Heliyon 7 (2021) e06393

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Impact of SARS-CoV-2 on the clinical outcomes and placental pathology of pregnant women and their infants: A systematic review

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ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Pregnant women
Placental pathology
Neonates
Placenta diseases

ABSTRACT

Pregnant women are susceptible to viral infections due to physiological changes such as cell-mediated immunity. No severe adverse pregnancy or neonatal outcomes have been consistently reported in 2019 novel coronavirus disease (COVID-19) positive pregnancy cases. There are controversies around the role of COVID-19 in pregnancy. A systematic review was conducted to examine clinical maternal and neonatal clinical outcomes. Studies were included if they reported SARS-CoV-2 infection among pregnant women and/or COVID-19 positive neonates as validated by positive antibody testing or viral testing using polymerase chain reaction. Case series, case reports, case-control studies, and comparative studies were included. Eight hundred and thirty-seven records were identified, resulting in 525 records for level I screening. Forty-one were included after full-text review. Results suggest elevated rates of intensive care unit (ICU) admission, gestational diabetes, preeclampsia, C-sections, preterm birth, and C-reactive protein (CRP) in comparison to pregnant women without SARS-CoV-2. Careful monitoring of pregnancies with SARS-CoV-2 is recommended.

1. Introduction

On January 30, 2020, the World Health Organization (WHO) declared the SARS-CoV-2 outbreak a public health emergency of international concern. Not two months later, the WHO characterized SARS-CoV-2 as a pandemic, reflecting its worldwide spread [1]. Although the virus is prevalent across all age groups, individuals that are immune-compromised such as the elderly and those with comorbidities are disproportionally affected with respect to severity of symptoms [2, 3]. Pregnant women and their foetuses are particularly susceptible to infections such as pneumonia, pyelonephritis, and periodontal disease due to physiological changes such as cell-mediated immunity, immaturity of the adaptive immune system, and dysregulation of cytokines [4, 5, 6, 7].

The vertical transmission of SARS-CoV-2 virus and its impact on neonatal clinical outcome has yet to be confirmed [8], however, several newborns have tested positive for SARS-CoV-2 [9, 10, 11]. Perinatal SARS-CoV-2 infection may not have the same adverse effects on neonatal outcome, including problems such as respiratory distress, thrombocytopenia accompanied by abnormal liver function, and even death in contrast to severe acute respiratory syndrome (SARS) and middle eastern respiratory syndrome (MERS) [12, 13]. Moreover, no severe adverse pregnancy outcomes, such as gestational hypertension, intrauterine growth restrictions, fetal distress, or stillbirth have been consistently reported in COVID-19 positive pregnancy cases [14, 15, 16]. Additional data needs to be accumulated to examine clinical outcomes of women infected with SARS-CoV-2 and their babies [12].

Given the inconclusive clinical findings, it is appropriate to conduct a systematic review on the evidence around placental pathology and SARS-CoV-2 to help contribute to the understanding of this disease and its impact on pregnancy. At present, relevant literature has relatively small sample sizes and results are diverse, inhibiting generalizability. As such, we aimed to conduct a systematic review of available literature to illustrate findings in a narrative fashion pertaining to SARS-CoV-2 on placental pathology, maternal, and neonatal outcomes.

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https://doi.org/10.1016/j.heliyon.2021.e06393
Received 18 September 2020; Received in revised form 18 November 2020; Accepted 25 February 2021

2. Methods

2.1. Search strategy and selection criteria

This is a systematic review only. The following databases were searched: MEDLINE including Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946–April 17, 2020) and Embase (1947–April 17, 2020) using the Ovid interface and Global Health (from inception) using the CAB Direct interface. Searches were developed and conducted by librarian experienced in systematic reviews, using a method designed to optimize term selection [17] and the MEDLINE search was peer reviewed by a second librarian before being translated for the other databases.

A search of Google Scholar (April 8th, 2020) through Publish or Perish was screened until 50 consecutive apparently irrelevant citations were found. Results to that point were saved as an RIS file and edited to remove patents, reports, and books. The WHO database on COVID-19 as of April 17th, 2020 was downloaded and searched within Reference Manager. Disaster Lit: Database for Disaster Medicine and Public Health, MedRxiv and OSF Preprints were searched April 19th, 2020 and relevant publications were selected and downloaded. Search strategies are presented in the supplementary file. Search alerts for MEDLINE, Embase and Google Scholar were in place throughout the review to identify newly emerging research.

After duplicate records were removed online, records retrieved by the electronic search were downloaded and imported into a Reference Manager database, and then uploaded to InsightScope [(www.insightscope.ca)] for title and abstract screening and full text review. Prior to gaining access to the full set of citations, each reviewer (JT, BR, CB, and YN) screened a test set of 50 citations (containing 5 true positives, 45 true negatives) requiring accuracy of $\geq$ 80% to qualify as a reviewer. At both the title/abstract and full text review stages, citations were excluded only if both reviewers agreed to exclude; disagreements were reviewed and resolved by the study leads, where necessary (DD and IO). Citation screening for titles/abstract and full-text review was conducted independently and in duplicate by a team of seven reviewers recruited from the University of Ottawa and Children's Hospital of Eastern Ontario (CHEO) to allow for rapid completion. The study co-lead (IO) reviewed all eligible citations to identify potential duplicates and confirm eligibility. Consensus and/or resolution of conflicts were managed between reviewers and a third reviewer was not necessary.

2.2. Inclusion criteria

Case series, case reports, case-control, and comparative studies on SARS-CoV-2 infection among pregnant women and/or neonates as validated by positive antibody testing or viral testing using polymerase chain reaction (PCR) were included. Studies included both asymptomatic carriers and patients with symptomatic infection. The endpoints were: pregnancy outcomes (e.g., still birth), radiology (e.g., pulmonary consolidation), laboratory findings (e.g., lymphopenia) and placental pathology syndromes, as identified by the Amsterdam placental workshop group consensus in addition to documented neonatal and maternal death or survival [18].

2.3. Exclusion criteria

Studies were excluded if the population of interest was non-pregnant mothers, general patients, or children older than one month. There were no language restrictions since we had language specialists who worked in the medical profession available to translate foreign findings (JT, JD, NZ, MK). Systematic reviews, literature reviews, editorials, letters to the editor, conference abstracts, and commentaries were excluded.

2.4. Data analysis

Four authors (DD, IO, JT, and BR) extracted summary estimates using a pre-designed, piloted, and modified data abstraction sheet in Excel Version 16.46. The data abstraction form was piloted against a total of five eligible studies. The extracted information included: citation details (title of the article and the year of publication); study details including study design; location of the study and its sample size; patient demographics including age, sex, gestational age (in weeks), maternal body mass index (BMI), asthma, signs and symptoms of COVID-19 in mothers and neonates, mode of delivery, type of pregnancy, and neonatal outcomes. The Methodological Index for Non-Randomized Studies (MINORS) criteria was used to assess study quality [19]. The study protocol has been registered in PROSPERO (CRD42020180538).

3. Results

Five hundred and twenty-five records were identified for level I (title and abstract) screening, of which 292 were excluded according to title, abstract, and research question relevance. Two hundred and thirty-three were selected for full-text review, of which 192 were excluded due to an ineligible population (n = 39), study design (n = 141), no mention of our outcomes of interest (n = 6), or inability to locate text (n = 6). After full-text screening, there were 41 eligible studies remaining (Figure 1).

