Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Maternal clinical characteristics and perinatal outcomes among pregnant women with coronavirus disease 2019. A systematic review

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ABSTRACT

Objective: To describe the maternal clinical characteristics, maternal and perinatal outcomes in COVID-19-positive pregnant women.

Methods: Articles in all languages on the SARS-CoV-2 infection in pregnant women were sought from MEDLINE, EMBASE, Cochrane Library and LILACS; China National Knowledge Infrastructure Database (CNKI), Chinese Science and Technology Periodical Database (VIP) and Wan Fang Data between December 1, 2019 and April 27, 2020. Bulletins and national reports were also searched.

Results: From 12,168 retrieved articles, 143 were selected for full-text assessment; 33 for descriptive analyses, and 4 case-controls for meta-analysis. In 322 infected pregnant women, aged 20–45 years, the most frequent maternal comorbidity was obesity (24.2%). Forty-two (28.4%) were asymptomatic at admission. Cough (n = 148,59.7%) and fever (n = 147,59.3%) were the most prevalent symptoms. In the meta-analysis, fever (OR: 0.13,95% CI 0.05 to 0.36) and cough (0.26,95% CI 0.11 to 0.59) were lower in pregnant women with COVID-19 than non-pregnant women with COVID-19.195 (60.6%) delivered, and 125 (38.8%) remained pregnant during the study. Cesarean was reported in 99 (50.8%) women and vaginal delivery in 64 (32.8%). The main adverse obstetric outcome was premature birth (n = 37,18.9%). Thirty patients (10.3%) with COVID-19-related complications required intensive care, one (0.3%) died. SARS-CoV-2 was absent in breast milk, amniotic fluid, placenta or umbilical cord blood.

Conclusions: The maternal clinical characteristics of COVID-19-positive pregnant include frequently fever and cough; however significantly less frequently than non-pregnant women with COVID-19. Iatrogenic preterm birth is the main adverse obstetric outcome. Current data does not support vertical transmission in the third trimester.

1. Introduction

On February 11, 2020, the International Committee on Taxonomy of Virus officially named a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), as the causative agent of the new viral pandemic creating a global health crisis sickening over 51 million and killing about 1.2 million people hitherto [1,2]. The Coronavirus Disease 2019 (COVID-19) is highly transmissible, and the case fatality rate (CFR) is around 3.4%. However, this could vary depending on factors such as age, comorbidities and healthcare capacity [3]. Older people and those with pre-existing medical conditions—high blood pressure, heart problems and diabetes—are more vulnerable [4,5]. Moreover, owing to the major physiological changes pregnant women undergo—increased minute ventilation, diaphragm elevation and thorax deformation, edema of respiratory tract mucosa, altered cell immunity among others—pregnant women might be at a higher risk of infection and complications compared to non-pregnant women [6].

According to previous studies, 50% of pregnant women affected by Severe Acute Respiratory Syndrome (SARS), caused by a different coronavirus termed SARS-CoV, required intensive care; and 50% of

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them died [7]. Additionally, owing to the 79% shared similarity between SARS-CoV and SARS-CoV-2, COVID-19 could be seriously harmful for pregnant women [8].

Since despite the increasing cases COVID-19 in pregnant women, current clinical evidence is based on small series. We aim to review all cases from the current literature and provide up-to-date scientific evidence on the clinical characteristics, maternal outcomes, perinatal outcomes and the possibility of vertical transmission in the infected pregnant women.

2. Methods

2.1. Information sources, search strategy and eligibility criteria

The protocol for this systematic review was registered in the PROSPERO international prospective register of systematic reviews (Registration ID: CRD42020176534). This revision followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [9]. Our wide search criterion included every article in any language on SARS-CoV-2 across MEDLINE, EMBASE, Cochrane Library and LILACS; and Chinese medical databases: China National Knowledge Infrastructure Database (CNKI), Chinese Science and Technology Periodical Database (VIP), and Wan Fang Data between December 01, 2019 and April 27, 2020. MeSH (medical subject heading) term, keywords or their variants were constructed. Moreover, bibliographic references of relevant articles were reviewed to search for additional reports (search formulas are available in Appendix A). Case-control studies, case series, case reports, letters and comments that reported SARS-CoV-2 in pregnant women, confirmed by a quantitative real-time polymerase chain reaction (qRT-PCR) on a nasopharyngeal sample, and a short-term outcome were included. The references of all identified articles for additional resources were examined. Official governmental e-sources with detailed description of cases such as Dutch Society Obstetrics & Gynecology were also included [10]. Articles were excluded if 1) they did not include pregnant women in their population, 2) their cases were reported in a previous article, 3) their full text was unavailable or 4) there was insufficient data or undefined outcome.

2.2. Study selection and data extraction

Three reviewers (R.N., W.Q. and P.Ll.) first independently screened articles by titles and abstracts. There was a consensus on the titles selected, and a fourth reviewer (W·V.) resolved the differences. Articles not meeting the selection criteria were excluded. The full-text was then reviewed in detail, and data about the characteristics of the study, the clinical characteristics of the infection and the maternal and perinatal outcomes was extracted, using Microsoft Excel (2013 version, Microsoft Corporation, Redmond, WA, USA). The inconsistencies were discussed, and a consensus was reached. Data duplication was avoided by choosing the most informative study from among cases published more than once. Only full-text articles were included and reviewed. The authors of articles were contacted as needed.

2.3. Assessment of methodological quality and risk of bias

The Newcastle Ottawa Scale (NOS) was employed to assess the risk of bias for case-control studies [11]. using which, a maximum of 9 points was allocated in four domains: 4 points for study group selection, 2 for group comparability and up to 3 points for exposure and outcome ascertainment. Additionally, a modified Newcastle Ottawa Scale (NOS) was used for case reports and case series to remove items relating to comparability and adjustment (irrelevant to non-comparative studies) and retaining items that focused on selection and were representatives of cases and outcome and exposure ascertainment. This modified NOS was tested in several systematic reviews with good interrater agreement [12]. We obtained five binary responses (yes/no) to questions, indicating whether the item suggests poor methodological quality or not. The quality of the report was deemed to be good when all five criteria were fulfilled, moderate when four were fulfilled and poor when three or less were fulfilled. The three reviewers assessed the methodological quality of the studies and discussed any disagreements.

2.4. Statistical approach

The distributions of absolute, relative and accumulated frequencies of the categorical variables were reported using descriptive analysis. For numerical variables, summary measures were calculated as averages and ranges. Observational studies reporting the proportion of symptoms, clinical and laboratory characteristics and perinatal outcomes were included for quantitative synthesis (meta-analysis). Since case reports lack a denominator for a given variable, they were excluded for the meta-analysis. Statistical analysis was performed using Stata Software (Stata Corp., College Station, TX, USA). The meta-analyses were performed using Review Manager 5.3 (RevMan version 5.3 Cochrane Collaboration). For the categorical variable, the Mantel-Haenszel M − H fixed effect model calculated the odds ratio (OR) and its 95% confidence interval (CI). Continuous data were analyzed using weighted mean difference (WMD). The degree of statistical heterogeneity was estimated using the I^2 test. Funnel plots were used to investigate publication bias (Supplemental Fig. 1). The outcomes were compared in two subgroups [1]: pregnant women with COVID-19 versus pregnant women without COVID-19 and [2] pregnant women with COVID-19 versus non-pregnant women with COVID-19.

