigated the bio distribution of SARS-CoV-2 among different tissues in patients with confirmed SARS-CoV-2 detection and found that bronchoalveolar lavage showed the highest positive rates of 93%, nasal swabs were positive in only 63% of cases and blood in only 1%.

The higher percentage of asymptomatic patients (14/43; 32.5%) reported by Breslin N et al[9] in a study conducted in New York, where more broad testing indications have been adopted, indicates that the rate of asymptomatic patients likely surpasses the one encountered by this review (and this is probably the case for all SARS-CoV-2 infection). This same study drives attention to the higher number of vaginal deliveries (10/18; 55.5%) since SARS-CoV-2 infection was not considered an indication for C-section by international guidelines[31,32].

The variation in reported methodology in the included studies and in the available literature is a potential limitation of our systematic review. Missing information was detected from demographic characteristics to selected outcomes, making standardization of the data a challenge. Detecting possible overlaps between studies characterized one of our biggest obstacles since authors failed to provide sufficient information on each patient and to outline previously reported patients. This was addressed to the best of our abilities by reviewing location and patient demographic but the possibility overlapping patient cohorts cannot be reliably excluded. The available data on SARS-CoV-2 infection in pregnancy is still limited, but the strength of the present systematic review is that it included more recent studies with more pregnant women infected by the SARS-CoV-2. Therefore, this review contributes to the growing body of evidence. For a more robust data, large multicenter database studies are necessary with the adoption of high-quality methodology (Clinicaltrials.gov identifier: NCT04315870, NCT04323839).

Conclusion

Current evidence proposes a similar rate of severe cases of SARS-CoV-2 infection in pregnant women and the general population. The most common presenting symptom is fever and the number of asymptomatic patients is likely still underestimated. Even with current guidelines advising against C-section for pregnant women with SARS-CoV-2 infection, the frequency of cesarean deliveries is high in this population of patients,

requiring clarification. The studies have suggested lack of clinical evidence of vertical transmission, but a recent report has shown the presence of IgM antibodies in one newborn two hours after birth. There is need to monitor the emerging body of information and improve the level of quality of the studies to allow evidence-based decisions regarding pregnant patients.

Appendix 1- Detailed search strategy

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials February 2020, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 19, 2020, Embase 1974 to 2020 March 24, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 24, 2020

Search Strategy:

#	Searches	Results
1	((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV or HCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and wuhan) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,hw,kw.	4640
2	Fetal Diseases/	37947
3	fetus disease/	13101
4	exp Fetus/	346783
5	exp Pregnancy/	1558125
6	exp Pregnancy Complications/	551825
7	exp Prenatal Care/	176224
8	exp Obstetric Surgical Procedures/	289204
9	exp Pregnancy Outcome/	133368
10	(abortion* or antenatal* or birth or births or "Cesarean Section*" or "child bearing" or "child birth*" or childbearing or childbirth* or "c-section*" or delivery or embryopath* or episiotom* or fetal or fetopath* or Fetoscop* or fetus or fetus* or foetal or foetopath* or foetus* or gestation* or "in utero" or labor or obstetric* or parturition* or placenta* or postcesarean* or "postc-section*" or postpartal* or postpartum or pregnan* or prenatal* or prepartal* or prepartum or pseudopregnan* or "umbilical cord*").ti,ab,hw,kw.	4365582
11	or/2-10	4410318
12	1 and 11	131
13	limit 12 to yr="2019 -Current"	85
14	remove duplicates from 13	59

Scopus

1	TITLE-ABS-KEY((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV or HCoV) W/4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and wuhan) or "Corona virinae19" or "Corona

virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2")

2 TITLE-ABS-KEY(abortion* or antenatal* or birth or births or "Cesarean Section*" or "child bearing" or "child birth*" or childbearing or childbirth* or "c-section*" or delivery or embryopath* or episiotom* or fetal or fetopath* or Fetoscop* or fetus or fetus* or foetal or foetopath* or foetus* or gestation* or "in utero" or labor or obstetric* or parturition* or placenta* or postcesarean* or "postc-section*" or postpartal* or postpartum or pregnan* or prenatal* or prepartal* or prepartum or pseudopregnan* or "umbilical cord*")

3 1 and 2

4 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)

5 3 and not 4

ClinicalTrials.gov

Disease or Conditon
"2019 novel coronavirus" OR "2019-nCoV" OR Coronavirus OR "COVID 19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2"

Other Terms
abortion* OR antenatal* OR birth OR births OR "Cesarean Section*" OR "child bearing" OR "child birth*" OR childbearing OR childbirth* OR "c-section*" OR delivery OR embryopath* OR episiotom* OR fetal OR fetopath* OR Fetoscop* OR fetus OR fetus*

foetal OR foetopath* OR foetus* OR gestation* OR "in utero" OR labor OR obstetric* OR parturition* OR placenta* OR postcesarean* OR "postc-section*" OR postpartal* OR postpartum OR pregnan* OR prenatal* OR prepartal* OR prepartum OR pseudopregnan*

"umbilical cord*"

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01/01/2019 to 03/25/2020

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Complications and outcomes of SARS-CoV-2 in Pregnancy: Where and What is the Evidence?