Most studies were conducted in Wuhan, China (n = 26). Eighteen of the included studies were case reports, 11 case series, eight retrospective cohort studies, one prospective cohort study, and three case control studies (Table 1). A total of 315 women with laboratory confirmed SARS-CoV-2 by PCR were included in the selected 41 articles with a mean age of 30 years. Most of them were in their third trimester of pregnancy (e.g., 35–38 gestational weeks). Their average body mass index (BMI) varied from 22 to 30.9 kg/m^2. There were six cases of maternal intensive care admission (1 · 9%). Overall, the most prevalent complications on admission or during pregnancy were gestational hypertension (2 · 5%), gestational diabetes (3 · 5%), and type II diabetes (2 · 2%). There were two cases of abnormal cord insertion and abnormal amniotic fluid volume with oligohydramnios and polyhydramnios (0 · 63% each) (Table 1). Upon admission, fever and cough were the most common maternal symptoms reported (55 · 2% and 40 · 3%, respectively). There were twenty cases of documented intrauterine foetal distress (7 · 6%) and fifteen cases of premature ruptures of membranes (5 · 7%) (Table 2). Typical symptoms of neonates after birth were similar to that of mothers, including cough (2 · 3%), fever (4 · 2%), shortness of breath (2 · 7%), and respiratory difficulties or distress (2 · 3%) (Table 3).

Table 4 illustrates neonatal outcomes with the most data coverage. When reported, the majority (56 · 1%) of neonates born to SARS-CoV-2 positive mothers tested negative; however, there were 8 positive cases validated by RT-PCR (3 · 1%). Twenty-one percent of neonates were born preterm (Table 4). There were two cases of rashes and one neonatal death; however, they were occasional overall (0 · 8% and 0 · 4%, respectively).

Preeclampsia was the most frequent disease of the placenta (eight cases; 2 · 5%) (Table 5). An equal number of pregnant women experienced placental abruption or abnormal placenta/placenta previa (three cases each; 0 · 95%).

More than half of infected pregnant women had viral pneumonia (160 cases; 50 · 8%). When examining the lungs on computer tomography (CT), pregnant women with SARS-CoV-2 were frequently classified as demonstrating pure (18 cases; 5 · 7%), bilateral (12 cases; 3 · 8%) or

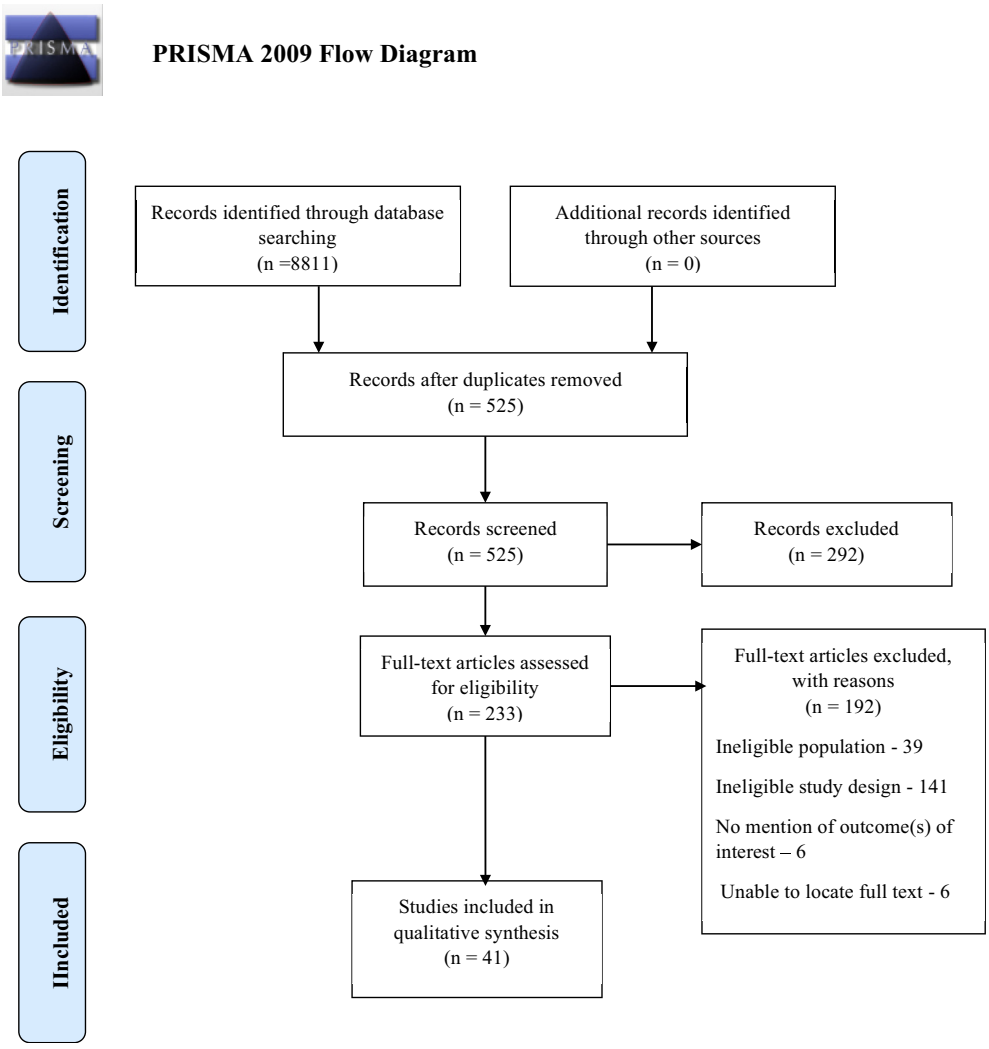

Figure 1. PRISMA Flow Diagram for Included Studies

patchy ground-glass opacities (GGO) (15 cases; 4 · 8%) (Table 6). There were 87 (30%) cases of elevated (>4 · 0 mg/L) C-reactive protein (CRP), 21 cases of leukocytosis (6 · 7%), and 25 cases of lymphopenia (7 · 9%) (Table 6).

Table 7 displays the results from the critical appraisal for 39 studies written in the English language. We achieved substantial or almost perfect agreement between two independent reviewers on half of the domains from the MINORS 2015 criteria (Table 6). MINORS scores for comparative studies (n = 9) ranged from 20-23, with mean 22 ± 1·0. MINORS scores for non-comparative studies (n = 32) ranged from 13-16, with a mean of 15 ± 0·7. The ideal global score is 16 for non-comparative studies and 24 for comparative studies, which indicates excellent studies based on this definition [19].

4. Discussion

Given the evolving nature of the virus, understanding the potential implications of SARS-CoV-2 in vulnerable populations such as pregnant women is warranted worldwide. This review summarizes the findings from 315 women confirmed to have SARS-CoV-2 and 262 neonates who underwent PCR testing.