3. Results

3.1. Study selection

We identified 12,168 articles, removing 1054 duplicates and reviewing 11,114 as per titles and abstracts. Further, 10,971 without clinical information about pregnant women were removed. We evaluated 143 in full-text for eligibility. The references included in publications, websites of national reports and academic non-government organizations yielded 22 new articles fitting our criteria. We excluded 106 articles and, ultimately, included 37 articles in this review (Fig. 1): four case-control studies [13–16], nine cases series [17–25], 23 case reports [26–48], and one national report [10].

This review excluded 106 articles (Supplemental Table 1); 53 were excluded due to non-relevance to our scope (national reports, practice guidelines, etc.), 14 due to different population, five due to insufficient data, six due to wrong outcome (psychological evaluation of the pregnant woman), and 28 due to duplicate cases. The different characteristics of articles to consider duplication were evaluated: author, city, hospital of data source, number of pregnant women, period of admission or recruitment and specific characteristics attributed to patients (symptoms, laboratory results, birth weight). Twenty-six articles with Chinese pregnant women [49–74], were excluded as the patients were also included in a recent case series from Yan J. et al. [22] Two articles from USA [75,76], were also excluded since Breslin et al. [17] published a case series including the same population from the same hospitals (Appendix B) [17].

A descriptive analysis based on 33 articles and a meta-analysis based on 4 case-control studies was performed. For the descriptive analysis, we included a total of 322 pregnant women, 111 (34.5%) patients from Netherlands [10], 80(24.8%) from USA [17,19,21,40,42,46], 76 (23.6%) from China [22,23,26,27,30,32,33,37,39,47], 43(13.3%) from Italy [18,29], 2(0.6%) from Canada [20], and one each from Honduras [28], South Korea [31], Sweden [34], Germany [35], Turkey [36], Iran [38], Australia [41], Spain [43], Peru [44], and India [45] (Supplemental Table 2). One case series(24) and one case report(48) from China were considered for analysis of vertical transmission. A different case series was consider to summarize immunoglobulin levels [25]. Of note,

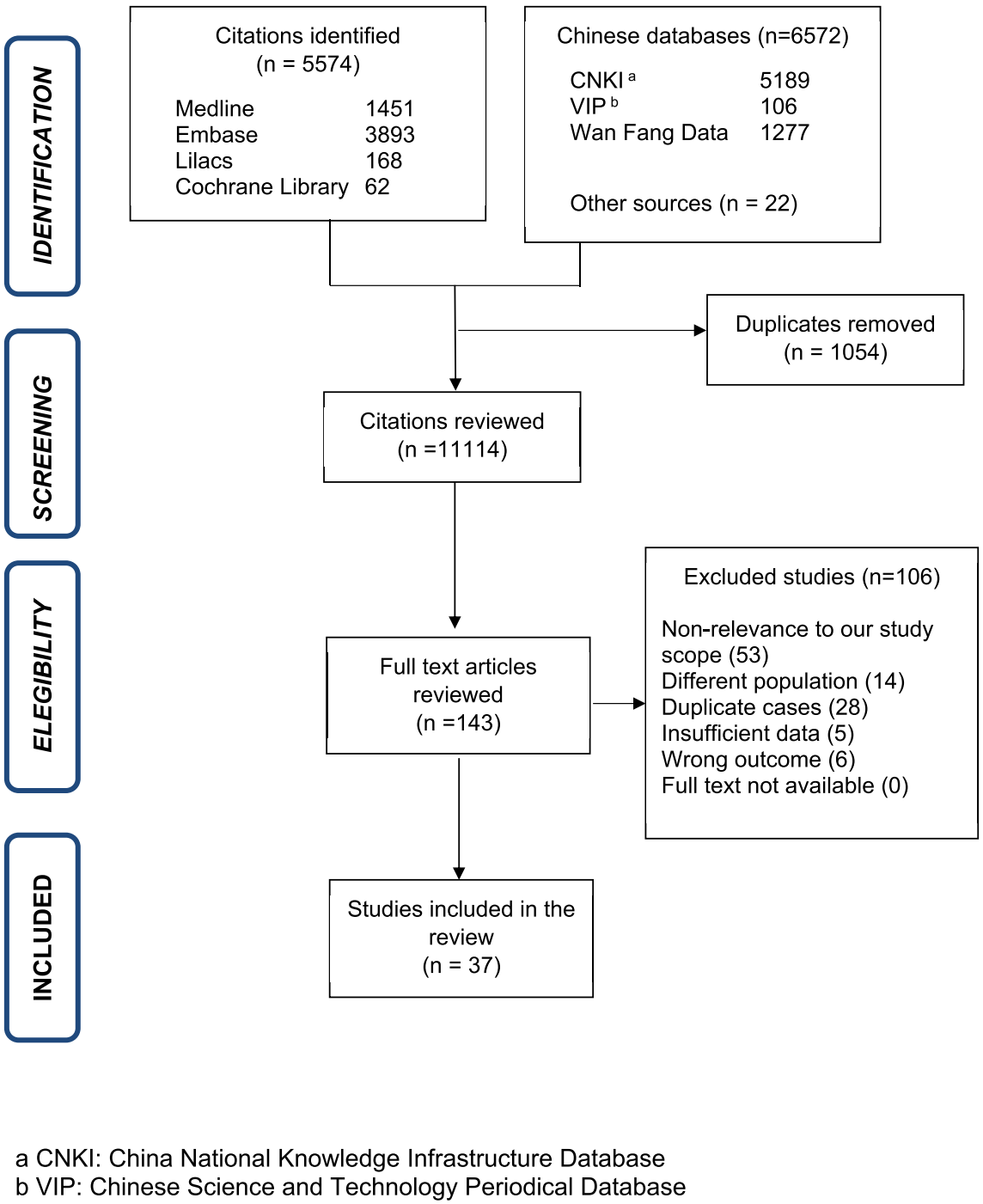


Fig. 1. Selection of studies.

until April 27, around 400 cases were reported by different national reports; however, they were excluded because they were summary reports without descriptive information and some may have been included in previous research papers.

3.2. Risk of bias of included studies and quality assessment

Using NOS in the case-control studies, out of a maximum of nine stars, the highest score was eight; the lowest six. Every study had a proper case definition and was representative of the cases in hospitals; however, bias risk was considered in controls selection. Only two studies tried to control for some confounders by age-matching [14,16]. All studies had ascertainment of exposure with a standard method. Most studies had the same rate of non-response for both groups (Supplemental Table 3a). The quality of case series and case reports evaluated using the modified NOS were: three studies were deemed to be good [20,26,46], 23 were moderate [17,19,22–24,27–31,34–44,47,48], and six were poor in methodological quality (Supplemental Table 3b) [18,21,25,32,33,45]. The Dutch Association for Obstetrics and Gynecology's official report was no assessed for quality [10].

3.3. Synthesis of results

3.3.1. - Maternal clinical characteristics

The main characteristics are summarized in Table 1 and detailed description in Supplemental Table 4. Maternal age between 20 and 45

Table 1
Maternal demographic, clinical characteristics and comorbidities.

