



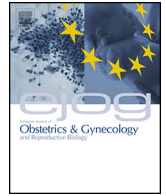
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## Review article

## Maternal and perinatal outcomes in pregnant women infected by SARS-CoV-2: A meta-analysis

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## ABSTRACT

Evidence concerning coronavirus disease-19 (covid-19) in pregnancy is still scarce and scattered. This meta-analysis aims to evaluate maternal and neonatal outcomes in covid-19 pregnancies and identify factors associated with perinatal viral transmission. Medline, Scopus, CENTRAL, Web of Science and Google Scholar databases were systematically searched to 3 June 2020. Overall, 16 observational studies and 44 case reports/series were included. Fever was the most frequent maternal symptom, followed by cough and shortness of breath, while about 15 % of infected were asymptomatic. Severe disease was estimated to occur in 11 % of women in case reports/series and in 7 % (95 % CI: 4 %–10 %) in observational studies. Two maternal deaths were reported. The rate of neonatal transmission did not differ between women with and without severe disease (OR: 1.94, 95 % CI: 0.50–7.60). Preterm birth occurred in 29.7 % and 16 % (95 % CI: 11 %–21 %) in data obtained from case series and observational studies, respectively. Stillbirth occurred in 3 cases and 2 neonatal deaths were observed. Vertical transmission was suspected in 4 cases. Fever was the most common neonatal symptom (40 %), followed by shortness of breath (28 %) and vomiting (24 %), while 20 % of neonates were totally asymptomatic. In conclusion, the maternal and neonatal clinical course the infection is typically mild, presenting low mortality rates. The risk of vertical transmission is suggested to be low and may not be affected by the severity of maternal disease. Further large-scale studies are needed to clarify the risk factors associated with viral transmission and severe infection in the neonatal population.

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## Introduction

COVID-19 (coronavirus disease 2019) is an emerging infectious disease, first reported in Wuhan, Hubei region, Canhina, in December 2019 [1]. It is caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) which is a single-stranded RNA virus, subgenus Sarbecovirus of the genus Betacoronavirus, probably originated from bats [2]. COVID-19 rapidly triggered a global health emergency alert and spread to numerous countries, causing the WHO to announce the start of a new pandemic on 12 March 2020 [3,99]. According to the 24th April 2020 WHO bulletin, 2626321 confirmed cases and 181938 deaths have occurred globally so far [4].

Data concerning pregnant women and neonates is still scarce and scattered and evidence regarding management of pregnancy, delivery and neonates in case of suspected or confirmed COVID-19 diagnosis in either the mother or the offspring remains fragmented [5,6]. To date, the incidence of COVID-19 intended as a positive nasopharyngeal swab for SARS-CoV-2 in newborn babies is roughly 1.5 % [7] and neonatal symptoms, such as mild respiratory distress and transient thrombocytopenia, seems mainly related to late prematurity or elective C-sections due to severe maternal conditions, rather than to the neonatal infection itself [8]. Although horizontal transmission seems predominant not only in adulthood but also in infancy and childhood, the shortage of data regarding pregnancies impede to draw conclusions about vertical transmission, which seems rare but still possible [9]. The new challenge for obstetricians and neonatologists during the SARS-CoV-2 pandemic is to find a balance between implementing special measures to ensure the safety of both patients and healthcare providers and encouraging bonding and interaction between the newborn and the mother. Moreover, some questions are still to be addressed, such as the effects of SARS-CoV-2 infection during the first trimester of pregnancy or the causes underlying the apparent lower incidence and severity of COVID-19 in neonates born to affected mothers.

The purpose of the present study is to systematically accumulate current literature knowledge in the field and evaluate maternal and perinatal outcomes among pregnant women infected by SARS-CoV-2. In this line, this meta-analysis aims to shed light on the transmission pattern of the virus to neonates, as well as to clarify the disease course of COVID-19 infection in this specific population.

## Materials and methods

### Study design

This meta-analysis was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) guidelines [10]. The process of study selection was performed in 3 consecutive stages. The titles or abstracts of all electronic articles were initially screened to evaluate their potential eligibility and subsequently, all articles that were presumed to meet the pre-defined eligibility criteria were retrieved as full-texts papers. At the final stage, all studies that were in accordance with the inclusion criteria and did not meet any of the exclusion criteria were included in the present review. Study selection, data collection, quality assessment and data analysis were planned to be independently conducted by two researchers (IB and AP), while any potential discrepancies were resolved by the consensus of all authors.