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Figure 1: PRISMA flow chart for Covid-19 in pregnancy

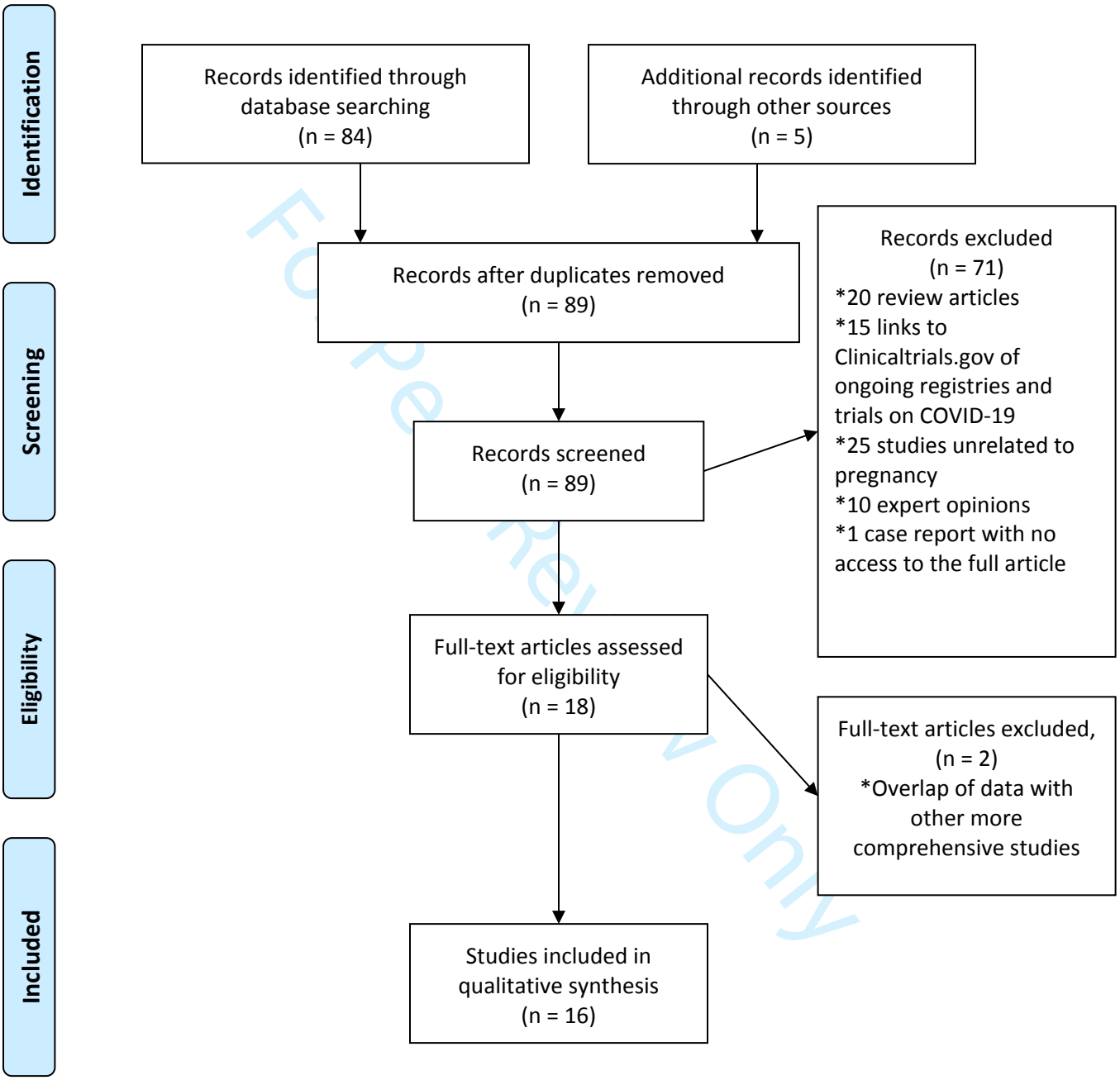

Table 1. Collected data on SARS-CoV-2 in pregnancy

	Zhu H [8]	Wang X [10]	Chen S [19]	Liu Y [16]	Yang L [15]	Chen H [5]	Liu D [17]	Wen R [11]	Zhang L [6]	Li N [7]	Chen R [14]	Xia H [9]	Yu N [18]	Dong L [20]	Breslin N [12]	Juusela A [13]	Total
	10-Feb-20	28-Feb-20	3-Mar-20	5-Mar-20	5-Mar-20	7-Mar-20	7-Mar-20	7-Mar-20	9-Mar-20	13-Mar-20	16-Mar-20	17-Mar-20	24-Mar-20	26-Mar-20	26-Mar-20	3-Apr-20	
Maternal characteristics																	
Number of patients	9	1	3	13	1	9	15	1	16	16	17	1	7	1	43	2	155
Maternal age range	25-35	N/A	23-34	22-36	30	26-40	23-40	31	24-34	26-37	N/A	27	29-34	29	20-39	26-45	
Maternal age mean	30	28	30	29	30	30	32	31	29	31	29	27	32	29	27	N/A	
Gestational age at infection (n)																	
First trimester	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Second trimester	0	0	0	2	0	0	3	0	0	0	0	0	0	0	0	0	5
Third trimester	9	1	3	11	1	9	12	1	16	16	17	1	7	1	43	2	150
Days from presentation until delivery (range)	1 to 6	4	N/A	N/A	4	1 to 7	0 to 17	N/A	N/A	N/A	N/A	4	2 to 9	25	N/A	0	
Obstetric comorbidity																	

Pre-eclampsia	0	0	0	0	0	1	0	0	1	1	0	0	0	N/A	0	1	4
Gestational hypertension	0	0	0	0	0	1	0	0	0	3	1	0	0	N/A	0	0	5
Gestational diabetes	0	0	0	0	0	0	1	0	3	3	2	0	0	N/A	0	1	10
Cesarean section	7	1	3	10	1	9	10	0	16	14	17	1	7	1	8	2	107
Ongoing pregnancy at end of study	0	0	0	3	0	0	4	1	0	0	0	0	0	0	25	0	33
Symptoms at presentation																	
Cough	4	0	0	0	1	4	9	0	N/A	2	4	0	1	0	19	0	44
Fever	8	0	3	10	0	7	13	0	N/A	12	4	1	6	1	14	1	80
Dyspnea/ Shortness of breath	0	0	0	3	0	1	1	0	N/A	2	1	0	1	1	7	2	19
Gastrointestinal alterations	1	0	0	0	0	1	1	1	N/A	2	1	0	1	0	0	0	8