Demographic characteristics	Patient n (%)
Number of pregnant women	322
Maternal age in years	20–45
Single pregnancy	177/179 (98.9)
Exposure to relevant environment [a]	44/132 (33.3)
Contact with infected person	48/132 (36.4)
Trimester of pregnancy at infection	
First trimester	5/179 (2.8)
Second trimester	9/179 (5.0)
Third trimester	165/179 (92.2)
Maternal comorbidities	
Obesity	31/128 (24.2)
Previous cesarean	14/128 (10.9)
Asthma	10/128 (7.8)
Gestational diabetes	7/128 (5.5)
Type 2 diabetes	4/128 (3.1)
Chronic hypertension	3/128 (2.3)
Hypothyroidism	1/128 (0.8)
Clinical characteristics	
Asymptomatic at admission	42/169 (28.4)
Cough	148/248 (59.7)
Fever at admission	147/248 (59.3)
Tachypnea	25/248 (10.1)
Myalgia	23/248 (9.3)
Fatigue	16/248 (6.5)
Dyspnea	14/248 (5.6)
Sore throat	13/248 (5.2)
Tachycardia	13/248 (5.2)
Headache	12/248 (4.8)
Chest pain	8/248 (3.2)
Malaise	4/248 (1.6)
Diarrhea	4/248 (1.6)
Intra-partum fever	2/248 (0.8)
Nasal congestion	2/248 (0.8)
Post-partum fever	1/248 (0.4)

[a] Exposure to a close area with active infection, i.e., Wuhan city.

years, and the gestational age ranged from 5 + 2 to 40 + 5 weeks (+days). Two twin pregnancies were reported. Data regarding time to diagnosis COVID-19 by trimester in 179 women were collected. Five (2.8%) were in the first trimester, nine (5.0%) in the second and 165 (92.2%) in the third. Forty-four (33.3%) patients reported exposure to a close area with active infection (i.e. Wuhan city). Forty-eight (36.4%) reported direct contact with an infected person. Maternal comorbidities were reported in 128 women, including obesity (n = 31,24.2%), asthma (n = 10,7.8%), gestational diabetes (n = 7,5.5%), type 2 diabetes (n = 4,3.1%), chronic hypertension (n = 3,2.3%) and hypothyroidism (n = 1,0.8%). Fourteen patients (10.9%) reported previous cesarean.

Among 169 pregnant women, 42 (28.4%) were asymptomatic at admission but qRT-PCR tested SARS-CoV-2-positive. Among 248 women, the most common being cough (n = 148,59.7%) and fever (n = 147,59.3%). Less common symptoms were tachypnea (n = 25,10.1%), myalgia (n = 23,9.3%), fatigue (n = 16,6.5%), dyspnea (n = 14,5.6%), sore throat (n = 13,5.2%), tachycardia (n = 13,5.2%), headache (n = 12,4.8%), chest pain (n = 8,3.2%), malaise (n = 4,1.6%) and diarrhea (n = 4,1.6%). There were 125 ongoing pregnancies during the report. Among 111 of them, 92 (82.9%) were in home isolation with no or mild symptoms. (Detailed description in Supplemental Table 5).

Twenty articles including 88 patients reported the laboratory characteristics [19,20,22,28,30,31,33–38,40,42–44,46,47]. Table 2 describes lymphopenia (n = 52,59.1%), elevated concentrations of C-reactive protein (n = 46, 52.3%) and leukopenia (n = 23,26.1%) as the most common findings. Leukocytosis (n = 9, 10.2%), high alanine transaminase ALT (n = 8,9.1%), high aspartic transaminase AST (n = 7, 8.0%), high erythrocyte sedimentation rate (n = 6,6.8%), anemia (n = 6, 6.8%) and thrombocytopenia (n = 5,5.7%) were also reported. All four patients from two studies had high IL-6 values(23, 35) and all 3 patients from one study had high IL-10 levels (100.0%) [23]. (Detailed description in Supplemental Table 6).

Table 2
Maternal laboratory and imaging characteristics.

Laboratory characteristics	Patient n (%)
Lymphopenia (<1.0 × 10^9/L)	52/88 (59.1)
Elevated concentrations of CRP (>8.1 mg/L)	46/88 (52.3)
Leukopenia (<4 × 10^9/L)	23/88 (26.1)
Leukocytosis (>10 × 10^9/L)	9/88 (10.2)
High ALT [a] (>33 U/L)	8/88 (9.1)
High AST [b] (>33 U/L)	7/88(8.0)
Erythrocyte sedimentation rate (>47 m/h)	6/88 (6.8)
Anemia (<11 g/dL)	6/88(6.8)
Trombocytopenia (<150 x 10^9/L)	5/88 (5.7)
Serum ferritin (>117ng/mL)	3/88 (3.4)
High creatine kinasa (>75 units/L)	3/88 (3.4)
High creatinine	1/88 (1.1)
High bilirubin (>1.1 mg/dL)	0/88 (0.0)
Chest CT imaging characteristics [c]	
CT evidence of pneumonia	77/82 (93.9)
Ground-glass opacity	65/82 (79.3)
Consolidation	9/82 (11.0)
Pleural effusion	5/82 (6.1)

[a] AST: Alanine aminotransferase.
[b] ALT: Aspartate aminotransferase.
[c] CT: Computed tomography.

Table 2 additionally shows 16 studies including 82 patients imaged by chest CT. with 77 (93.9%) diagnosed of pneumonia. The most characteristic findings on CT were ground-glass opacity (GGO) regions in 65 (79.3%), consolidation in nine (11.0%) and pleural effusion in five (6.1%). Data from 15 patients showed bilateral lesions in 13 (86.7%). Albeit other modalities were rarely reported, it is noteworthy that seven cases were reported with pneumonia by x-chest ray (77.8%) [19,20,37,38,40,42,43], and 2 reports found signs of pneumonia on ultrasound lung examination [36,40]. (Detailed description in Supplemental Table 6).

3.3.2. - *Maternal outcomes*

Maternal outcomes are listed on Table 3 and detailed description in Supplemental Table 7). Out of 322 pregnant women, 195 (60.6%) delivered and 125 (38.8%) were still pregnant during the study. Delivery occurred at term (≥37 weeks) in 127/195 (64.8%). Thirty-two (16.3%) did not reported gestational age. Adverse obstetrics outcomes included: preterm delivery in 37 out of 195 reporting gestational age (18.9%), premature labor treated with tocolysis in five cases (1.7%), intrauterine fetal distress (i.e. fetal hypoxia as stated in each article) in 17 (5.9%) and premature rupture of membranes in five (1.7%) women. There were 1 (0.3%) stillbirth at 30 weeks of gestation that was delivered vaginally while the mother was on mechanical ventilation, who died subsequently because of severe COVID-19 complications [38]. One (0.3%) patient had a miscarriage presenting with fever and fatigue [22], and one (0.3%) opted for termination of the pregnancy at six-weeks' gestation after receiving oxygen support and antiviral therapy [23]. Other adverse obstetrics outcomes were preeclampsia in three women (2.3%), gestational hypertension in 2 (1.6%) and cholestasis of pregnancy in 1 (0.8%). Cesarean was reported in 99 (50.8%) women and vaginal delivery in 64 (32.8%). There was no report on the delivery route in 32 (16.4%) cases. The main indication for cesarean was: COVID-19 (n = 31, 31.3%). A total of 73 cases reported the median time between the onset of symptoms and delivery as five days (IQR 3–10 and range 1–38).

Table 3 shows 30 patients (10.3%) with COVID-19 complications requiring intensive care unit. Nine patients had data on the risk factors for admission to ICU being the most frequent obesity 3/9 (30%). All nine patients were admitted after 29 weeks of gestation, i.e. third trimester. Eight patients (8/9) underwent delivery by cesarean section. One patient had a preterm vaginal delivery spontaneously in the ICU.

The main complications were severe pneumonia occurred in 24 patients (13.4%) and acute respiratory distress syndrome in 19(10.6%). In

Table 3
Maternal outcomes.