### Eligibility criteria

Both observational studies and case reports or case series were included in the present meta-analysis. Studies were deemed eligible if they reported clinical outcomes of neonates born to mothers infected by SARS-CoV-2, as well as of infected neonates independently of maternal infection status. When the same cases were suspected to be both included in case reports and an observational study, the latter one was only included in the analysis. Deduplication of studies was performed by two researchers (IB and AP) and any disagreements were resolved through their consensus. On the other hand, studies not reporting any perinatal outcomes of infected pregnant women and those examining exclusively infants after 28 days of life were excluded from the present study. Moreover, review articles, conference proceedings/abstracts, animal and *in vitro* studies, as well as unpublished data from clinical registries were not included.

### Literature search

The literature search was conducted using the Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science databases. Google Scholar database and the full-list of all the included studies ("snowball" method<sup>11</sup>), were also screened to identify potential additional papers. Search was performed from inception to 3 June 2020 and was based on the following algorithm: "(("Coronavirus"[Mesh] OR "COVID-19" [Supplementary Concept] OR "SARS Virus"[Mesh] OR sars-cov OR covid OR novel coronavirus) AND ("Pregnancy"[Mesh] OR "Infant, Newborn"[Mesh] OR pregnan\* OR neonat\* OR infant\* OR newborn). No language restrictions were applied during literature search.

### Data extraction

The following data were planned to be extracted from each of the included studies: name of first author, country, maternal age,

medical history (diabetes mellitus, hypothyroidism or polycystic ovary syndrome), symptoms (fever, cough, shortness of breath, diarrhea, nausea/vomiting, myalgia, fatigue, headache, sore throat, nasal congestion, abdominal pain, chest pain), radiological signs, presence of co-infection (bacterial or influenza), laboratory tests (lymphopenia, thrombocytopenia, increased C-reactive protein, procalcitonin, ferritin, liver function tests and D-dimers), type of treatment, pregnancy outcomes (fetal distress, premature rupture of membranes-PROG, placenta previa, preeclampsia, preterm birth, cesarean section, stillbirth), maternal outcomes (admission to intensive care unit-ICU or death), neonatal outcomes (gender, gestational age, birthweight, 1-minute/5-minute Apgar score, horizontal/vertical transmission, admission to ICU, mechanical ventilation, sepsis and death).

**Quality assessment**

Observational studies of incidence data were evaluated by taking into account the following parameters: sample frame, representativeness and size, subjects and setting, coverage bias, classification bias, outcome measurement, statistical analysis and response rate [11]. The quality of case reports and case series was assessed by judging the potential risk of bias concerning the domains of selection, ascertainment, causality and reporting [12]. For each domain, “Major concerns”, “Some concerns” or “No concerns” of bias risk were assigned independently by two researchers, while any disagreements were resolved by discussion with all authors.

**Data analysis**

The pooled analysis was separately performed for case reports/series which provided individual participant data and

observational studies reporting aggregate data. Regarding the analysis of case reports/series, descriptive statistics were calculated and cases were categorized depending on the transmission of SARS-CoV-2 in neonates. Subsequently, maternal characteristics and perinatal outcomes were compared between the two groups. Continuous variables were expressed as median and interquartile range, while the Mann-Whitney *U* test was implemented to test differences in medians [13]. The comparison of categorical variables was performed using the chi-squared or the Fisher's exact test [14]. Multivariate logistic regression analysis was performed to assess the relative importance of maternal factors (country, age, comorbidities, symptoms and pregnancy complications) in the prediction of perinatal transmission. Statistical significance was defined as *p-value* <0.05. Missing data were treated by pair-wise deletion [15].

Pooling of observational studies was performed by proportion meta-analysis using a random-effects (*DerSimonian-Laird*) model [16]. Confidence intervals (CI) were set at 95 %. Inter-study heterogeneity was quantified by calculating the inconsistency index (*I*<sup>2</sup>), with values >50 % denoting significant heterogeneity [17]. Publication bias was assessed by the visual inspection of funnel plots and the potential presence of asymmetry was evaluated by the Egger's regression test [18]. The cut-off of *p-value* <0.10 was used to define the significance of Egger's regression test. In case of small-study effects suspicion, the trim-fill method was implemented to provide new estimates accounting for statistically imputed missing studies [19]. Meta-regression analysis was used to evaluate the potential influence of country (China vs. other). In case of statistically significant outcomes, subgroup analysis was performed to assess the exact effects of study country. Statistical analysis was conducted in R-3.6.3 (“*metafor*” [20] package).