In our systematic review, similar symptoms (e.g., fever, cough, and shortness of breath) were reported among pregnant women and their neonates [8, 20, 21, 22]. The clinical symptoms caused by SARS-CoV-2 are comparable to severe acute respiratory syndrome (SARS), whereby after being infected, the first symptoms are typically fever, cough, and respiratory difficulties akin to upper respiratory tract infections, suggesting that the target cells of the virus may be located in the lower respiratory tract [23]. Furthermore, SARS-Cov-2 is reported to share the same angiotensin-converting enzyme 2 (ACE2) receptor as with SARS-CoV, indicating ACE2 virus receptor expression in type II alveolar cells [24]. Once the virus makes contact with the human airway, its spike proteins can bind to surface receptors of sensitive cells, permitting the entrance of the virus into target cells for further replication [25, 26, 27, 28]. The clinical maternal symptomology findings reported in this review clearly align with prior literature reporting fever, cough, breathing difficulties, malaise, chills, and rigors as prevalent symptoms of SARS during pregnancy, from manifestation of the virus in the respiratory tract of infected patients [29].

We found six cases of maternal ICU admission [20, 21, 22, 30] representing 1 · 9% of total SARS-CoV-2 laboratory confirmed pregnancies. In contrast, the ICU admission rate for pregnant or postpartum women admitted to Canadian hospitals in 2019 was 0 · 32 per 100 pregnancies [31]. Therefore, the rate of ICU admission in this systematic review is six times higher than in healthy pregnant women from the general population. ICU admission is also associated with maternal comorbidity [OR 1 · 88 (1 · 86, 1 · 99)] [31]. Thus, the potential reasons for admission to the ICU could be as a result of underlying conditions during pregnancy such as gestational hypertension or pre-existing conditions like chronic hypertension [32], type II diabetes [33], and high body mass index (BMI)

Table 1. Study characteristics (n = 41).

Author	Study location	n (pregnant women with laboratory confirmed SARS-CoV-2)	n (uninfected neonates tested for SARS-CoV-2 unless specified)	Maternal and Neonatal Interventions	Comparator	Maternal Medication Treatment	Fetal Medication Treatment	Follow-up after delivery (days)	MINORS Score
Case report									
Diaz et al 2020 [20]	Spain	1	1	Chest radiography; RT-PCR; chest x-ray; C-reactive protein assessment	N/A[1]	Mechanical ventilation	Continuous nasal pressure device	6, 8, and 13	15
Wang et al 2020 [93]	Wuhan, China	1	1	Two throat-swab samples; RT-PCR; and chest tomography scan (CT)	N/A	Arbitol tablets; lopinavir and ritonavir tablets; cefoperazone sodium; sulbactam sodium; and human serum albumin	Dexamethasone and magnesium sulfate as prophylaxis	10, 15, and 18	15
Wang et al 2020 [94]	Wuhan, China	1	1	CT scan; rPT-PCR[2]	N/A	Recombinant human interferon; sterilization injection; ganciclovir. Abipenem; moxifloxacin; methylprednisolone	Not mentioned	4	15
Iqbal et al 2020 [95]	Washington, United States of America	1	1	Chest radiographs; nonstress test; ultrasound; nasopharyngeal and oropharyngeal swabs	N/A	Oxytocin	Not mentioned	6	15
Song et al 2020 [96]	Wuhan, China	1	1	Throat swabs and fecal samples by rPT-PCR; viral respiratory test; chest CT; pinprick test	N/A	CSEA[3]; hyperbaric ropivacaine; oxytocin; dolasetron; tramadol; sodium chloride	Not mentioned	1	16
Zhao et al 2020 [97]	Wuhan, China	1	1	Serum biochemical test; CT scan; B-ultrasound; throat swabs by PCR	N/A	Azithromycin; oseltamivir; moxifloxacin; ganciclovir	Not mentioned	4	15
Lowe et al 2020 [98]	Southport, Australia	1	1	COVID-19 testing	N/A	Artificial rupture of membranes; oxytocin infusion; CTG[4]; epidural; gentamicin; metronidazole; cephazolin	Not mentioned	10	16
Lee et al 2020 [99]	Republic of Korea	1	1	Chest radiographs; CT scans; blood and urine tests; RT-PCR for placenta, amniotic fluid, and cord blood	N/A	Spinal anesthesia; Marcaine; fentanyl; phenylephrine; Hartmann solution; colloid; carbetocin; oxytocin; crystalloid; colloid; analgesia pump	Not mentioned	Unknown	16
Kalafat et al 2020 [30]	Turkey	1	1	RT-PCR for throat, nasal, and breast milk; fetal ultrasound; lung ultrasound; CT angiography	N/A	Azithromycin; hydroxycholorquine; oseltamivir; favipiravir; steroids	Not mentioned	2	15
Karami et al 2020 [22]	Iran	1	1	Fern test; chest CT; chest X-ray; echocardiography; RT-PCR; lung autopsy	N/A	Oseltamivir, azithromycin, ceftriaxone, lopinavir/ritonavir/hydroxychloroquine, meropenem, vancomycin	Not mentioned	2	16
Kamali et al 2020 [21]	Tehran, Iran	1	1 (infected)	Pharyngeal swab via RT-PCR; chest X-ray; echocardiography	N/A	Not mentioned.	Proper fluid therapy; oxygen therapy; vancomycin; amikacin, oseltamivir	14	16
Zeng et al 2020 [100]	Wuhan, China	1	1 (infected)	Pharyngeal and nasal swabs; COVID-19 nucleic acid test; pulmonary imaging; blood tests; suction pharyngeal swabs; immunofluorescence tests; echocardiogram	N/A	Not mentioned.	Vitamin K1 and fluid replacement	Unknown	15
Wang et al 2020 [101]	Wuhan, China	1	1 (infected)	Nucleic acid test; lung CT; chest imaging; abdominal X-ray; adenovirus antigen test	N/A	Not mentioned	Interferon treatment; nasal spray; fluid replacement	Unclear	15
Schnettler et al 2020 [102]	Cincinnati, Ohio	1	1	Chest x-ray; vital assessment; respiratory viral laboratory analysis; nasopharyngeal	N/A	Intubation with mechanical ventilation; antenatal corticosteroids; magnesium sulphate; benzodiazepines and narcotics;	Electronic monitoring	5	15

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Table 1 (*continued*)