Obstetric outcomes	Patient n (%)
Preterm delivery	37/195 (18.9)
Miscarriage	1/322 (0.3)
Interruption of pregnancy	1/322 (0.3)
Intrauterine fetal distress	17/290 (5.9)
Premature rupture of membrane	5/290 (1.7)
Stillbirth	1/290 (0.3)
Pre-eclampsia	3/128 (2.3)
Gestational hypertension	2/128 (1.6)
Cholestasis of pregnancy	1/128 (0.8)
Delivery characteristics	
Cesarean	99/195 (50.8)
COVID-19 infection	31/99 (31.3)
Intrauterine fetal distress	16/99 (16.2)
Labor dystocia	10/99 (10.1)
Previous cesarean	10/99 (10.1)
Preeclampsia	3/99 (3.0)
Other obstetrics reason	6/99 (6.1)
Not reported	23/99 (23.2)
Vaginal	64/195 (32.8)
Not reported	32/195 (16.4)
Medical complications	
Severe pneumonia	24/179 (13.4)
Acute respiratory distress syndrome	19/179 (10.6)
Acute hepatic failure	2/179 (1.1)
Acute renal failure	2/179 (1.1)
Coagulopathy	3/179 (1.7)
Cardiomyopathy	2/179 (1.1)
Septic shock	3/179 (1.7)
Intensive care unit admis[a]ion	30/290 (10.3)
Maternal mortality	1/322 (0.3)
Treatment	
No[b]treatment	129/183 (70.5)
Oxygen support	52/290 (17.9)
Antivirals	67/248 (27.0)
Antibiotics	97/248 (39.1)
Corticosteroid	41/248 (16.5)
Hydroxychloroquine	13/248 (5.2)
Mechanical ventilation	11/290[a]3.8)
Immune gamma globulin	2/248 (0.8)
Extracorporeal Membrane Oxygenation	1/290 (0.3)

six cases, the specific complication was unstated. One (0.3%) woman died of pneumonia by SARS-Cov-2 and multiorgan failure [38]. Table 3 also shows that 129 (70.5%) patients did not receive any medical treatment. Fifty-two (17.9%) patients reported the need for oxygen support; 67(27.0%) patients received some antiviral treatment such as oseltamivir, lopinavir, ritonavir and ganciclovir. Antibiotics were given to 97(39.1%) patients (moxifloxacin, cephalosporin, azithromycin, penicillin). Corticosteroids were given to 41(16.5%) patients. Other treatments reported were hydroxychloroquine (n = 13,5.2%), immune gamma globulin (n = 2,0.8%). Eleven (3.8%) patients needed mechanical ventilation and one needed extracorporeal membrane oxygenation ECMO (0.3%) (Detailed description in Supplemental Table 8).

3.3.3. - Perinatal outcomes

Neonatal outcomes are listed in Table 4. Apgar scoring was higher than 7 at 1-min and 5-min in 84 (96.6%) and 85 (97.7%) newborns respectively. Breastfeeding restriction was reported in 28 (25.7%) infants. Low birth weight was reported in 9/62 newborns (14.5%). In this low birth weight group, we found seven neonates reporting some data. All seven patients had preterm delivery. One out of seven neonates were reported to have COVID-19 infection.

Two infants had asphyxia (5.6%), two (5.6%) respiratory distress syndrome and one (2.8%) developed pneumonia. Twenty-four (27.9%) newborns were severely ill, requiring NICU admission, but only two (5.6%) required mechanical ventilation. We made a sub-analysis to identify risk factors and characteristics of patients for NICU admission. However, only seven neonates had some data. One out of seven had COVID-19 infection and five out of seven (71%) had preterm delivery.

Table 4
Neonatal outcomes.

Neonatal outcomes	Patient n (%) [a]
APGAR >7	
1-minute	84/87 (96.6)
5-minute	85/87 (97.7)
Low birth weight	9/62 (14.5)
NICU admission for treatment [b]	24/86 (27.9)
Respiratory distress syndrome	2/36 (5.6)
Mechanical ventilation	2/36 (5.6)
Asphyxia	2/36 (5.6)
Pneumonia	1/36 (2.8)
Sepsis	0/36 (0.0)
Neonatal death	1/118 (0.8)
No breastfeeding	28/109 (25.7)
Discharge from hospital	87/112 (77.7)

[a] 196 neonates (including one pair of twin).
[b] NICU: Neonatal intensive care unit.

Yan J et al. [22] reported a newborn of 35 + 2 weeks delivered by cesarean with severe neonatal asphyxia treated with invasive ventilation died 2 h after birth. The mother developed severe pneumonia and septic shock. Eighty-seven (77.7%) infants had been discharged during the report (Detailed description in Supplemental Table 9).

Table 5 shows the data on vertical transmission. Every mother (322, 100%) included in this study was tested qRT-PCR positive for SARS-CoV-2 in a nasopharyngeal swab. Some patients were additionally tested in different type of samples. One out of 16 (6.25%) were vaginal swab-positive. SARS-CoV-2 was not found in breast milk (0/17), amniotic fluid (0/25), umbilical cord (0/16) or placenta (0/15). We found data of IgG and IgM antibodies on eight mothers and their neonates. Seven of them were qRT-PCR SARS-CoV-2 tested negative in nasopharyngeal swabs. Six infants had high IgG levels (i.e.>10AU/mL) and three had high IgM levels. Of note, the one qRT-PCR tested positive had no detection of IgG and IgM antibodies [44]. Among 138 neonates tested with nasopharyngeal swab, four (3.6%) were tested SARS-CoV-2 positive between 16 and 36 h after birth. Three of them had additionally a positive anal test. These four newborns were delivered by cesarean. Two infants had fever and two shortness of breath. Two of them required

Table 5
Results of SARS-CoV-2 testing on mothers and neonates.

Type of test	Tested	Positive	(%)
Mother			
Nasopharyngeal swabs	322	322	100.00
Breast milk	17	0	0.00
Vaginal swab	16	1	6.25
Cervical secretion	1	0	0.00
Sputum	3	2	66.67
Feces	2	0	0.00
Serum	1	0	0.00
IgM [a]	8	6	75.00
IgG [a]	8	7	87.50
Conception products			
Amniotic fluid	25	0	0.00
Umbilical cord blood	16	0	0.00
Placenta	15	0	0.00
Neonate			
Nasopharyngeal swab [b]	138	4	3.60
Serum	4	0	0.00
Anal [b]	6	3	50.00
Feces	2	0	0.00
Gastric juice	1	0	0.00
Urine	1	0	0.00
IgM [a]	8	3	37.50
IgG [a]	8	6	75.00

[a] We consider additional data of immune globulin levels from two articles: Zeng H et al.[25] and Dong L et al.[48].
[b] We consider additional data of newborns with qRT-PCR positive for SARS-CoV-2 from the article of Zeng L et al.[24].

mechanical ventilation; however, none of these neonates died (Detailed description in Supplemental Table 10).

3.4. Meta-analysis

Two case-control studies compared clinical characteristics, laboratory and chest CT findings between pregnant women with COVID-19 and non-pregnant women with COVID-19 (Fig. 2) [15,16]. Among the clinical characteristics, fever (OR:0.13,95%CI 0.05–0.36) and cough (0.26,95%CI 0.11–0.59) were significantly lower in pregnant women with COVID-19 than non-pregnant women with COVID-19. There was no significant difference in dyspnea (OR:1.08, 95% CI 0.29–4.02). Leukocytosis (OR: 50.42, 95% CI 11.38–233.41) and high levels of C-reactive protein (OR:4.39,95%CI 1.9–10.14) were significantly higher in pregnant women with COVID-19 than non-pregnant COVID-19-infected women. The rates of lymphopenia between the two groups was comparable, OR:0.80 (95% CI 0.34–1.88). Similarly, signs of pneumonia on chest CT were not significantly different, OR: 0.11, (95% CI, 0.01–1.01). Two different case-controls studies compared pregnant women with and without COVID-19 (Fig. 3) [13,14]. The ORs for premature delivery (2.69, 95%CI 0.98–7.41, $p = 0.05$), fetal distress (0.6, 95%CI 0.13–2.79, $p = 0.52$) and neonatal asphyxia (2.93, 95%CI 0.17–49.86, $p = 0.46$) were not significantly different. The pooled estimate showed a comparable birth weight in newborns of women with and without COVID-19 (mean difference MD (IV, fixed-effect): 172 g, (95%CI-357 to 12.61).

