Perinatal outcomes and vertical transmission by SARS-CoV2 infection (COVID-19) during pregnancy: systematic review and meta-analysis.

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Abstract

Background: COVID-19 is a new pandemic disease with severe respiratory outcome. However, there is little evidence of this condition during pregnancy based on small case series reports. Objective: to perform a systematic review and meta-analysis of proportions of case series focused on maternal and perinatal outcomes of COVID-19 during pregnancy. Search strategy: LILACS and Medline were searched from inception until April 24th, 2020. Selection criteria: all case series or case control studies involving SARS-CoV2 infection during pregnancy and neonatal period were identified. Excluded were duplicated data, case reports of individual patients or without clinical data. Data collection and analysis: a total of 14 studies were included. When possible, pooled proportions with 95% confidence interval through a random effect model were estimated. Heterogeneity was estimated with the use of I2 statistics and Tau2 test. Main results: Most common symptoms were fever (58%; I2= 69%) and cough (33%; I2= 65%). A pathognomonic CT-Scan was observed in 92% of patients (I2= 0%). Lymphopenia and increased D-dimer were observed in 50% (I2= 82%), and 80% (I2= 0%) of patients at admission, respectively. There were no maternal deaths, with 2 cases of neonatal death, both with negative SARS-CoV2 PCR. Vertical transmission was observed in 5 neonates. Conclusions: This systematic review and meta-analysis confirms that COVID-19 during pregnancy is associated with good maternal and perinatal outcome. Evidence of vertical transmission should be confirmed with larger cohorts. Funding: none. Key words: meta-analysis, COVID-19, vertical transmission, perinatal outcome, pregnancy.

Introduction

Coronaviruses are single-strain RNA viruses, that belongs to*Coronaviridae* family. Within this group, some could affect only animals and others could also affect humans. Human infection could induce respiratory and gastrointestinal symptoms, in a wide range from a self-limited cold until severe lower tract respiratory compromise such as severe acute respiratory syndrome (SARS-CoV1) or the Middle East respiratory syndrome (MERS)[1]. Both, SARS-CoV1 and MERS have been reported to compromise pregnant patients, with adverse perinatal outcomes such as preterm delivery, pre-eclampsia, miscarriage, stillbirth or neonatal evidence of vertical transmission[2].

The novel coronavirus 2019 disease (COVID-19) is caused by a new coronavirus (SARS-CoV2) and has evolved into a worldwide sanitary emergency[3,4], first described in Wuhan, China on December 2019 [5]. It is characterized by a fast infection rate and a short incubation period[6]. Moreover, it has a great affinity with lower respiratory tracts. In cases of COVID-19 pneumonia, SARS has been observed in 17 – 29% of cases, with intensive care unit admission in 23 – 32%[7–9]. Mortality rate increases with patient´s age, mainly in adults above 70 years-old[10].

There is a lack of knowledge on the impact of COVID-19 in pregnancy, not only for the mother, but also for the fetus and newborn. Until now, there is increasing evidence of case reports and case series, mostly in China, regarding this disease concomitant with gestation[4].

Therefore, the aim of this article was to perform a systematic review and meta-analysis of case series and case controls focused on maternal and perinatal outcomes of COVID-19 during pregnancy.

Methods

Search Strategy and Selection Criteria

This systematic review was performed according to recommendations of Henderson *et al* and following PRISMA guidelines[11,12]. A literature search was performed in MEDLINE and LILACS since inception until April 24th, 2020. No language or study design restriction was applied at first phase. Key words used were: "COVID 19" OR "*coronavirus* " OR "*SARS-CoV2* " AND "*pregnancy* " OR "*perinatal outcome* " OR "*vertical transmission* " OR "*gestation* ". No gray literature was considered (conference abstracts, published theses, government/social media data or non-indexed journal papers).

On a second phase, all titles and abstracts were revised, excluding reviews, individual case reports, guidelines, consensus, letters and editorials. For final review, only case series or case-control studies of symptomatic pregnant patients with nasopharyngeal PCR-confirmed or clinical diagnosis of COVID-19 based on CT-scan with epidemiological risk factors were included. Additionally, a manual search was performed in accepted online articles of indexed journals for identification of new data.