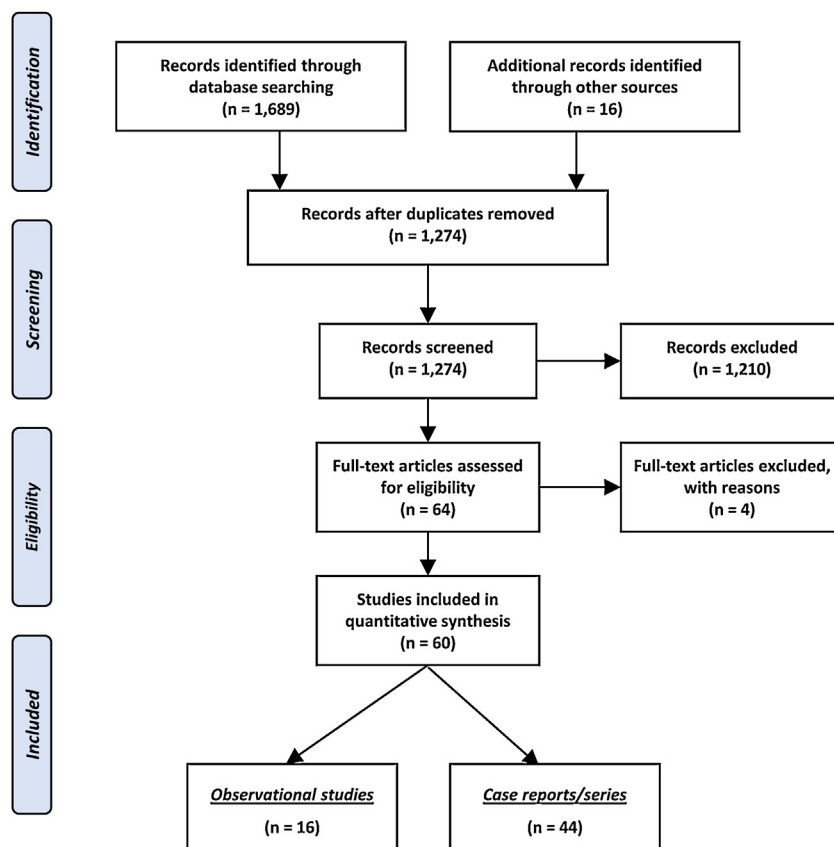


Fig. 1. Search plot diagram.

## Results

### Study selection

The outcomes of the literature search are schematically illustrated in Fig. 1. Overall, 1,705 records were identified and 1,274 of them were initially screened after removal of duplicates. The majority of them were then excluded for not meeting the eligibility criteria and thus a cohort of 64 articles was retrieved as full-texts. Subsequently, 4 studies [21–24] were excluded, as 2 studies examined infants and children but not neonates [23,24], while another 2 did not report any perinatal outcomes of pregnancies infected by SARS-CoV-2 [21,22]. As a result, the present meta-analysis was based on 16 observational studies

[25–40] and 44 case reports/series [41–84], including a total of 920 neonates born to women with SARS-CoV-2 infection.

### Quality assessment

The outcomes of risk of bias evaluation are summarized in Appendix 1 (Suppl. Tables 1, 2). Concerning case reports/series, concerns of bias were mainly raised in the domains of ascertainment and reporting due to missing data about exposure and outcomes, while some concerns were assigned in the domain of causality in 3 studies due to inadequate description of maternal baseline characteristics and comorbidities. On the other hand, evaluation of observational studies raised concerns mainly in the domain of sample size, while moderate risk of classification bias

**Table 1**

Maternal clinical characteristics and outcomes among pregnancies with and without transmission to neonates. Continuous variables are expressed as median [interquartile range].