Author	Study location	n (pregnant women with laboratory confirmed SARS-CoV-2)	n (uninfected neonates tested for SARS-CoV-2 unless specified)	Maternal and Neonatal Interventions	Comparator	Maternal Medication Treatment	Fetal Medication Treatment	Follow-up after delivery (days)	MINORS Score
				swab via RT-PCR; chest X-ray; lung ultrasound imaging;		ceftriaxone; azithromycin; oseltamivir; hydroxycholoroquine			
Peng et al 2020 [103]	Chongqing, China	1	1	Chest CT; throat swab via RT-PCR;	N/A	Interferon nebulization; oral lopinavir; intravenous antibiotics; oxygen supplements; dexamethasone	Nasal continuous positive airway pressure; pulmonary surfactant; gentamycin; ampicillin; procalcitonin	1,2,3,7 and 14	15
Xiong et al 2020 [104]	Beijing, China	1	1	Chest X-ray; throat swab via RT-PCR test; chest CT	N/A	Antiviral; anti-infection; corticosteroid therapies	Not mentioned.	3	16
Han et al 2020 [105]	Seoul, Korea	1	1 (infected)	Chest radiograph; physical examination; laboratory examination; nasopharyngeal and orophargyngeal swabs via RT-PCR	N/A	Not mentioned.	No antiviral or antibacterial agents	29	16
Shojaei et al 2020 [106]	Tehran, Iran	1	1	Spiral lung and mediastinal CT scan; portable chest X-ray; echocardiography; nasopharyngeal swab via RT-PCR	N/A	Oseltamivir; ceftriaxone; hydroxycholorquine; azithromycin; lopinavir/ritonavir; O_2 therapy with mask; fentanyl and propofol injection and mechanical ventilation; vancomycin; meroprenem; fresh frozen plasma; norepinephrine infusion	Not mentioned	Terminated pregnancy.	16
Case series									
Chen et al 2020 [107]	Wuhan, China	5	5	Serum testing; chest imaging; RT-PCR	N/A	Ceased breastfeeding (n = 5); oseltamivir (n = 5); azithromycin (n = 5)	Not mentioned	Not mentioned	14
Zhu et al 2020 [8]	Wuhan, China	9	10	Chest CT; ultrasound; [5]NAT testing	N/A	Oseltamivir (n = 3); nebulized inhaled interferon (n = 1)	Symptomatic supportive treatments (n = 10); transfusion of platelets (n = 1); oxygen therapy (n = 1)	7,9	14
Liu et al 2020 [108]	Wuhan, China	10	19	Chest CT; chest x-ray; RT-PCR in urine, throat and feces	N/A	No mother received prenatal steroids; antiviral drugs (n = 6)	Not mentioned	Not mentioned	15
Liu et al 2020 [109]	Wuhan, China	3	3	CT scans; oropharyngeal swabs, breast milk, placenta, vaginal mucus and feces testing via RT-PCR;	N/A	Oxygen therapy (n = 3), antiviral (n = 2) (i.e., atomized inhalation of interferon and ganciclovir), and anti-inflammatory treatment (n = 2); oral arbidol hydrochloride (n = 2)	Not mentioned	2,6	15
Breslin et al 2020 [33]	New York, United States of America	7	2	Chest X-ray; PCR	N/A	Ampicillin (n = 1); gentamicin (n = 1); acetaminophen (n = 1); endotracheal intubation (n = 1); hydroxycholoroquine (n = 2); furosemide (n = 1); azithromycin (n = 1); ceftriaxone (n = 1); ongoing oxygen supplementation (n = 1)	Not mentioned	2,4,5	15
Khan et al 2020 [37]	Wuhan, China	3	3	Nasopharyngeal swab; CT scan	N/A	Azithromycin (n = 1); Lianhua Qingwen capsules (n = 2); oseltamivir (n = 1); antibiotics (n = 2); antiviral drugs (n = 2); oxygen inhalation (n = 2)	Not mentioned	Not mentioned	16
Chen et al 2020 [64]	Wuhan, China	4	4 (3 uninfected; 1 did not provide consent)	Throat swab via RT-PCR; laboratory examination; CT scans; chest radiograph	N/A	Respiratory support (n = 1)	Nasal-continuous positive airway pressure (n = 1)	3,5	16
Chen et al 2020 [14]	Wuhan, China	3	3	Pharyngeal swabs via nucleic acid test; tissue and lung CT; laboratory examination	N/A	Not mentioned	Not mentioned	Not mentioned	13

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Table 1 (*continued*)

Author	Study location	n (pregnant women with laboratory confirmed SARS-CoV-2)	n (uninfected neonates tested for SARS-CoV-2 unless specified)	Maternal and Neonatal Interventions	Comparator	Maternal Medication Treatment	Fetal Medication Treatment	Follow-up after delivery (days)	MINORS Score
Fan et al 2020 [38]	Wuhan, China	2	2	Nasopharyngeal swab, maternal serum, placenta tissue, umbilical cord blood, amniotic fluid, vaginal swabs, and breast milk via RT-PCR; laboratory examination; CT chest scan; CT of thorax	N/A	*Lianhua qingwen* capsule (n = 2); cefaclor (n = 1); beclomethasone (n = 1); calamine tropical (n = 1); azithromycin (n = 1); oseltamivir (n = 2); methylprednisolone (n = 1); cefotiam hydrochloride (n = 1); ornidazole (n = 1); diclofenac sodium (n = 1); ceftazidime (n = 1);	Antibiotic therapy (n = 2)	3,4,8,18,19	16
Liu et al 2020 [110]	Wuhan, China	15	15	RT-PCR; CT scan	N/A	Oxygen support via nasal cannula (n = 14); antibiotic treatment (n = 15); antiviral treatment (n = 11);	Not mentioned	4,6	15
Chen et al 2020 [111]	Wuhan, China	17	17	RT-PCR; general anaesthesia (n = 3); epidural anaesthesia (n = 14)	General anaesthesia group	Not mentioned	Not mentioned	6,13	20
Retrospective cohort									
Yue et al 2020 [112]	Wuhan, China	14	13	Chest CT; throat swabs via RT-PCR; CSEA	Patients with suspected SARS-CoV-2 infection	Intraspinal anaesthesia (n = 30); dezocine and morphine via epidural catheter (n = 30)	Not mentioned	N/A	21
Chen et al 2020 [15]	Wuhan, China	9	6	Chest CT; throat swab samples via RT-PCR; amniotic fluid samples; cord blood and neonatal throat swabs; breast milk samples	N/A	Oxygen support via nasal cannula (n = 9); antibiotic treatment (n = 9); antiviral therapy (n = 6)	Not mentioned	N/A	14
Yu et al 2020 [113]	Wuhan, China	7	3 (2 uninfected; 1 infected)	Throatswab samples via RT-PCR; chest CT; laboratory examinations; sputum or endotracheal aspirates; CSEA; general anaesthesia	N/A	Oxygen therapy via nasal catheter (n = 7); antiviral therapy (i.e., oseltamivir, ganciclovir, interferon, arbidol) (n = 7); Jinyebaidu and Lianhuaqingwen capsules (n = 7); antibiotic treatment (i.e., cephalosporins, quinolones, macrolides) (n = 7);	Not mentioned	28	15
Nie et al 2020 [114]	Wuhan, China	33	26 (25 uninfected; 1 infected)	RT-PCR; clinical presentation; laboratory examination; chest CT information; chest X-ray	N/A	Oxygen supplementation via nasal cannula or mask (n = 29); noninvasive mechanical ventilation (n = 1); antibiotic treatment (n = 29); glucocorticoids (n = 11); traditional Chinese medicine (n = 12)	No treatment (n = 1)	4, 8, 15	15
Breslin et al 2020 [32]	New York, USA	43	18 (15 uninfected; 3 infected)	Nasopharyngeal swab via RT-PCR; imaging; and treatment; chest X-ray; neuraxial anesthesia; intraoperative conversion	Asymptomatic patients on presentation	No supplemental oxygen (n = 29); hydroxycholoroquine (n = 2); ceftriaxone (n = 2); supportive therapy with intravenous hydration (n = 2); azithromycin (n = 1); oxygen support via nasal cannula (n = 1); antibiotics (ampicillin and gentamicin) (n = 5); misoprostol (n = 3)	Not mentioned	14	21
Zhang et al 2020 [115]	Wuhan, China	4	4	Nasopharyngeal or anal swabs via RT-PCR; CT scans	N/A	Not mentioned	Supportive treatment (n = 4); mechanical ventilation (n = 0)	Not mentioned	15
Zhang et al 2020 [16]	Wuhan, China	16	10	Biochemical tests; pharyngeal swab collection via RT-PCR; chest radiographs; laboratory examinations	Pregnant women without SARS-CoV-2	Dexamethasone (n = 1)	Not mentioned	Not mentioned	21