4. Discussion

4.1. Main findings

This systematic review summarizes information about maternal clinical characteristics; and maternal and perinatal outcomes among 322 pregnant women with COVID-19.

We report that maternal mortality is rare. However, but there is a considerable proportion of women that required ICU due to complication of COVID-19 infection. Additionally, we report that maternal clinical characteristics are slightly different in pregnant women compared with the general population. The common symptom reported is cough and fever if they are symptomatic, but these are frequently less than the general population. There is a considerable proportion of asymptomatic pregnant women presenting at hospital for obstetric reasons. The main adverse obstetric outcome found is iatrogenic preterm delivery (i.e. cesarean or induction delivery due to worsening of the medical or obstetric condition). Additionally, there was a considerable proportion of low birth weight infants and neonates requiring admission to the NICU. The data collected hitherto does not support vertical transmission.

COVID-19 has posed a daunting challenge to the public health worldwide leading to researchers to focus their efforts in shedding light on our understanding of the disease. Consequently, we are facing an unprecedent number of articles being published, making it difficult to endeavor an updated systematic review. Yet, as there are several published large case series of COVID-19 in adults, there are still few published case series focusing on pregnant women. Furthermore, several articles include cases that had been previously included in different articles, even with different authors. This has raised serious concern since it represents a lapse in ethical standards of scientific reporting and potentially misleads our understanding of the disease and responding to it with ineffective public health decision [77]. In order to adhere to our strict protocol, we had to exclude many articles with every reason stated in Supplemental Table 1.

4.2. Comparison with existing literature

4.2.1. - Clinical characteristics

Among pregnant women with COVID-19 presented at hospital for obstetric reasons, three hospital-based studies recently reported the proportion of asymptomatic pregnant women at presentation in the range of 66%–88% when a universal testing was performed in areas with high prevalence of the disease [17,21,78]. A lower proportion of asymptomatic pregnant women, of about 28%, was found here, since we included most cases from the patients being admitted to hospitals, likely reflecting a bias selection for more complicated cases. Furthermore, we should consider that some of the women were asymptomatic at admission, but they might have developed symptoms later, i.e. they were presymptomatic rather than asymptomatic, which is unstated in the three previous reports. An epidemiological study reported the proportion of asymptomatic in the general population being 50% at first testing; and after data modelling, they could estimate that only 18% would be truly asymptomatic [79]. In the pediatric population, the disease is known to be mild, with mortality being extremely low; even among them, the proportion of truly asymptomatic children is 4%, and 50% of them will have very mild symptoms [80]. Thus, the proportion of asymptomatic in pregnant women could be less than what is stated by the three studies. Nevertheless, people in the asymptomatic or presymptomatic period can be transmit the virus, and as health-workers, we should bear in mind the potential risk of managing pregnant women and, where possible, include a universal screening protocol according to the capabilities of our health system [81]. We found fever and cough as the most frequent symptoms reported among pregnant women with COVID-19. However, cough was present in less proportion than in the general population as confirmed in the meta-analysis when compared with non-pregnant women with COVID-19 [5]. Similarly, fever can be found in 89% of the general population and here we reported a lower frequency of fever, highlighted in the meta-analysis when compared with non-pregnant women with COVID-19 [5,82,83].

A number of infections in pregnancy are presenting with little symptoms or even they are asymptomatic. For instance, less than 5% of cytomegalovirus infection are reported to be symptomatic in pregnancy [84]. Similarly, in toxoplasmosis infection around 10% of pregnant women become symptomatic [85]. Similar to other infections, in COVID-19 fever is the commonest symptom was found pregnant women. Influenza is another common infection during pregnancy and it usually presents with fever, cough, sore through, rhinorrhea, accompanied of unspecific symptoms such as fever, headache, fatigue, body aches among others. The symptoms are enhanced in the third trimester due to the physiological changes that are more evident as pregnancy progresses. Similarly, here we found more symptomatic pregnant women in the third trimester [86].

Although anosmia and dysgeusia were reported as common signs in some reports including non-pregnant adult population, the number of articles reporting these symptoms in our systematic search were scarce.

Among the laboratory findings, lymphopenia and elevated CRP was also commonly found in pregnant women [5,83]. Among pregnant women, data from Liu H et al. and Qiancheg X. et al. shows that leukocytosis is significantly more frequently observed in pregnant COVID-19-afected women compared with COVID-19-afected non-pregnant women, though an analysis of the data reported by Liu H et al. shows that the number of leukocytes is nearly in the high normal range of values for pregnant women, where it is far known that the total number of leukocytes in blood increases especially in the third trimester [15,16]. Among women reporting contact with a possible infected patient or living in an infected area, a third reported positively. However, most articles did not report on this and it is likely that coming articles will not report this epidemiological characteristic as COVID-19 is currently everywhere. It is important to highlight that obesity was found in 24% of those reporting comorbidities which is a major risk factor for contracting COVID-19 [4,5].

Similar to adult population, findings of pneumonia were found in about 94% of pregnant women with COVID-19 undergoing chest CT [5,87]. When compared with non-pregnant women with COVID-19, there is no significant difference, but there is a tendency in the diagnosis of