Maternal characteristics	All patients (N = 158)	Transmission		p-value
		Yes (N = 17)	No (N = 141)	
China	144/158 (91.1 %)	13/17 (76.5 %)	131/141 (92.9 %)	0.072
Age (years)	30 [29–34]	32.5 [28.25–34]	30 [29–33.25]	0.558
<b>History</b>				
Diabetes mellitus	3/122 (2.5 %)	1/10 (10 %)	2/112 (1.8 %)	0.228
Hypothyroidism	6/122 (4.9 %)	4/10 (40 %)	2/112 (1.8 %)	<0.001
Polycystic ovary syndrome	1/122 (0.8 %)	0/10 (0 %)	1/112 (0.9 %)	1
<b>Symptoms</b>				
Asymptomatic	21/157 (13.4 %)	1/16 (6.3 %)	20/141 (14.2 %)	0.698
Fever	109/157 (69.4 %)	12/16 (75 %)	97/141 (68.8 %)	0.778
Cough	55/157 (35 %)	6/16 (37.5 %)	49/141 (34.8 %)	0.790
Shortness of breath	17/157 (10.8 %)	4/16 (25 %)	13/141 (9.2 %)	0.076
Diarrhea	12/157 (7.6 %)	2/16 (12.5 %)	10/141 (7.1 %)	0.352
Nausea / vomiting	2/157 (1.3 %)	1/16 (6.3 %)	1/141 (0.7 %)	0.194
Myalgia	6/157 (3.8 %)	2/16 (12.5 %)	4/141 (2.8 %)	0.115
Fatigue	15/157 (9.6 %)	2/16 (12.5 %)	13/141 (9.2 %)	0.652
Sore throat	11/157 (7.0 %)	1/16 (6.3 %)	10/141 (7.1 %)	1
Nasal congestion	4/157 (2.8 %)	1/16 (6.3 %)	3/141 (2.1 %)	0.352
Headache	4/157 (2.8 %)	0/16 (0 %)	4/141 (2.8 %)	1
Abdominal pain	2/157 (1.3 %)	0/16 (0 %)	2/141 (1.4 %)	1
Chest pain	3/157 (1.9 %)	0/16 (0 %)	3/141 (2.1 %)	1
<b>Radiology</b>				
Signs of pneumonia	145/147 (98.6 %)	16/16 (100 %)	129/131 (98.5 %)	1
<b>Co-infection</b>				
Bacterial	8/158 (5.1 %)	1/16 (6.3 %)	7/141 (4.9 %)	0.587
Influenza	3/158 (1.9 %)	0/16 (0 %)	3/141 (2.1 %)	1
<b>Laboratory tests</b>				
Lymphopenia	43/89 (48.3 %)	5/7 (71.4 %)	38/82 (46.3 %)	0.256
Thrombocytopenia	10/36 (27.8 %)	2/3 (66.7 %)	8/33 (24.2 %)	0.181
Increased C-reactive protein	46/66 (69.7 %)	5/5 (100 %)	41/61 (67.2 %)	0.312
Increased procalcitonin	14/23 (60.9 %)	1/2 (50 %)	13/21 (61.9 %)	1
Increased ferritin	7/12 (58.3 %)	2/2 (100 %)	5/10 (50 %)	0.470
Increased liver function tests	19/76 (25 %)	1/6 (16.7 %)	18/70 (25.7 %)	1
Increased D-dimers	26/36 (72.2 %)	2/2 (100 %)	24/34 (70.6 %)	1
<b>Treatment</b>				
Hydroxychloroquine	7/111 (6.3 %)	2/8 (25 %)	5/103 (4.9 %)	0.080
Azithromycin	11/111 (9.9 %)	2/8 (25 %)	9/103 (8.7 %)	0.180
Oseltamivir	23/111 (20.7 %)	2/8 (25 %)	21/103 (20.4 %)	0.669
Umifenovir	25/111 (22.5 %)	1/8 (12.5 %)	24/103 (23.3 %)	0.681
Lopinavir / ritonavir	6/111 (5.4 %)	1/8 (12.5 %)	5/103 (4.9 %)	0.369
Interferon	14/111 (12.6 %)	2/8 (25 %)	12/103 (11.7 %)	0.265
Antimicrobial	43/111 (38.7 %)	6/8 (75 %)	37/103 (35.9 %)	0.053
<b>Complications</b>				
Fetal distress	9/148 (6.1 %)	0/17 (0 %)	9/131 (6.9 %)	0.599
Premature rupture of membranes	14/148 (9.5 %)	1/17 (5.9 %)	13/131 (9.9 %)	1
Placenta previa	4/148 (2.7 %)	0/17 (0 %)	4/131 (3 %)	1
Preeclampsia	8/148 (5.4 %)	1/17 (5.9 %)	7/131 (5.3 %)	1
Preterm birth	47/158 (29.7 %)	2/17 (11.8 %)	45/141 (31.9 %)	0.099
Cesarean section	132/158 (83.5 %)	16/17 (94.1 %)	116/141 (82.3 %)	0.310
Admission to ICU	17/155 (11 %)	3/17 (17.6 %)	14/141 (9.9 %)	0.398
Death	2/155 (1.3 %)	1/16 (6.3 %)	1/141 (0.7 %)	0.196

Bold text indicates statistical significance. ICU: intensive care unit.

may have arisen from studies defining SARS-CoV-2 infection based exclusively on clinical or radiological criteria.