Study design

From selected studies, the following data was obtained: maternal age, gestational age at diagnosis and delivery, symptoms at diagnosis or during follow-up, laboratory findings, pregnancy diseases, mode of delivery, neonatal outcome, maternal and perinatal survival, evidence of vertical transmission and evidence of SARS-CoV2 in breast milk. All results were stored in a dedicated database for future analysis. Given the emergency-need for this meta-analysis, PROSPERO registration of study protocol was not performed.

Assessment of bias

Quality assessment of selected studies was performed by two authors (A.S-M. y S.L.) with a dedicated scale proposed by Munn Z, *et al* [13] designed for case series reports. This scale considers 10 questions divided in two domains. In case of discordance between both reviewers, a third reviewer (N.R.) performed the final analysis.

Statistical analysis

Dichotomic variables were expressed as rates and percentages, continuous variables were expressed as median (range). For this study, we performed a meta-analysis of proportions using a random effect model with Mantel-Haenszel method to provide a pooled proportion of dichotomic variables. Heterogeneity was assessed with I^2statistics and Tau^2 test. All statistical analyses and forest plots were performed with Stata® 16.1 (Statacorp, College Station USA). Funnel plots for publication bias were performed in outcomes with more than 10 reporting studies and asymmetry of funnel plots was assessed with Egger´s test.

Results

Characteristics of included studies in systematic review

Of 24 studies related with pregnancies affected by COVID-19 and assessment of vertical transmission, 14 fulfilled selection criteria and were included in the systematic review[14,15,24–27,16–23] (Figure 1). All except one were carried out in China, with one report from United States of America (New York) (Table S1). There was one case control study[22] and 13 case series, ranging from 3 to 116 patients, with a pooled sample size of 292 pregnancies. The study of Yan J, *et al* contributed with 40% (116/292) of the pooled sample size.

Bias assessment

All studies presented low risk of bias regarding reporting of outcomes and selection criteria. Only a 14% (2 studies) established a clear reporting of the site demographic. A 43% of studies did not show a clear definition of inclusion of all COVID pregnancies during the study period. Importantly, an 86% of studies (13 of 14) used valid methods for identification of SARS-CoV2 infection, with a standard measurement (Table S2). Publication bias assessment was performed for fever and cough. Both symptoms showed symmetric funnel plots with low publication bias (p values of 0·12 and 0·75 for fever and cough, respectively, Figure 2)

Clinical and biochemical characteristics at diagnosis or follow-up

The median (range) maternal age at diagnosis was 30 (22 – 41) years-old, with a gestational age of 38+2 (5+0 – 41+2) weeks. Most common symptoms described were fever (58%; I^2= 69%, Figure 3) and cough (33%; I^2= 65%, Figure S1), followed by dyspnea (10%; I^2= 5%), myalgia (8%; I^2= 82%), dysphagia (4%; I^2= 0%), and abdominal pain (2%; I^2= 0%) (Table 1).

A pathognomonic CT-Scan (patchy lesions in one or both lungs) was observed in 242/263 (92%; I^2= 0%, Figure S2) of patients. In one study, no description of CT-Scan was identified. In descending order, the reported biochemical results were: lymphopenia (50%; I^2= 82%; 9 studies, Figure 4), increased C-reactive protein (CRP) (55%; I^2= 64%; 9 studies), leukocytosis (13%; I^2= 89%; 8 studies), altered liver function (16%; I^2=0%; 6 studies), increased D-dimer (80%; I^2= 0%; 5 studies) and presence of hypoalbuminemia (63%; 2 studies). There were nine severe pneumonia cases, but only three required mechanic ventilation (Table 2).

Perinatal outcome and vertical transmission

Perinatal and neonatal outcomes are described in Table 3. There were 13/227 (6%; I^2= 30%) patients with gestational hypertension (7 pre-eclampsia and 6 non-specified gestational hypertension). No cases of maternal death were described. An 86% (251/292) of patients delivered during the study period, with a median gestational age of 38+0 (22+0 – 41+5) weeks. Of these, 176/220 (80%; I^2= 62%) delivered by a C-section, however, in 31 patients no delivery mode was described. A twin pregnancy was delivered vaginally[18]. A spontaneous miscarriage of 5+2 weeks was described in one case[25]. Of 252 newborns, 2 perinatal deaths were identified. One case was delivered at 34+5 weeks and developed a multiple organ failure with disseminated intravascular coagulation. He died at 9 days of life[18]. The other neonatal death was delivered at 35+2 weeks by emergency C-section due to maternal septic shock with mechanic ventilation. He died at 2 hours after birth due to a severe asphyxia[25]. Both cases had negative SARS-CoV2 test. Vertical transmission was analyzed in 12 studies. In 5 newborns (2%; I^2= 0%) a positive nasopharyngeal SARS-CoV2 test was identified. All neonatal tests were performed with nasopharyngeal PCR, with no description of cord-blood test. Only 22 patients analyzed the presence of SARS-CoV2 in breast milk, with no identified case.