Figure 2a. Forrest plot for fever

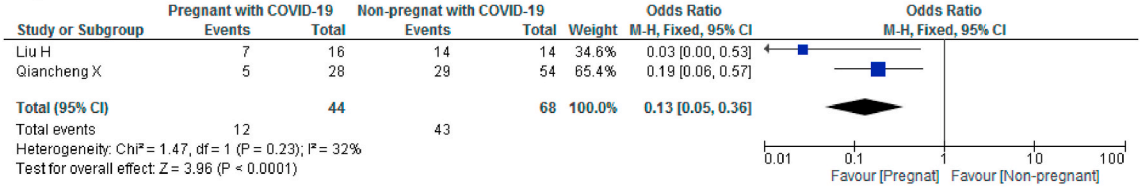


Figure 2b. Forrest plot for cough

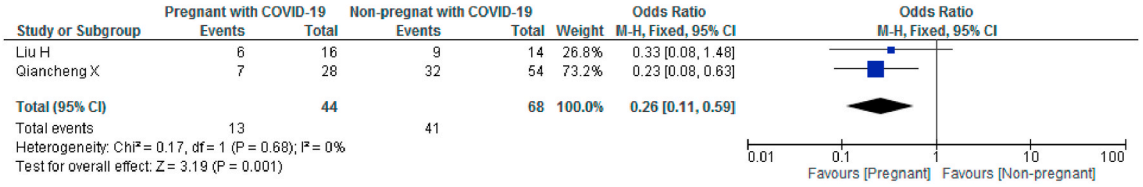


Figure 2c. Forrest plot for dyspnea

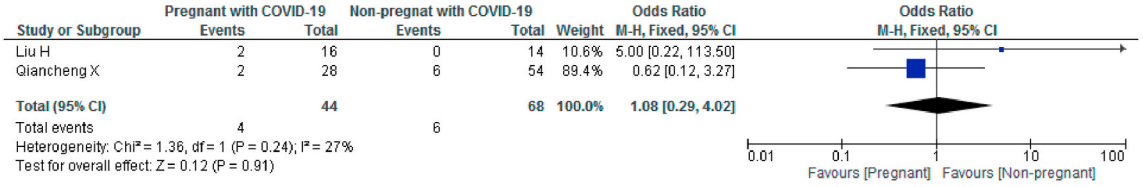


Figure 2d. Forrest plot for leukocytosis

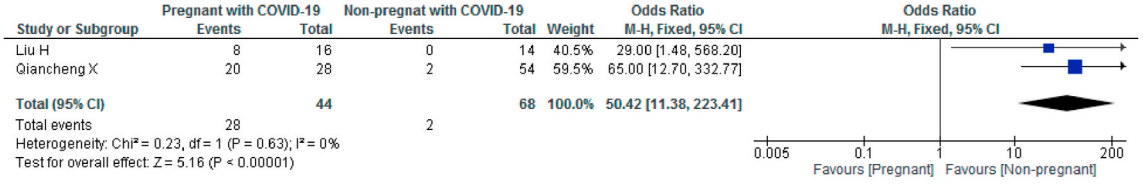


Figure 2e. Forrest plot for elevated C-reactive protein

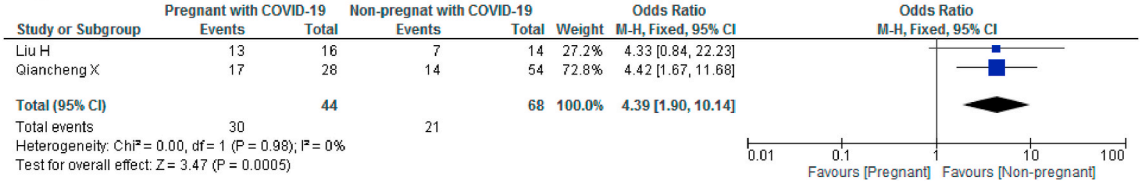


Figure 2f. Forrest plot for lymphopenia

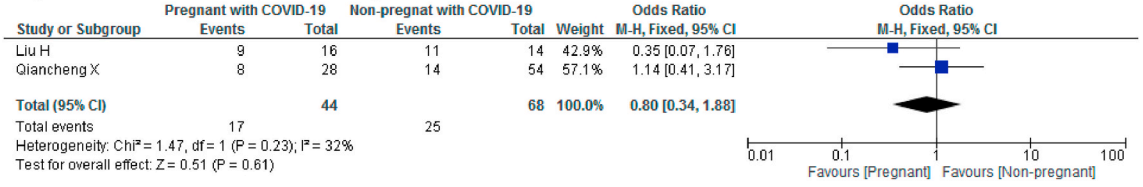
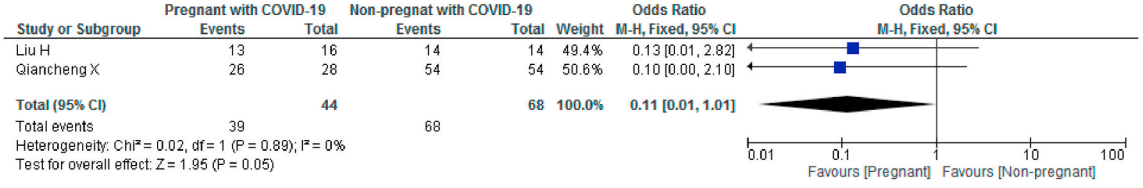


Figure 2g. Forrest plot for pneumonia on chest CT



(caption on next page)

Fig. 2. Meta-analysis: Pregnant women with COVID-19 vs. non-pregnant women with COVID-19
2a Forrest plot for fever
2b. Forrest plot for cough
2c. Forrest plot for dyspnea
2d. Forrest plot for leukocytosis
2e. Forrest plot for elevated C
-reactive protein
2f. Forrest plot for lymphopenia
2g. Forrest plot for pneumonia on chest CT.

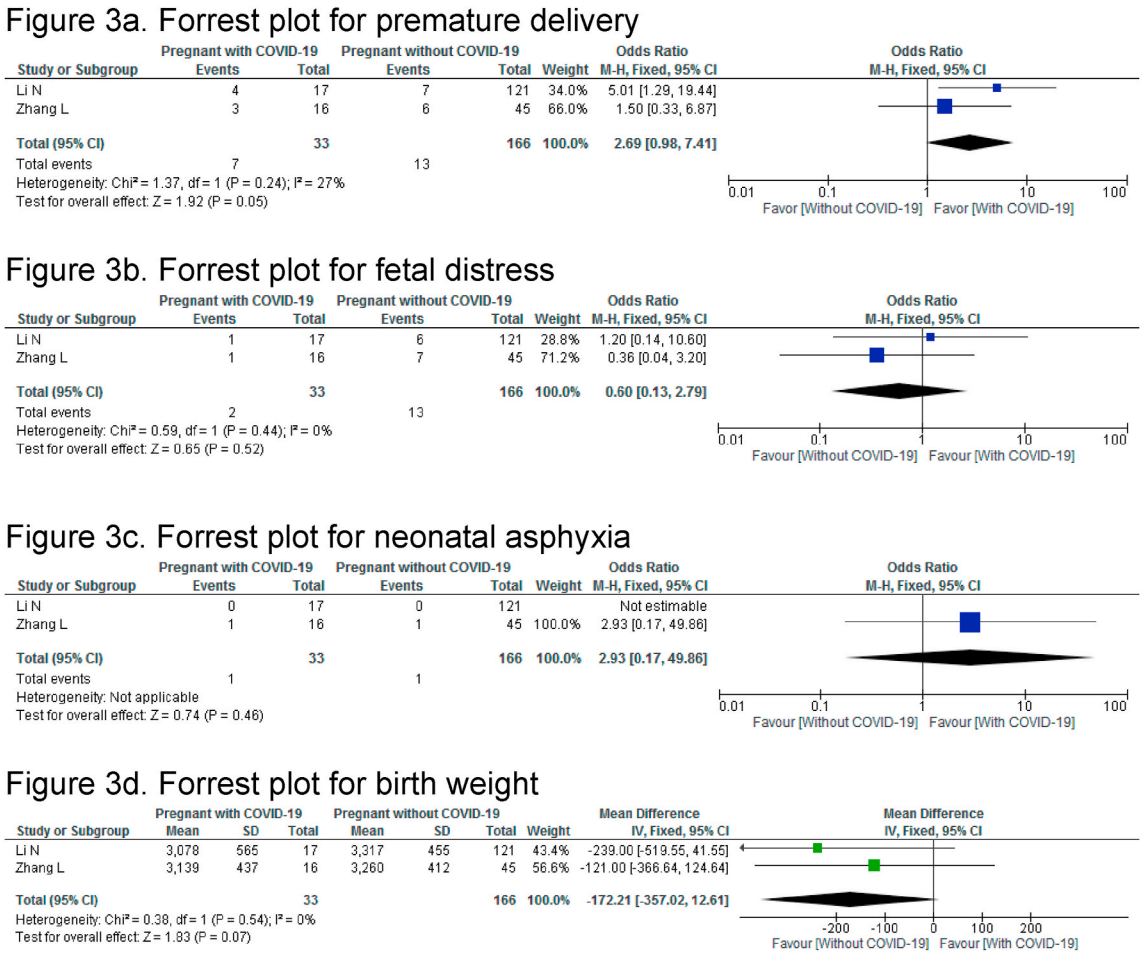


Fig. 3. Meta-analysis: Pregnant women with COVID-19 vs pregnant women without COVID-19
3a. Forrest plot for premature delivery
3b. Forrest plot for fetal distress
3c. Forrest plot for neonatal asphyxia
3d. Forrest plot for birth weight.

pneumonia to be more present in pregnant women. Lung ultrasound may help diagnose pneumonia as was shown in the general population [88]. Inchingolo R. et al. have recently reported pneumonia diagnosis using lung ultrasound in symptomatic pregnant women with COVID-19 [89]. Thus, further research should clarify the use of chest CT or lung ultrasound in pregnant women with COVID-19 showing no or mild symptoms.