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Table 1 (*continued*)

Author	Study location	n (pregnant women with laboratory confirmed SARS-CoV-2)	n (uninfected neonates tested for SARS-CoV-2 unless specified)	Maternal and Neonatal Interventions	Comparator	Maternal Medication Treatment	Fetal Medication Treatment	Follow-up after delivery (days)	MINORS Score
Yin et al 2020 [116]	Wuhan, China	31	17	Amniotic fluid; placenta; neonatal throat and anal swab samples; breastmilk samples via RT-PCR; laboratory and radiology examinations	Non-pregnant women with SARS-CoV-2	Antiviral therapy (n = 30); glucocorticoid therapy (n = 16); oxygen therapy (n = 35)	Not mentioned	9–40	22
Prospective cohort									
Yang et al 2020 [117]	Wuhan, China	7	7	Umbilical cord blood, amniotic fluid, and pharyngeal swabs via RT-PCR; chest X-ray; laboratory examination	N/A	Not mentioned	nCAP[6] treatment (n = 2); no respiratory support or oxygen therapy (n = 0); piperacillin tazobactam (n = 4); feeding and nursing care (n = 3)	2-5, 7	15
Case-control									
Zhang et al 2020 [118]	Wuhan, China	89	90	SARS-CoV-2 nucleic acid test; CT imaging; spinal anaesthesia; epidural anaesthesia; general anaesthesia; inhalational anaesthesia	Pregnant women without SARS-CoV-2	Intraoperative oxytocin (n = 94)	Not mentioned	Not mentioned	23
Yang et al 2020 [11]	Wuhan, China	13	20	CT scan; throat swab test via RT-PCR; routine blood test; laboratory and radiology examination	Pregnant women without laboratory confirmed SARS-CoV-2 infection	Not mentioned	Not mentioned	Unclear	23
Li et al 2020 [57]	Wuhan, China	11	17	CT scan; laboratory examination; throat swabs via RT-PCR	Pregnant women without SARS-CoV-2	Antibiotics (n = 34); antivirals (n = 4)	Not mentioned	4,14	21

[1] Not applicable to the study design.
[2] Real-time reverse transcription polymerase chain reaction.
[3] Combined spinal and epidural anesthesia.
[4] Continuous cardiotocography.
[5] Nucleic acid testing.
[6] Non-invasive continuous positive airway pressure ventilation.

Table 2. Maternal Characteristics from 315 women with confirmed SARS-CoV-2 Infection.

	Case reports (N = 18 studies)[1]	Case series (N = 11 studies)[2]	Retrospective cohort (N = 8 studies)[3]	Prospective cohort (N = 1 study)[4]	Case control (N = 3 studies)[5]	Total, n/N (%)
Maternal Characteristics						
Age (y) (mean ± SD)	31 · 5	30 · 7 ± 5	30·0 ± 13	N/A	31·2 ± 3	
Gestational age (mean ± SD) or range in weeks	35·0 ± 6	35·3 ± 5	38·1 ± 0·9	36–37	38·1 ± 2	
Body mass index (BMI) (kg/m^2) (mean ± SD)	24·7	N/A[6]	30·9 ± 5	N/A	22·7	
Maternal Intensive Care Unit (ICU) admission	4	0	2	0	0	6/315, 1·9%
Complications						
Gestational hypertension	0	N/A	3	2	3	8/315, 2·5%
Chronic hypertension	0	1	3	N/A	2	6/315, 1·9%
Hypothyroidism	1	1	1	N/A	2	5/315, 1·6%
Gestational diabetes	0	3	5	N/A	3	11/315, 3·5%
Type II diabetes	0	4	3	N/A	0	7/315, 2·2%
Abnormal amniotic fluid	0	2	0	0	0	2/315, 0·63%
Abnormal cord insertion	0	2	0	0	0	2/315, 0·63%
Delivery Characteristics						
Total number of deliveries	14	58	94	7	116	289/315, 91·7%
Delivery by caesarean section	9	46	75	7	112	249/315, 79·0%
Vaginal delivery	5	12	19	0	4	40/315, 12·7%
Spontaneous preterm delivery	1	0	0	0	0	1/315, 0·3 %
Pregnancy type						
Singleton	11	35	46	7	70	169/315, 53·7%
Twin	2	2	0	0	5	10/315, 3·2%
Multiple	0	0	0	0	88	88/315, 27·9%
Presenting signs and symptoms						
Fever on admission	11	40	69	6	48	174/315, 55·2%
Cough	10	27	52	6	32	127/315, 40·3%
Dyspnea	3	4	15	6	9	37/315, 11·7%
Shortness of breath	4	0	9	6	0	19/315, 6·0%
Myalgia	3	6	17	6	8	40/315, 12·7%
Muscular soreness	1	0	5	6	0	12/315, 3·8%
Sore throat	2	2	5	6	0	15/315, 4·8%
Diarrhea	0	4	9	6	7	26/315, 8·3%
Clinical Outcomes						
Intrauterine fetal distress	0	7	9	2	2	20/262, 7·6%
Premature rupture of membranes	1	3	9	0	2	15/262, 5·7%

[1] Diaz et al 2020 [20], Wang et al 2020 [93], Wang et al 2020 [94], Iqbal et al 2020 [95], Song et al 2020 [96], Zhao et al 2020 [97], Lowe et al 2020 [98], Lee et al 2020 [99], Kalafat et al 2020 [30], Karami et al 2020 [22], Kamali et al 2020 [21], Zeng et al 2020 [100], Wang et al 2020 [101], Schnettler et al 2020 [102], Peng et al 2020 [103], Xiong et al 2020 [104], Han et al 2020 [105], Shojaei et al 2020 [106].

[2] Chen et al 2020 [107], Zhu et al 2020 [8], Liu et al 2020 [108], Liu et al 2020 [109], Breslin 2020 [33], Khan et al 2020 [37], Chen et al 2020 [64], Chen et al 2020 [14] Fan et al 2020 [38], Liu et al, 2020 [110], Chen et al, 2020 [111].

[3] Yue et al 2020 [112], Chen et al 2020 [15], Yu et al 2020 [113], Nie et al 2020 [114], Breslin et al 2020 [32], Zhang et al 2020 [115], Zhang et al 2020 [16], Yin et al 2020 [116].

[4] Yang et al 2020 [117].

[5] Zhang et al 2020 [118], Yang et al 2020 [11], Li et al 2020 [57].

[6] indicates the lack of data collected on this outcome.

[32]. Similarly, the presence of pre-existing comorbid conditions is more common in an older population with severe SARS-CoV-2 than among those with nonsevere disease (38 · 7% vs. 21 · 0%) [34, 35]. As such, a deeper examination into the role of comorbidities in pregnant women with SARS-CoV-2 is warranted [36].