Discussion

Main findings

Our meta-analysis demonstrated that COVID-19 during pregnancy is associated with good maternal and perinatal outcome. The main symptoms are fever and cough and the main laboratory findings are an increased D-dimer, lymphopenia and increased CRP. Pathognomonic thorax CT-scan is seen in more than 90% of patients, including patients with a negative PCR result. Vertical transmission appears to be low, but it is based only in neonatal nasopharyngeal PCR and not in serum immunoglobulin levels.

Interpretation

Despite that in recent publications there are two systematic reviews (one of those with a meta-analysis), our article has the larger sample size until now. The first systematic review of Di Mascio D[2], *et al* included 41 pregnancies with COVID-19 in six studies. They presented a 41% of preterm delivery and 7% of perinatal death but without evidence of vertical transmission. Regarding symptoms at diagnosis, the most common were fever (82%), cough (57%) and dyspnea (27%). However, this analysis included 38 pregnancies with other coronaviruses (MERS and SARS). In combined coronavirus during pregnancy, 91% presented a viral pneumonia and almost 80% developed lymphopenia.

Another systematic review that included 108 pregnancies with confirmed COVID-19 demonstrated that fever (68%), cough (34%), elevated CRP (70%) and lymphopenia (59%) were the most common symptoms and laboratory findings[28]. Our results are in line with these studies, were fever and cough were the most frequent symptoms at diagnosis.

In our systematic review there was no cases of maternal death. However, a recent individual case report of Karami P[29] *et al* from Iran, described a pregnant patient with 30+3 weeks of gestation presenting with fever, myalgia and cough. An altered chest CT-scan with no typical viral pneumonia was followed with a fast-pulmonary deterioration that required a C-section. The newborn presented an Apgar score of 0 and did not survive to reanimation maneuvers. The mother also died due to a multi-organ failure. Autopsy revealed presence of SARS-CoV2 in lung tissue. To our knowledge, this is the first case of maternal death for COVID-19 in published articles.

Even more, recent evidence from non-pregnant severe COVID-19 patients have demonstrated that this condition is associated with a higher risk of thrombosis and pulmonary thromboembolism, with embolic events even in patients with full anticoagulant therapy[30,31]. Based on these results, Zhang L, *et al* proposed that a D-dimer at admission in COVID-19 patients > 2.0μg/mL could be a good predictor of in-hospital mortality[32]. Interestingly, severe COVID-19 cases with high levels of D-dimer or high sepsis score, mortality was reduced with association of low molecular weight heparin[33]. Therefore, our results, with 80% of patients with a high D-dimer at admission (although described in less than 50% of included studies) are in line with these results and should be considered a relevant parameter to determine in affected pregnancies until more evidence arises.

The results of the current study could be used for the clinical management of pregnancies with a suspected diagnosis of COVID-19. Firstly, the pooled proportion of maternal symptoms demonstrated that despite fever and cough are the most common clinical presentation at diagnosis, this is observed just in 58% and 33%. Therefore, several patients could be oligosymptomatic or asymptomatic. The proposal of universal screening for every patient in labor or with a planned delivery could be an optimal management to detect this group[19]. Secondly, our laboratory findings demonstrated that D-dimer determination should be part of the study of every suspected or confirmed COVID-19 pregnancy, due to the high proportion of pregnant patients with altered values, and the new evidence that demonstrate the association of COVID-19 with thromboembolic disease. However, it is important to consider that pregnancy is a condition per-se associated with higher D-dimer values. Therefore, thromboprophylaxis and the use of reference values adjusted by gestational age is recommended[34]. Finally, our results demonstrated that more than 90% of patients showed a typical pattern of radiologic affection at chest CT-scan. Therefore, despite the recommendation to avoid radiologic tests during pregnancy, in cases of highly suspected or confirmed COVID-19 in pregnancy, CT-scan should always be part of management.