#### Outcomes of case reports/series

The maternal and perinatal outcomes of pregnancies infected by SARS-Cov-2 are presented in Appendices 2–3 (Suppl. Tables 3–4). Overall, 158 cases were included in the individual participant data meta-analysis and the majority of them came from China (91.1 %). The median age of women was 30 years and the most common comorbidity was hypothyroidism (4.9 %). Fever was the most frequent symptom (69.4 %), followed by cough (35 %) and shortness of breath (10.8 %), while 13.4 % of women with the disease were asymptomatic. The vast majority of cases presented radiological signs of pneumonia (98.6 %). Co-infection with influenza virus was uncommon (1.9 %), while bacterial super-infection occurred in 5.1 % of patients. Concerning laboratory tests, lymphopenia and thrombocytopenia were found in 48.3 % and 27.8 % of cases, respectively, while the majority of women presented increased C-reactive protein (69.7 %) and procalcitonin (60.9 %). Serum ferritin and D-dimers were sparsely reported, although when tested, their values were found to be elevated in 58.3 % and 72.2 % of cases, respectively. Treatment options included the administration of hydroxychloroquine (6.3 %), azithromycin (9.9 %), antiviral agents, such as oseltamivir (20.7 %), umifenovir (22.5 %), lopinavir/ritonavir (5.4 %) and interferon (12.6 %), as well as various antimicrobial agents (38.7 %).

The majority of neonates were delivered by cesarean section (83.5 %), with preterm birth (<37 weeks) occurring in 29.7 % of cases. Other pregnancy complications included premature rupture of membranes (9.5 %), fetal distress (6.1 %), preeclampsia (5.4 %) and placenta previa (2.7 %). Moreover, 17 women (11 %) developed severe disease and were admitted to ICU, while 2 of them (1.3 %) eventually died (Table 1). The median gestational age at delivery was 38 weeks, while the median birthweight was estimated to be 3120 g with 7.9 % of neonates being small-for-gestational age. In addition, stillbirth occurred in 3 cases and 2 neonatal deaths were observed (Table 2). Both neonatal deaths occurred in SARS-CoV-2-negative neonates that were born to mothers with severe disease requiring admission to the ICU.

Transmission of SARS-CoV-2 was confirmed in 17 cases. The maternal characteristics and perinatal outcomes were similar between pregnancies with and without viral transmission, with the exception of maternal hypothyroidism (Odds ratio: 36.67, 95 % CI: 5.56–241.69). Multivariate regression analysis indicated that hypothyroidism was the only factor associated with increased perinatal transmission ( $p$ -value: 0.004), while no association was found for maternal age, other comorbidities, symptoms or pregnancy complications. Importantly, the rate of neonatal transmission did not differ between women admitted to the ICU and those with the non-severe form of the disease (OR: 1.94, 95 % CI: 0.50–7.60) (Table 1). Vertical transmission was assumed to

occur in 4 cases [43,68,73,74] due to positive placental/amniotic fluid SARS-CoV-2 polymerase chain reaction (PCR) testing or detection of neonatal IgM antibodies against the virus shortly after delivery. Possible vertical transmission was also suspected in 6 cases due to immediate strict neonatal isolation, although direct evidence was lacking. No neonates born to SARS-CoV-2-positive mothers were breastfed, due to concerns of potential transmission. However, the presence of SARS-CoV-2 in breast milk was tested in 27 cases and all samples were negative. Stool samples were tested in 23 neonates with SARS-CoV-2 being detected in 5 of them (21.7 %). The clinical characteristics of SARS-CoV-2-positive neonates are presented in Table 3. Fever was the most common symptom (40 %), followed by shortness of breath (28 %) and vomiting (24 %), while 20 % of neonates were totally asymptomatic. The outcomes of complete blood count were reported for 8 cases; 2 of them presented lymphopenia and another 2 thrombocytopenia. Moreover, two neonates needed mechanical ventilation, while another one received noninvasive positive pressure ventilation. Neonatal sepsis occurred in two patients and one of them developed septic shock requiring inotropic support, although survived, was extubated and finally discharged.