Seven pregnant women with SARS-CoV-2 had type II diabetes (2 · 2%). Gestational diabetes was the most frequent complication during pregnancy (3 · 5% of SARS-CoV-2 laboratory confirmed pregnancies) [32, 37, 38]. This result is 1 · 3 times higher than in a population of pregnant women without SARS-CoV-2 in Japan, where 2 · 7% were diagnosed with gestational diabetes [39]. Prior literature has established a relationship between elevated BMI and gestational weight gain on the presence of gestational diabetes; however, lack of reporting on BMI in women with gestational diabetes in this review inhibits us from inferring the same in SARS-CoV-2 positive pregnant women [40, 41].

A considerable percentage (i.e., 5 · 7%) of pregnant women with SARS-CoV-2 experienced premature rupture of membranes. This particular finding is unique in that prior research on the SARS-CoV-1 outbreak from 2002 to 2003 described adverse outcomes such as miscarriages in the first trimester of pregnancy and intrauterine growth restriction in the second and third trimesters but nothing explicitly on premature rupture of membranes or preterm birth [42, 43, 44]. It remains unclear as to how SARS-CoV-2 may influence timing of delivery (e.g., preterm versus term), maturity, or membrane rupture. However, viral infection influences pregnancy and foetal growth by penetrating the placenta and decidua via the lower reproductive tract contributing to the presence of such adverse outcomes [45]. The rate of preterm birth (i.e., 21%) was high in our review. Whether premature labour is evidence of increased psychological stress in expectant mothers with SARS-CoV-2 or a direct effect of the virus, remains to be investigated

Table 3. Neonatal Characteristics from 262 neonates who underwent PCR laboratory testing for SARS-CoV-2.

	Case reports (N = 18 studies)[1]	Case series (N = 11 studies)[2]	Retrospective cohort (N = 8 studies)[3]	Prospective cohort (N = 1 study)[4]	Case control (N = 3 studies)[5]	Total, n/N (%)
Neonatal Characteristics						
Neonatal sex						
Males	6	24	16	[6]N/A	8	54/262, 20·6%
Females	2	10	10	N/A	6	28/262, 10·7%
Mean birth weight (g)	3196·4	3117	3063·5	2096	3129·1	
Signs and symptoms after birth						
Respiratory difficulties or distress	5	0	1	N/A	N/A	6/262, 2·3%
Cough	2	4	0	N/A	N/A	6/262, 2·3%
Fever	7	4	0	N/A	N/A	11/262, 4·2%
Shortness of breath	1	6	0	N/A	N/A	7/262, 2·7%
Apnea	0	0	N/A	N/A	N/A	0/262, 0%
Vomiting	3	0	0	N/A	N/A	3/262, 1·1%
No symptoms	0	5	0	N/A	N/A	5/262, 1·9%

[1] Diaz et al 2020 [20], Wang et al 2020 [93], Wang et al 2020 [94], Iqbal et al 2020 [95], Song et al 2020 [96], Zhao et al 2020 [97], Lowe et al 2020 [98], Lee et al 2020 [99], Kalafat et al 2020 [30], Karami et al 2020 [22], Kamali et al 2020 [21], Zeng et al 2020 [100], Wang et al 2020 [101], Shnettler et al 2020 [102], Peng et al 2020 [103], Xiong et al 2020 [104], Han et al 2020 [105], Shojaei et al, 2020 [106].

[2] Chen et al 2020 [107], Zhu et al 2020 [8], Liu et al 2020 [108], Liu et al 2020 [109], Breslin 2020 [33], Khan et al 2020 [37], Chen et al 2020 [64], Chen et al 2020 [14], Fan et al 2020 [38], Liu et al, 2020 [110], Chen et al, 2020 [111].

[3] Yue et al 2020 [112], Chen et al 2020 [15], Yu et al 2020 [113], Nie et al 2020 [114], Breslin et al 2020 [32], Zhang et al 2020 [115], Zhang et al 2020 [16], Yin et al 2020 [116].

[4] Yang et al 2020 [117].

[5] Zhang et al 2020 [118], Yang et al 2020 [11], Li et al 2020 [57].

[6] indicates the lack of data collected on this outcome.

Table 4. Neonatal Outcomes from 262 neonates who underwent PCR laboratory testing for SARS-CoV-2.

	Case reports	Case series	Retrospective cohort	Prospective cohort	Case control	Total, n/N (%)
Neonatal Intensive Care Unit (NICU) admission	3	37	4	5	147	196/262, 74 · 8%
Preterm	4	11	27	6	7	55/262, 21 · 0%
Full term	1	0	1	3	1	6/262, 2 · 3%
Low birth weight (e.g., <2500g)	0	1	9	0	3	13/262, 5.0%
Neonatal death	0	1	0	0	0	1/262, 0 · 38%
Mean Apgar Score						
1 min (mean)	8 · 17	8 · 45	8 · 19	[1]N/A	9 · 6	
5 min (mean)	9 · 15	9 · 35	9 · 22	N/A	10	
Fetal tachycardia	0	2	0	0	1	3/262, 1 · 1%
Rashes	0	2	0	0	0	2/262, 0 · 8%

[1] indicates the lack of data collected on this outcome.

[46, 47]. It is possible that pregnancy outcome is influenced by elective premature delivery in attempts to improve maternal symptoms. In general, neonatal complications were found to be more prevalent after elective preterm delivery in hypertensive mothers versus low risk controls (i.e., uneventful pregnancies delivered due to spontaneous preterm labour or premature membrane rupture) [48]. Elective caesarean sections due to worsening dyspnea in pregnant women with SARS-CoV-2 may also increase the proportion of adverse neonatal outcome like preterm birth [49].

Preeclampsia was also common (i.e., 2 · 5%) in our systematic review and is an indicator for preterm birth [50]. The rate of preeclampsia in a population-based retrospective study on women admitted to hospital for delivery from 1980 to 2010 in the United States was 3 · 4%, higher by 1 · 36 times than the rate reported in this review [51]. When compared to a large cohort study in China, the incidence of preeclampsia among healthy pregnant women was 2 · 28%, 1 · 1 times lower than we have found in the COVID-19 positive population [52]. Both preeclampsia and premature membrane rupture can precipitate a preterm birth [53, 54], and it is unknown whether SARS-CoV-2 directly influences preterm birth alone or in conjunction with elevated late gestational hypertension and membrane rupture. Therefore, a more detailed analysis and longitudinal approach that controls for various confounders and pre-existing conditions is needed to discern the true impact of SARS-CoV-2 on preterm birth.

Caesarean Sections (C-section) were disproportionally performed in pregnant COVID-19 positive women (i.e., 79 · 0%). In some cases, emergent caesarean sections were attributed to foetal distress [15, 36, 55]. C-section is normally recommended to prevent adverse neonatal outcomes in the presence of elevated maternal viral infection; as such, when women tested positive for SARS-CoV-2, the clinical recommendation may have been to undergo an elective C-section to prevent possible vertical transmission of infection to the neonate [56]. Moreover, Li and colleagues determined a lower rate of C-section among controls without SARS-CoV-2 (47 · 1%) [57].

As mentioned, a significant percentage (21%) of neonates born to SARS-CoV-2 positive mothers were born preterm. However, Zhang and colleagues found that preterm birth and neonatal asphyxia were not statistically different between cases and controls without SARS-CoV-2

Table 5. Placental Pathology outcomes in 315 SARS-CoV-2 confirmed pregnant women.