Strengths and limitations

The main strength of this systematic review is the large sample size, including almost 300 patients. To our knowledge, this is the larger meta-analysis of COVID-19 during pregnancy until now. However, it is not without weaknesses. The main weakness is the nature of included studies. All except one, were non-controlled studies, which is associated with higher risks of bias. However, we used a validated bias assessment tool for this type of studies, and within cases series, selected studies were moderate or low risk of bias in most of domains. We also excluded individual case reports to improve quality selection. Another weakness is related to underreported data of laboratory findings in several studies, that could necessarily affect our results. Finally, regarding vertical transmission, it is important to reinforce that none of selected studies performed PCR cord blood test or serum immunoglobulin determination and ruled-out vertical transmission only based on nasopharyngeal samples. This is important, because nasopharyngeal PCR is associated with 30% of false negative results, especially when viral count is low. Therefore, vertical transmission should be based on blood detection of SARS-CoV2, to confirm a placental viral passage. Moreover, a recent classification system proposed for maternal and neonatal SARS-CoV2 infection established that a confirmed neonatal infection in a live newborn should be based on a positive PCR in cord blood, neonatal blood collected the first 12-

hours of life or in amniotic fluid sample obtained before rupture of membranes. Diagnosis based only in nasopharyngeal swab should only be considered as a probable diagnosis[35]. This strategy was demonstrated on a case report recently published in JAMA. Despite a negative nasopharyngeal PCR test in a newborn of a COVID-19(+) mother, cord blood immunoglobulin titers were elevated at birth and in a two weeks follow-up[36], reflecting vertical transmission.

Conclusion

In conclusion, our meta-analysis confirms that COVID-19 during pregnancy is associated mostly with fever, cough, lymphopenia, an altered D-dimer and with a typical radiologic pattern in one or both lungs in a large proportion of patients. Furthermore, our results confirm that COVID-19 is associated with a good maternal and neonatal outcome, but current evidence is inconsistent to determine the truly risk of vertical transmission.

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None.

Author´s contribution

A.S-M. wrote the draft, performed literature review, assessment of bias and all statistical analyses. S.L. co-wrote the article and performed assessment of bias. N.R. performed assessment of bias and approved the final document, MC.S. review and approved the final version of the study. H.M. and M.P-C. designed the study, made statistical critics and approved the final version of the study.

Ethics statement

Due to the nature of the study, no ethical approval from local Ethics Committee was required.

Funding

None.

Declaration of interests

None.

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Tables

Table 1. Maternal characteristics and symptoms after diagnosis of COVID-19.

Reference	**Maternal age (years)**	**GA at diagnosis (weeks)**	**Fever n/N (%)**	**Dyspnea n/N (%)**	**Cough n/N (%)**	**Myalgia n/N (%)**	**Dysphagia n/N (%)**	**Abdon pain n/ (%)**
Yu N, *et al.* Lancet Infect Dis 2020[14]	33 (29 – 34)	38+5 (37+0 – 41+2)	6/7 (86)	1/7 (14)	1/7 (14)	0/7 (0)	0/7 (0)	4/7 (57