Pneumonia	0	1	3	1	0	9	15	0	0	8	0	0	7	N/A	29	1	74
ICU admission	0	0	0	1	0	0	0	0	1	0	0	0	0	0	2	1	5
Asympto	0	1	0	1	0	0	2	0	N/A	2	9	0	0	0	14	0	29

matic																	
Covid 19 diagnosis																	
RT-PCR SARS-CoV 2 +	8	1	2	13	1	9	15	1	16	16	17	1	7	1	43	2	153
CT alterations	9	1	3	N/A	1	8	15	1	N/A	16	17	1	7	1	N/A	2	82
Laboratory alterations																	
Lymphopenia	N/A	1	0	N/A	0	5	12	0	0	2	5	1	5	1	N/A	0	32
Neutrophilia	N/A	1	0	N/A	1	0	0	0	0	0	0	0	5	1	N/A	0	8
Interventions																	
Supportive measures	0	1	0	1	0	9	14	1	N/A	0	0	1	7	1	1	2	38
Antiviral	4	1	0	0	1	6	11	1	N/A	1	0	0	7	1	2	1	36
Antibiotics	0	1	0	0	1	9	15	0	N/A	16	0	1	7	1	7	1	59
Corticosteroids	0	1	0	0	1	0	0	0	N/A	0	0	0	5	1	0	1	9
Neonatal characteristics																	

Number of children	10	1	3	10	1	9	11	0	10	17	17	1	7	1	18	2	118
Gestational age at delivery																	
<28 weeks	0	0	0	0	0	0	0	N/A	0	0	N/A	0	0	0	N/A	0	0
28-31 6/7 weeks	0	1	0	0	0	0	0	N/A	0	0	N/A	0	0	0	N/A	0	1
32-35 6/7 weeks	6	0	1	6	1	0	3	N/A	1	0	N/A	0	0	0	N/A	1	19
>36 weeks	4	0	2	4	0	9	8	N/A	9	17	14	1	7	1	N/A	1	77
Comorbidities																	
Premature rupture of membranes	3	0	0	1	0	2	0	N/A	3	1	0	0	0	0	0	0	10
Fetal distress	6	1	0	3	0	2	0	N/A	1	1	0	1	0	0	3	1	19
Outcomes																	
Pneumonia	4	0	0	0	0	0	0	N/A	3	0	0	0	1	1	0	N/A	9
NICU admission	N/A	1	1	0	0	0	0	N/A	0	0	17	0	1	1	3	N/A	24
RT-PCR SARS-CoV-2 +	NO	NO	NO	NO	NO	*NO	N/A	N/A	NO	**NO	NO	NO	**1	***0	NO	N/A	0
Stillbirth	0	0	0	;	0	0	0	N/A	0	0	0	0	0	0	0	N/A	1
Low	7	1	1	0	0	2	0	N/A	0	3	0	0	0	0	N/A	N/A	14

birth weight																	
Neonatal death	1	0	0	0	0	0	0	N/A	0	0	0	0	0	0	0	0	1

N/A = information not available

RT-PCR = reverse transcriptase polymerase chain reaction

*only six were tested

**only three were tested

***negative for PCR but positive SARS-CoV-2 IgM and IgG