Author and Study ID	Zhu et al., 2020 [8] 174620	Yang et al., 2020 [117] 174628	Schnettler et al., 2020 [102] 174968	Chen et al., 2020 [107] 174619	Liu et al., 2020 [109] 174662	Chen et al., 2020 [14] 174527	Liu et al., 2020 [108] 174625	Iqbal et al., 2020 [95] 174572	Li et al., 2020 [57] 174856	Diaz et al., 2020 [20] 174520	Chen et al., 2020 [15] 174627	Zhang et al., 2020 [16] 174510	Chen et al., 2020 [64] 174821	Kalafat et al., 2020 [30] 174581	Total, n/N (%)
Chorioamnionitis	..	..	..	0	1	0	..	..	..	..	..	..	..	..	1/315, 0 · 32%
Meconium stained amniotic fluid (MSAF)	..	..	..	..	1	..	..	..	..	..	..	..	..	..	1/315, 0 · 32%
Placental abruption	..	..	..	..	..	1	..	..	2	..	..	..	..	..	3/315, 0 · 95%
Preeclampsia	..	2	..	1	..	..	..	..	1	1	2	1	..	..	8/315, 2 · 5%
Abnormal placenta/ placenta previa	1	..	..	..	..	1	..	..	..	..	..	..	1	..	3/315, 0 · 95%

Table 6. Radiology and Laboratory findings across all studies (n = 41) for 315 women confirmed with SARS-CoV-2.

Radiology results	Total n/N, (%)
Bilateral/viral pneumonia	160/315, 50 · 8%
Pneumonia aggravation	1/315, 0 · 32%
Pulmonary consolidation	4/315, 1 · 3%
Lesions	5/315, 1 · 6%
Pure ground-glass opacity (PGO)	18/315, 5 · 7%
Bilateral ground-glass opacities (GGO)	12/315, 3 · 8%
Patchy GGO	15/315, 4 · 8%
Patch like shadows	8/315, 2 · 5%
Pleural effusion	7/315, 2 · 2%
Pleural thickening	4/315, 1 · 3%
Increased vascular marking	2/315, 0 · 63%
Laboratory results	
Mean number of white blood cells (WBC) ($\times 10^9$/L)	9 · 1
Mean number of neutrophils ($\times 10^9$/L)	7 · 0
Elevated Procalcitonin	7/315, 2 · 2%
Leukopenia	1/315, 0 · 32%
Leukocytosis (>10 × 109/L)	21/315, 6 · 7%
Lymphopenia (<1 × 109/L)	25/315, 7 · 9%
Thrombocytopenia	3/315, 0 · 95%
Mean number of Lymphocytes (x109/L)	2 · 1
Mean albumin (g/L)	25 · 7
Mean haemoglobin (Hb) (g/L)	98 · 4
Mean C-reactive protein (CRP) (mg/L)	33 · 1
Elevated CRP (>4 · 0 mg/L)	87/315, 27 · 6%
Elevated alkaline phosphatase	7/315, 2 · 2%
Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	12/315, 3 · 8%

[16]. In this review, nearly three quarters of neonates (74.8%) born to mothers who tested positive were admitted to the NICU. However, admission protocols in some areas of the world, such as China, may immediately separate neonates from their mothers, with neonates admitted to a neonatal quarantine observation ward as a safety precaution, not necessarily because neonates require NICU admission due to abnormalities [58, 59]. There was one case of neonatal death in our systematic review. Zhu and colleagues reported a neonate who developed thrombocytopenia complicated by abnormal liver function, and later died from refractory shock and multiple organ failure but did not

Table 7. Quality Appraisal of Eligible Articles in English using MINORS 2015 criteria (n = 39).

Domain	Inter-rater reliability coefficient (Kappa)	[a]Interpretation
Clearly stated aim	*Not estimable	N/A
Inclusion of patients	0 · 55	Moderate
Prospective collection	0 · 79	Substantial
Appropriate endpoints	1 · 00	Almost perfect
Unbiased endpoint	*Not estimable	N/A
Follow up period	0 · 23	Fair
Follow up loss	*Not estimable	N/A
Study size calculation	*Not estimable	N/A
Adequate control	1 · 00	Almost perfect
Contemporary groups	1 · 00	Almost perfect
Baseline equivalence	1 · 00	Almost perfect
Statistical analyses	1 · 00	Almost perfect

[a] Kappa was interpreted as follows: <0 "poor", 0-0·2 "slight", 0 · 21–0·4 "fair", 0 · 41–0·6 "moderate", 0 · 61–0·8 "substantial", 0 · 81–0·99 "almost perfect". *Not estimable: Kappa could not be estimated.

test positive for SARS-CoV-2 despite being born to a SARS-CoV-2 positive mother [8]. Many autopsies on non-pregnant adults with SARS-CoV-2 also demonstrate thrombocytopenia as well as disseminated intravascular coagulation [60]. The preliminary case fatality rate in asymptomatic and symptomatic patients hospitalized with SARS-CoV-2 also appears to be around 1% (95% CI: 0·5-4%) in contrast to MERS (35–40%) and SARS (9 · 6%) [61]. Literature describes high viral load of SARS-CoV-2 in patients' respiratory tracts as a positive predictor of lung disease severity and subsequent lung injury [62, 63]. Thus, the impact of viral load on neonatal respiratory outcomes or overall adverse clinical outcomes (e.g., stillbirth, intrauterine fetal demise (IUFD) etc.) should be explored further.

There were two cases of rashes, described as skin ulcerations on the forehead or scattered rashes over the body. Chen and colleagues propose that an inflammatory toxin might be the cause [64]. In particular, authors have speculated that the dysregulation of neutrophil extracellular traps (NETs) formation (i.e., web-like DNA with antimicrobial proteins that trap and kill microorganisms) [65] is caused by SARS-CoV-2 infection, and NET formation is heightened in infected children with Kawasaki disease. In fact, Yoshida et al determined that spontaneous NET formation was enhanced in neutrophils in patients with acute KD, suggesting that NETs play a role in COVID-19 pathogenesis [66]. One of the main features of KD, and consequently adverse inflammatory reactions, is extensive skin rashes [67]. Therefore, it is reasonable to infer that the rashes reported in Chen et al could be linked to the multisystem inflammatory disease in children associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (MISC-C) [67]. Recent literature has also raised concerns about potential post-viral severe inflammatory reactions of KD (i.e., rare acute pediatric vasculitis), in children infected with SARS-CoV-2. The systemic release of DNA histones and proteins (i.e., host autoantigens) caused by NET dysregulation [68, 69] can have detrimental complications such as pediatric coronary artery aneurysms requiring intensive care support [70, 71, 72], thrombosis, sepsis, cystic fibrosis, and autoimmune diseases like lupus, type I diabetes, and rare conditions affecting the lungs, skin, and kidneys [73]. At present, KD has not yet been described in neonates with SARS-CoV-2.