Reference	Maternal age (years)	GA at diagnosis (weeks)	Fever n/N (%)	Dyspnea n/N (%)	Cough n/N (%)	Myalgia n/N (%)	Dysphagia n/N (%)	Abdon pain n/ (%)
Chen S, *et al.* J Med Virol 2020[15]	29 (25 – 31)	39+1 (38+6 – 40+3)	5/5 (100)	0/5 (0)	1/5 (20)	0/5 (0)	1/5 (20)	0/5 (0)
Liu H, *et al.* J Infect 2020[20]	30 (22 – 42)	22+0 – 40+5	16/41 (39)	5/41 (12)	15/41 (37)	0/41 (0)	0/41 (0)	0/41 (0
Liu D, K *et al.* Am J Roentgenol 2020[21]	32 (23 – 40)	32+0 (12+0 – 38+0)	13/15 (87)	1/15 (7)	9/15 (60)	3/15 (20)	1/15 (7)	0/15 (0
Zhu H, *et al.* Transl Pediatr 2020[22]	30 (25 – 35)	NR	8/9 (89)	0/9 (0)	4/9 (44)	0/9 (0)	1/9 (11)	0/9 (0)
Breslin N, et al. AJOG MFM 2020[23]	29 (20 – 39)	37+0 [32+4 – 38+6]	14/29 (48)	7/29 (24)	19/29 (66)	11/29 (38)	0/29 (0)	0/29 (0
Chen Y, et al. Front Pediatr 2020[24]	29.5 (23 – 34)	NR	3/4 (75)	2/4 (50)	2/4 (50)	2/4 (50)	0/4 (0)	0/4 (0)
Khan S, et al. Infect Control Hosp Epi-demiol 2020[25]	28 (33 – 27)	38+2 (34+6 – 39+1)	2/3 (67)	1/3 (33)	3/3 (100)	0/3 (0)	0/3 (0)	0/3 (0)
Li N, et al. Clin Infect Dis 2020[26]	31 (26 – 37)	33+6 – 40+4	12/16 (75)	0/16 (0)	0/16 (0)	0/16 (0)	0/16 (0)	0/16 (0
Liu W, et al. Front Med 2020[27]	31 (26 – 38)	38+4 (35+2 – 41+2)	11/19 (58)	0/19 (0)	5/19 (26)	0/19 (0)	0/19 (0)	0/19 (0

Reference	Maternal age (years)	GA at diagnosis (weeks)	Fever n/N (%)	Dyspnea n/N (%)	Cough n/N (%)	Myalgia n/N (%)	Dysphagia n/N (%)	Abdon pain n/ (%)
Wu C, et al. Virol Sin 2020[16]	30 (26 – 35)	38+4 (33+6 – 40+4)	4/8 (50)	0/8 (0)	0/8 (0)	0/8 (0)	0/8 (0)	0/8 (0)
Yan J, et al. Am J Obstet Gynecol 2020[17]	31 (24 – 41)	38+0 (5+0 – 41+2)	59/116 (51)	12/116 (10)	33/116 (28)	6/116 (5)	10/116 (9)	0/116 (0)
Yang H, et al. J Infect 2020[18]	30.2 ± 2.3	NR	10/13 (77)	0/13 (0)	2/13 (15)	0/13 (0)	0/13 (0)	0/13 (0
Yang P, et al. J Clin Virol 2020[19]	NR	NR	5/7 (71)	0/7 (0)	1/7 (14)	0/7 (0)	0/7 (0)	1/7 (14
Total, n/N (%) or median (range)	**30 (22 – 41)**	**38+2 (5+0 – 41+2)**	**168/292 (58)**	**29/292 (10)**	**95/292 (33)**	**22/292 (8)**	**13/292 (4)**	**5/292 (2)**
N° studies in meta-analysis			**13**	**7**	**11**	**4**	**4**	**2**
Pooled proportion (REM)			**0.66**	**0.12**	**0.34**	**0.23**	**0.09**	**0.29**
Pooled 95 % CI			**0.55 – 0.77**	**0.07 – 0.17**	**0.23 – 0.44**	**0.03 – 0.44**	**0.04 – 0.13**	**0.07 – 0.50**
I^2 heterogeneity			**69%**	**5%**	**65%**	**82%**	**0%**	**0%**

Continuous variables expressed as median (range) or median [IQR].

GA= Gestational age; NR= not reported; NA= not applied; REM= random effect model; CI= confidence interval.

Table 2. Laboratory and CT-scan results of pregnant patients with COVID-19.