Albeit about 70% women were not treated, some women received oxygen support and a variety of antiviral and antibiotics as the most frequent treatments as observed in adult population since there is no evidence-based treatment for COVID-19 thus far. Since there are no clear recommendations on the use of antiviral in pregnancy, all patients reported here had delivered before using antivirals. Data is still scarce on effective medical treatment for COVID-19 in pregnant women as they are excluded in any known trial exploring treatment options for COVID-19. Corticosteroids were given in 16% patients, mostly after delivery, i.e. as medical management of COVID-19. We were unable to determine the number of pregnant women receiving corticosteroid prenatally as per protocol for lung maturation. Nonetheless, current guidelines recommend proceeding with caution and uniquely weighing the maternal risks and fetal benefits when considering its use, particularly in early preterm delivery [90].

4.2.2. - Maternal outcomes

Two recent reports from New York suggest that the overall clinical outcomes in pregnant women are similar to those in non-pregnant women [17,21]. A rationale to believe that COVID-19 may have a deleterious effect on pregnancy is the similarity of SARS-CoV-2 with the SARS-causing virus, which is more aggressive than COVID-19 in pregnant women, leading to high admission at ICU and high mortality [7]. A

rationale to believe that COVID-19 might have a deleterious effect on pregnancy is the similarity of SARS-CoV-2 with SARS-Cov-1 and MERS-CoV, which are more aggressive than COVID-19 in pregnant women [7], leading to higher rates of admission to ICU (MERS-CoV: 44.6%, SARS-CoV-1: 53.3% and SARS-CoV-2: 9.3%), need for mechanical ventilation (MERS: 40.9%, SARS-COv-1: 40% and SARS-CoV-2: 5.4%) and higher rate of mortality (MERS: 28.6%, SARS-COv-1: 25.8% and SARS-CoV-2: 0%) as reported in a recent systematic review [91].

Here, we found that about 10% pregnant women required intensive care because of respiratory complications. Similarly, Blitz MJ et al. described in a series of women with COVID-19 that the reason of admission to ICU due to worsening respiratory symptoms is 10% in pregnant and non-pregnant women [92]. Recently, the Public Health Agency of Sweden released a report on 13 pregnant and postpartum women with a substantial higher risk (RR: 5.4%, 95CI 2.89–10.08) of being admitted to ICU and, additionally, a higher risk of requiring mechanical ventilation support (RR: 4.0,95% CI 1.75–9.14%) raising concern about the real impact of COVID-19 in pregnant women [93]. However, further prospective studies will clarify whether pregnancy per se is a factor to become severe ill and require ICU admission or instead the comorbidities are the risk factor for clinical deterioration. The burden of COVID-19 on maternal mortality remains unclear as there may be a delay in reporting maternal death. Here, we report a case of maternal death due to COVID-19 in Iran [38]. However, following the closing date of this review, there have been a series of eight maternal deaths among women critically ill with COVID-19, surprisingly, from Iran again [82], and few reports from other low-income countries [94]. Though it is difficult to determine an exact case fatality rate (CFR), some researchers have suggested it to be around 0.4% among those between 10 and 49 years, regardless of the gender, which is the range where pregnant women are [95]. Thus, considering women have less mortality rate, pregnant women without comorbidity could have a CFR less than 0.4% [96].

It is still unclear whether pregnancy is an immunological contributor to severe and controlled COVID-19 infection.

In normal pregnancy, anti-inflammatory cytokines are secreted to enrich the intrauterine milieu. Similarly, in patients with COVID-19 infection there are increased secretion of T-helper-2 (Th2) cytokines that suppresses inflammation [83]. This suggests that in pregnancy is preserved the anti-inflammatory environment, suppressing the severity of the COVID-19 infection. It is unknown whether COVID-19 infection has any effect on placental hormone production [97].

4.2.3. - *Perinatal outcomes*

We report one miscarriage in a very symptomatic woman and one intrauterine death at 30 weeks in a woman with subsequent death due to COVID-19 [38]. Similarly, only one neonatal death was reported in a woman with severe disease. Data on the effects of the virus in the first and second trimester are sparse. Further prospective studies will clarify if the prolonged hypoxemia in those severe cases of the infected women could harm placentation and cause miscarriage, intrauterine death or fetal growth restriction. Regarding the route of delivery, at least half of the COVID-19-infected women underwent cesarean; in 30% of them, the main indication was stated as COVID-19-complication.

Respiratory viruses such as H1N1 possess women at higher risk for severe complications leading to iatrogenic preterm birth [98]. Therefore, there is some concern regarding COVID-19 and the risk of preterm birth. Here, we have found a risk of preterm birth of 19%, higher than that commonly reported in pregnant women (about 10%) [99]. Interestingly, most of the preterm births reported had a medical indication, supporting the thesis that COVID-19-complications lead to iatrogenic preterm birth rather than causing spontaneous preterm birth. Low birth weight was found slightly increased in neonates born to infected mothers and could be explained by the increased number of preterm births. Data on fetal growth restriction as a diagnosis were not collected. In our review, most of the neonates scored Apgar greater than 7 at first and 5 min, suggesting no acute intrauterine hypoxic environment at delivery in the infected women. A very high proportion (28%) of neonates being admitted to NICU was found. However, it is likely that a bias is present as we cannot exclude those admitted due to most common indications such as preterm birth and those admitted as a cautious measure to avoid any possible transmission or following a local protocol recommending temporally separating infants born to mothers with COVID-19. Data collected on the clinical manifestation among neonates is insufficient to draw any conclusion from this systematic review, though data from other studies suggest a mild clinical course with relatively quick recovery and no major concern about the morbidity of infants born to mother with COVID-19 [54,82].

4.2.4. - *Vertical transmission*

Mother-to-child transmission of SARS-CoV-2 has been intensively researched, as it could potentially occur prenatally (in utero), perinatally (labor and partum) or postnatally when breastfeeding [100,101].

Previous studies show no evidence of vertical SARS transmission [102]. Here, we report SARS-CoV-2 was not found in placenta, amniotic fluid, umbilical cord or breast milk. There are two reasons to believe that the SARS-CoV-2 could enter bloodstream and may be able to reach the placenta. First, it has been detected in blood samples, particularly from those severe cases [103,104]; and second, it utilizes the membrane-bound angiotensin-converting enzyme 2 (ACE2) to gain access to its target cell, known to be expressed in the human placenta, though in low levels [105]. Thus, in some severe cases, SARS-CoV-2 could be found in the placenta. Thus not surprisingly, Algarroba GN et al. [106] and Hosier et al. [107] recently reported a visualization of SARS-CoV-2 virions invading syncytiothrophoblasts using electron microscopy and positive immunohistochemical staining for SARS-CoV-2 spike protein, demonstrating viral localization in syncytiothrophoblasts cells. Their findings are based on infected women in their second trimester and in severe cases with high viremia. Though SARS-CoV2 was found in nasopharyngeal of four neonates, it does not prove vertical transmission since these neonates could have been contaminated in the hospital by professional health workers. Some other authors claim that the presence of SARS-CoV-2 IgM antibody found in blood of newborns could represent an evidence of vertical transmission [25,48]. Since IgM antibodies are too large to cross the placenta, it's reasonable to believe they could be produced by the fetus. However, the two reports could be false positive since they failed to demonstrate the presence of virus in newborns, along with the unknown performance characteristics of the blood antibodies test for SARS-CoV2 [108].