With respect to laboratory findings, there were three SARS-CoV-2 positive pregnant women with thrombocytopenia (0 · 95%). Based on a recent meta-analysis, a low platelet count is associated with enhanced risk of severe SARS-CoV-2 [74]. Furthermore, a study examining 138 SARS-CoV-2 positive non-pregnant patients reported about a third of patients (i.e., 46) had this condition ($<150\ 000 \times 10^6$/L) regardless of severity of illness [75]. In another systematic review, thrombocytopenia was reported in 2 pregnant patients without preeclampsia (platelet counts of $81,000$ and $91,000 \times 10^6$/L, respectively) [76]. In comparison, our study reported one additional patient with thrombocytopenia whose neonate died of multiple organ failure. The biological underpinning for thrombocytopenia is likely multifactorial; in fact, among SARS patients, the combination of mechanical ventilation and viral infection might have led to endothelial damage activating platelet aggregation and thrombosis in the lung, contributing to platelet consumption [77]. Platelets may also be released from fully mature megakaryocytes in the lung, yet a decrease or change in the pulmonary capillary bed could defragment platelets in the process [77]. In general, coronaviruses may infect elements of the bone marrow resulting in abnormal hematopoiesis, or activate an auto-immune response against blood cells [78]. Another possible explanation is that patients with SARS may consistently present with low grade disseminated intravascular coagulation (DIC), which might trigger low platelet counts [77]. However, regardless of these explanations, the pathophysiological mechanisms behind SARS-CoV-2 are still under investigation and are likely to differ from SARS.

The percentage of lymphopenia was high in this review (7 · 9%). Lymphocytes below the normal range ($<1 \cdot 1 \times 10^9$/L) and cases of lymphopenia ($<1 \cdot 0 \times 10^9$/L) have been reported in mothers infected with SARS-CoV-2 [15,64]. A systematic review also reported significantly lower lymphocyte count in severe SARS-CoV-2 patients [79]. Lymphopenia is a distinguishable feature of SARS infection, which either directly suppresses bone marrow or induces destruction of lymphocytes via an immune-mediated response [80]. SARS-CoV-2 has been suggested to contribute to direct infection and lymphocyte destruction as well as cytokine-mediated lymphocyte destruction, much like that of SARS virus [81, 82, 83].

Unlike the normal laboratory investigations reported in this systematic review, prior studies report lower counts of WBC, neutrophils, and CRP in pregnant women on admission in comparison to non-pneumonia controls [75]. However, increased CRP has been documented in postpartum blood tests, which supports our finding of elevated CRP [57]. Typically, CRP is a useful clinical marker of inflammation, involved in host defense against invading pathogens and inflammation. Dissociation of native pentameric CRP (pCRP) into subunits occurs in the inflammatory microenvironment, enabling newly generated modified/monomeric CRP (mCRP) to localize the inflammatory response; however, mCRP can also exert damaging pro-inflammatory actions on endothelial cells, endothelial progenitor cells, platelets, and leukocytes, elevating inflammation during viral infection [84]. Thus, elevated CRP could be used as an indicator of SARS-CoV-2 disease inflammation and progression, making it worthwhile to examine in the context of deteriorating maternal and fetal outcomes from the SARS-CoV-2 virus [85].

In terms of placental pathology findings, there were three cases each of placental abruption and abnormal placenta/placenta previa in SARS-CoV-2 women (6 cases total; 2 · 0%). Li and colleagues reported two cases of preterm delivery due to gestational hypertension/preeclampsia, and one suspected case due to placenta previa but a connection between placental abruption and preeclampsia was not directly mentioned [57]. Current risk factors of placental abruption include smoking and trauma, suggesting an interplay of complex factors dependent on maternal lifestyle behaviours in addition to chorioamnionitis and decidual vascular lesion [86]. Rodrigues and colleagues also found one instance of placental abruption in their systematic review [87]; therefore, although not a regular occurrence, future monitoring of placental abruption may be encouraged. In another study, placental abnormalities such as placenta previa, placenta accrete, and placental abruption were also prevalent in 2% of pregnant women with COVID-19 [88]. The total percentage of placenta previa reported among pregnant women without SARS-CoV-2 in Japan was 0·3–0·5% [89]. Globally, placental abruption of various degrees of severity occurs in around 1% of all pregnancies [90]. Thus, rates of placental abruption and placenta previa were higher in this review. Additional investigation of the potential relationship between SARS-CoV-2 and placental abruption and placenta previa is recommended for management strategies.

Radiology findings from this systematic review suggest the presence of viral pneumonia (50 · 8%) and pure, patchy or bilateral ground-glass opacities (GGOs) (14 · 3%) in pregnant women with SARS-CoV-2. These results are supported by a study conducted in the general population of patients with SARS-CoV-2 pneumonia, which demonstrated nearly half of patients had ground glass opacities and lung abnormalities on chest CT [91]. The presence of lesions like pure GGO was more prevalent in age-matched non-pregnant women with SARS-CoV-2 pneumonia (57 cases; 62%) versus pregnant women with SARS-CoV-2 (141 cases; 57%). Interestingly, pure consolidation increased to 95% and 82% from 27% and 24%, respectively, after baseline chest CT for pregnant and non-pregnant groups with significant differences [92].

The main limitations of this review pertain to the fact that several studies had missing outcome data (i.e., poor coverage) although being assessed as high-quality evidence. There was also a potential for selective reporting and misclassification bias when reporting data on certain outcomes (e.g., myalgia versus muscle soreness overlap). There is the potential for double covering since certain primary studies may have reported on clinical outcomes from patients in the same hospital institution; however, secondary studies like systematic reviews drawing on these primary studies were excluded, to minimize the risk of double

counting. Six studies could also not be obtained for inclusion due to accessibility issues. Moreover, most studies included are case studies or case series with small sample sizes; thus, there is a lack of generalizability to all pregnant women with SARS-CoV-2 and their neonates. Despite this, we included studies of pregnant women or their neonates with laboratory confirmed SARS-CoV-2 to ensure clinical assessments of maternal and neonatal outcomes and precise estimates. There was no language barrier during the screening stages, as we had experienced language specialists fluent in multiple languages. All available evidence was reviewed; as such, it is unlikely to have missed studies with relevant study designs in our capture period, at this time of submission for publication.

Results from this review suggest elevated rates of ICU admission, gestational diabetes, preeclampsia, placental abruption, placental previa, c-sections, pre-term birth, and CRP in comparison to pregnant women without SARS-CoV-2. When compared to non-pregnant patients with SARS-CoV-2, rates of viral pneumonia, lung abnormalities, and lower lymphocyte counts were similar while fewer cases of thrombocytopenia were reported in this review. This work advances current, limited knowledge around maternal and neonatal outcomes regarding placental pathology, radiology, and laboratory findings in the context of a global pandemic. A compelling area of future study is to examine clinical outcomes of SARS-CoV-2 positive women during their first and second trimester of pregnancy. In the future, longitudinal studies can examine development (i.e., cognitive and neurological) of infants older than one month born to SARS-CoV-2 positive mothers as well as the effects of maternal stress on prematurity.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2021.e06393.

Acknowledgements

We thank Katie O'Hearn, Msc, (Children's Hospital of Eastern Ontario Research Institute) for methodological assistance, Margaret Sampson, MLIS, PhD, AHIP (Children's Hospital of Eastern Ontario) for developing the electronic search strategies, Lindsey Sikora, MISt (University of Ottawa) for peer review of the MEDLINE search strategy, and Vid Bigelic, MSc, for determining inter-rater reliability using the MINORS instrument.

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