Reference	Mechanic ventila-tion %	Lymphopenia %	Leukocytosis %	High CRP %	Altered Liver Function %	Increased D-Dimer %	Hypo albumine-mia %	Altere CT-Sc %
Yu N, *et al.* Lancet Infect Dis 2020[14]	0/7 (0)	5/7 (71)	0/7 (0)	7/7 (100)	2/7 (29)	7/7 (100)	5/7 (71)	7/7 (100)
Chen S, *et al.* J Med Virol 2020[15]	0/5 (0)	4/5 (80)	3/5 (60)	4/4 (100)	0/5 (0)	3/3 (100)	5/5 (100)	5/5 (100)
Liu H, *et al.* J Infect 2020[20]	0/41 (0)	25/41 (61)	17/41 (42)	27/41 (66)	NR	NR	NR	38/41 (93)
Liu D, K *et al.* Am J Roentgenol 2020[21]	0/15 (0)	12/15 (80)	NR	10/15 (67)	NR	NR	NR	15/15 (100)
Zhu H, *et al.* Transl Pediatr 2020[22]	0/9 (0)	NR	NR	NR	NR	NR	NR	9/9 (100)
Breslin N, et al. AJOG MFM 2020[23]	0/29 (0)	NR	NR	NR	NR	NR	NR	NR
Chen Y, et al. Front Pediatr 2020[24]	1/4 (25)	2/4 (50)	0/4 (0)	4/4 (100)	0/4 (0)	4/4 (100)	0/4 (0)	4/4 (100)
Khan S, et al. Infect Control Hosp Epi-demiol 2020[25]	0/3 (0)	0/3 (0)	2/3 (67)	2/3 (67)	0/3 (0)	NR	NR	2/3 (67

Reference	Mechanic ventila-tion %	Lymphopenia %	Leukocytosis %	High CRP %	Altered Liver Function %	Increased D-Dimer %	Hypo albumine-mia %	Altere CT-Sc %
Li N, et al. Clin Infect Dis 2020[26]	0/16 (0)	2/16 (13)	0/16 (0)	5/16 (31)	0/16 (0)	NR	NR	15/16 (94)
Liu W, et al. Front Med 2020[27]	0/19 (0)	NR	NR	NR	NR	NR	NR	19/19 (100)
Wu C, et al. Virol Sin 2020[16]	0/8 (0)	6/8 (75)	1/8 (13)	8/8 (100)	NR	4/8 (50)	NR	6/8 (75
Yan J, et al. Am J Obstet Gynecol 2020[17]	2/116 (2)	51/116 (44)	3/116 (3)	51/116 (44)	5/8 (63)	6/8 (75)	NR	104/116 (90)
Yang H, et al. J Infect 2020[18]	0/13 (0)	NR	NR	NR	NR	NR	NR	12/13 (92)
Yang P, et al. J Clin Virol 2020[19]	0/7 (0)	NR	NR	NR	NR	NR	NR	6/7 (86
Total, *n/N (%)*	**3/292 (1)**	**107/215 (50)**	**26/200 (13)**	**118/214 (55)**	**7/43 (16)**	**24/30 (80)**	**10/16 (63)**	**242/26 (92)**
N° studies in meta-analysis	**2**	**8**	**5**	**5**	**2**	**2**	**-**	**7**
Pooled pro-portion (REM)	**0.02**	**0.57**	**0.31**	**0.53**	**0.45**	**0.64**	**NA**	**0.91**
Pooled 95% CI	**-0.01 – 0.04**	**0.40 – 0.75**	**0.05 – 0.56**	**0.38 – 0.67**	**0.22 – 0.69**	**0.42 – 0.87**	**NA**	**0.87 – 0.95**

Reference	Mechanic ventila-tion %	Lymphopenia %	Leukocytosis %	High CRP %	Altered Liver Function %	Increased D-Dimer %	Hypo albumine-mia %	Altere CT-Sc %
I^2 hetero-geneity	**0%**	**82%**	**89%**	**64%**	**0%**	**0%**	**NA**	**0%**

CRP= C-reactive protein; NR= not reported; REM= random effect model; CI= Confidence Interval.

Table 3. Perinatal and neonatal characteristics of pregnancies with COVID-19.

Reference	C-section %	GA at birth (Weeks)	Preeclampsia %	Maternal death %	Perinatal death %	5´APGAR <7 %	Vertical transmis-sion %	SARS-CoV2 breast milk %
Yu N, *et al.* Lancet Infect Dis 2020[14]	7/7 (100)	39+2 (37+0 – 41+5)	0/7 (0)	0/7 (0)	0/7 (0)	0/7 (0)	1/3 (33)*	NR
Chen S, *et al.* J Med Virol 2020[15]	2/5 (40)	39+1 (38+6 – 40+4)	1/5 (20)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	NR
Liu H, *et al.* J Infect 2020[20]	NR	NR	3/41(7)$^{+}$	0/41 (0)	0/41 (0)	NR	4/41 (10)	NR
Liu D, K *et al.* Am J Roentgenol 2020[21]	10/11 (91)	NR	0/11 (0)	0/11 (0)	0/11 (0)	0/11 (0)	NR	NR
Zhu H, *et al.* Transl Pediatr 2020[22]	7/10 (70)**	34+5 (31+0 – 39+0)	0/9 (0)	0/9 (0)	1/10 (10)**	0/10 (0)	0/10 (0)	NR
Breslin N et al. AJOG MFM 2020[23]	8/18 (44)	NR	NR	0/29 (0)	0/18 (0)	0/18 (0)	0/18 (0)	NR