4.3. *Strengths and limitations*

This is a systematic review based on case series and case reports, focusing on four small case-control studies with an overall small number of cases. No prospective longitudinal studies were identified; thus, the data is mainly descriptive. Moreover, the summarized findings are largely from hospitalized COVID-19 patients; therefore, the analysis is likely biased toward severe cases. This study was also performed over a four-month period, and since most of the included pregnant women were in their third trimester, the impact of COVID-19 in their first and second trimester remains unknown, including any effect on fetus development and long-term outcomes. Currently, with articles generated at an unprecedented rate, this systematic review warrants to be updated with the publication of new data published. An important strength of this systematic review is that we have included only patients confirmed by qRT-PCR testing for SARS-CoV-2 thus limiting population bias. Moreover, no previous systematic review on COVID-19 and pregnancy has included a thorough search including Chinese databases. Large and multinational prospective studies focusing on pregnant women from the first trimester and a complete follow-up are necessary to better estimate the impact of COVID-19 on pregnant women [109].

5. Conclusions

Maternal clinical characteristics in pregnant women with COVID-19 are slightly different than the general population. The usual symptom at presentation is cough and fever, but these two symptoms are significantly less frequent in pregnant women with COVID-19 compared with non-pregnant women with COVID-19. Iatrogenic preterm birth is the main adverse obstetric outcome. Maternal severe morbidity and mortality seems to be similar to those reported for non-pregnant women. However, impaired clinical course of COVID-19 could have some impact on morbidity and cause adverse obstetric and perinatal outcomes. No convincing evidence of vertical transmission exists, at least during the third trimester of pregnancy.

Author contribution

RHN and WV formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript. WQ, PL, KUQ, EGR refined the search strategy by conducting iterative database queries and incorporating new search terms. RHN, WQ, PLL, KUQ, and EGR searched and collected the articles. RHN and WQ conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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Disclosures

The authors have no conflict of interests.

Ethical approval

Approval was not required.

Declaration of competing interest

All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2020.101919.

Appendix A. Full search formula

MEDLINE ((((((((((("Novel coronavirus"[All Fields] OR "Novel coronavirus 2019"[All Fields]) OR "2019 nCoV"[All Fields]) OR "COVID-19"[All Fields]) OR "COVID-2019"[All Fields]) OR "COVID"[All Fields]) OR "Wuhan coronavirus"[All Fields]) OR "Wuhan pneumonia"[All Fields]) OR "SARS-CoV-2"[All Fields]) OR "2019nCoV"[All Fields]) OR "2019 novel coronavirus"[All Fields]) OR ((("COVID-19"[Supplementary Concept] OR "COVID-19"[All Fields]) OR "covid19"[All Fields])) OR "new coronavirus"[All Fields]) OR ("Wuhan"[Title/Abstract] AND (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR "coronaviruses"[All Fields])); EMBASE ('coronaviridae infection'/exp OR 'coronaviridae infection' OR 'novel coronavirus':ti,ab, kw OR 'novel coronavirus 2019':ti,ab, kw OR '2019 ncov':ti,ab, kw OR 'covid 19':ti,ab, kw OR 'covid-2019':ti,ab, kw OR covid:ti,ab, kw OR 'wuhan coronavirus':ti,ab, kw OR 'wuhan pneumonia':ti,ab, kw OR 'sars-cov-2':ti,ab, kw OR '2019ncov':ti,ab, kw OR '2019 novel coronavirus':ti,ab, kw OR covid19:ti,ab, kw OR 'new coronavirus':ti,ab, kw OR (wuhan:ti,ab, kw AND coronavirus:ti,ab,kw)); Cochrane library (("Novel coronavirus"):ti,ab, kw OR ("Novel coronavirus 2019"):ti,ab, kw OR ("2019 nCoV"):ti,ab, kw OR ("COVID-19"):ti,ab, kw OR ("COVID-2019"):ti,ab, kw OR (COVID):ti,ab, kw OR ("Wuhan coronavirus"):ti,ab, kw OR ("Wuhan pneumonia"):ti,ab, kw OR ("SARS-CoV-2"):ti,ab, kw OR ("2019nCoV"):ti,ab, kw OR ("2019 novel coronavirus"):ti,ab, kw OR (COVID19):ti,ab, kw OR ("new coronavirus"):ti,ab, kw OR ((Wuhan AND coronavirus)):ti,ab,kw); LILACS ((((("CORONAVIRUS" or "COVID-19") or "SARS-COV/") or "SARS-RELATED CORONAVIRUS") or "SARS-RELATED CORONAVIRUS/") or "2019NCOV") or ("WUHAN" AND "CORONAVIRUS") [Palavras]. The search terms used in Chinese medical databases were: "SARS-CoV-2", "新冠肺炎","2019年冠狀病毒", "武漢市□炎", "新型冠状病毒肺炎", "新型冠状病毒", "COVID-19". Limited for human studies. Subsequently, the search was restricted to pregnant women with COVID-19.

Appendix B. Detailed articles excluded because of duplicate cases

- Articles from China

Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Nan Yu of Tongji Hospital has three publications [51-53] with similar period of recruitment and probably some cases are the same. Furthermore, these cases are included in the report of Yan J et al. [22] Wang S et al. [50] reported a case of neonate infected with COVID-19, but this case has the same characteristics than reported by Nan Yu in two articles [51, 52]. Liu Wei et al. [54] and Liu W et al. [49] articles were excluded because probably the cases are the same of previous report in Tongji Hospital.[52]

Renmin Hospital of Wuhan University

Chen R et al.,[55] Fan et al.[57] and the two articles of Khan Suliman et al.[56, 58] were excluded because these cases probably overlap each other. They have similar period of recruitment and we consider that probably most of them are included in the report of Yan J et al.[22]

Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology, Wuhan

Chen Siyu et al.,[59] Yang H et al.[60] and Wu C et al.[61] have the same time period of recruitment and probably these cases are the same and they are included in the series of Yan J et al.[22]

Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

The patients reported by Chen S et al. [62] and Chen Y et al.[63] probably there were included in the article of Liu D et al.[64] and these cases are included in the series of Yan J et al.[22]

Zhongnan Hospital of Wuhan University

Chen H et al.[65] and Yang P et al.[66] probably have the same cases and we excluded them because of Yan J et al.[22] published a larger series including the same cases.

The First Affiliated Hospital, College of Medicine, Zhejiang University

Huang J-w et al.,[67], Li Y et al.[68] and Kang et al.[69] were excluded since they reported the same case. This case was published in the case series of Chen X et al.[23] that was included in our systematic review.

Central Hospital of Wuhan, Tongji Medical College

Wu X et al.[70] has the same period and probably these cases are included in the series of Yan J et al.[22]

Wuhan Red Cross Hospital

Xia et al.[71] was excluded because the case was included in Yan J et al.[22]

Multicenter

Liu Y et al.[73] and Zhu et al.[74] was excluded because Yan J et al.[22] published a larger series including the same cases. Chen L et al.[72] reported 118 patients of all 50 designated hospitals in Wuhan city and probably these cases overlap with as those reported by Yan J et al.[22]. We excluded Chen L et al.[72] because the data published by Yan J et al.[22] provides with more detailed description.

- Articles from USA

New York–Presbyterian Allen Hospital and Columbia University Irving Medical Center

Breslin et al.[75] was excluded because these 7 cases were included in the expanded series of 43 cases of Breslin et al.[17] Sutton et al.[76] was excluded because some of their cases were reported probably by Breslin et al.[17]

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