Reference	C-section %	GA at birth (Weeks)	Preeclampsia %	Maternal death %	Perinatal death %	5´APGAR <7 %	Vertical transmission %	SARS-CoV2 breast milk %
Chen Y, et al. Front Pediatr 2020[24]	3/4 (75)	38+0 (37+2 – 39+0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/3 (0)	NR
Khan S, et al. Infect Control Hosp Epidemiol 2020[25]	0/3 (0)	37+2 (22+0 – 41+2)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	NR
Li N, et al. Clin Infect Dis 2020[26]	14/16 (88)	38 ± 0.2	3/16 (19)$^{+}$	0/16 (0)	0/16 (0)	0/16 (0)	0/16 (0)	NR
Liu W, et al. Front Med 2020[27]	18/19 (95)	38.6 ± 1.5	NR	0/19 (0)	0/19 (0)	0/19 (0)	0/19 (0)	0/10 (0
Wu C, et al. Virol Sin 2020[16]	6/8 (75)	NR	0/8 (0)	0/8 (0)	NR	NR	NR	NR
Yan J, et al. Am J Obstet Gynecol 2020[17]	85/99 (86)	38+3 (28+1 – 41+2)	4/116 (3)	0/116 (0)	1/99 (1)	1/99 (1)	0/86 (0)	0/12 (0
Yang H, et al. J Infect 2020[18]	9/13 (69)	38.2 ± 2.3	NR	0/13 (0)	0/13 (0)	NR	0/13 (0)	NR
Yang P, et al. J Clin Virol 2020[19]	7/7 (100)	36+3 (36+0 – 38+2)	2/7 (29)	0/7 (0)	0/7 (0)	0/7 (0)	0/6 (0)	NR

Reference	C-section %	GA at birth (Weeks)	Preeclampsia %	Maternal death %	Perinatal death %	5´APGAR <7 %	Vertical transmission %	SARS-CoV2 breast milk %
Total, *n/N (%) or median (range)*	**176/220 (80)**	**38+0 (22+0 – 41+5)**	**13/227 (6)**	**0/292 (0)**	**2/252 (1)**	**1/198 (1)**	**5/223 (2)**	**0/22 (0)**
N° studies in meta-analysis	**10**		**5**	**-**	**2**	**-**	**2**	**-**
Pooled proportion REM	**0.79**		**0.07**	**NA**	**0.01**	**NA**	**0.10**	**NA**
Pooled 95% CI	**0.69 – 0.88**		**0.01 – 0.13**	**NA**	**-0.01 – 0.03**	**NA**	**0.02 – 0.19**	**NA**
I^2 heterogeneity	**62%**		**30%**	**NA**	**0%**	**NA**	**0%**	**NA**

*Of 7 neonates, SARS-CoV2 nasopharyngeal test was not performed in 4 cases that were asymptomatic. +Patients with hypertensive disease of pregnancy, no specification if preeclampsia or non-proteinuric hypertension. **One pair of twins with vaginal delivery.

GA= gestational age; NR= not reported; CI= confidence interval; REM= random effect model.

Figure legends.

Figure 1. PRISMA flowchart.

*Literature not related with SARS-CoV2 infection

Figure 2. Funnel plots for publication bias of fever and cough in pregnancies with COVID-19.

Publication bias assessment for fever (left) and cough (right) in affected pregnancies. Both plots showed a symmetrical distribution. Egger´s test was non-significant for both symptoms.

Figure 3. Forest plot for fever in COVID-19 affected pregnancies.

Analysis by random effect model.

Figure 4. Forest plot for lymphopenia in COVID-19 affected pregnancies.

Analysis by random effect model.