#### Outcomes of observational studies

Eleven observational studies were included, comprising 762 neonates born to SARS-CoV-2-positive women (Appendix 4, Suppl. Table 5). Proportion meta-analysis indicated that the incidence of asymptomatic pregnant women was 15 % (95 % CI: 9–20 %), while fever was present in 53 % (95 % CI: 44%–62%), cough in 34 % (95 % CI: 23%–46%), shortness of breath in 18 % (95 % CI: 11%–26%) and diarrhea in 3 % (95 % CI: 2%–5%) of women. Severe disease was estimated to occur in 7 % (95 % CI: 4%–10%) of cases. The majority of neonates were delivered by cesarean section (66 %, 95 % CI: 51%–80%), while the rate of preterm birth was calculated at 16 % (95 % CI: 11%–21%) (Appendix 6, Suppl. Figs. 1–8).

Inter-study heterogeneity was evaluated to be significant as  $I^2$  values ranged from 32 % to 91.9 %, being highest in the outcomes of cough ( $I^2$ : 91.9 %) and cesarean section ( $I^2$ : 88.3 %). Asymmetry of funnel plots was detected in the outcomes of asymptomatic disease ( $p$ -value = 0.036) and severe disease ( $p$ -value = 0.006) (Appendix 7, Suppl. Figs. 9–16). The adjusted estimates according to the trim-fill method indicated similar rates of asymptomatic disease (9.1 %), but significantly lower incidence of severe disease (1.8 %) after accounting for potential missing studies. No fetal or neonatal deaths were reported by observational studies, while only 6 cases of viral transmission were described by 2 studies (Suppl. Table 5). Meta-regression analysis indicated that study country exerted significant effects on the outcomes of shortness of breath, severe disease and cesarean delivery (Appendix 6, Suppl. Table 6). Specifically, the incidence of shortness of breath and severe disease was significantly lower in studies conducted in China (7.7 % vs. 28 % and 4.1 % vs. 10.3 %, respectively). Moreover, the rate of cesarean

**Table 2**

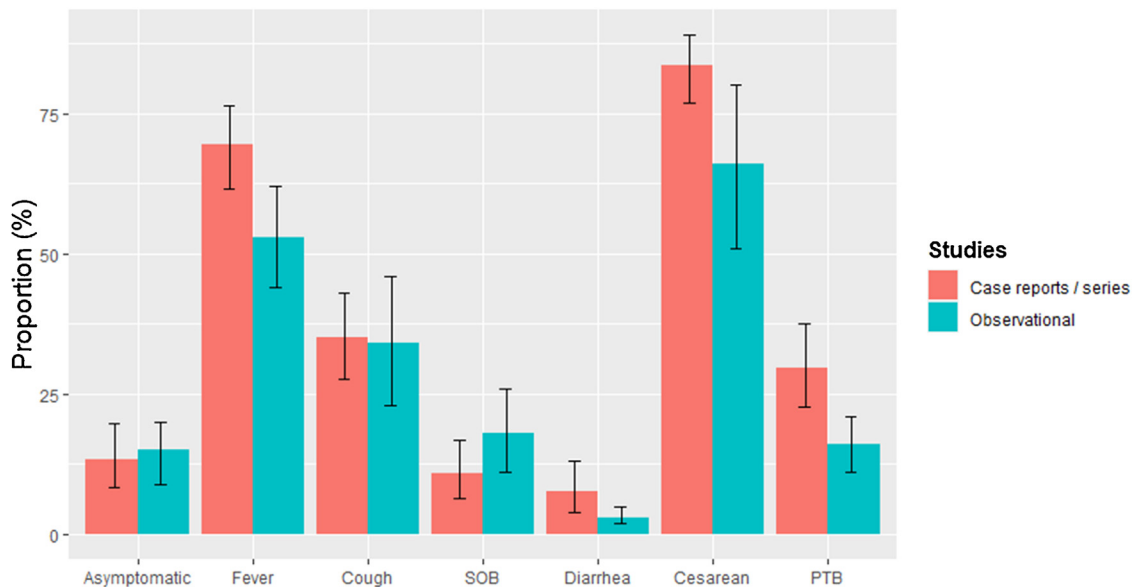
Clinical characteristics of infected and non-infected neonates. Continuous variables are expressed as median [interquartile range].

Neonatal characteristics	All neonates (N = 158)	Transmission		<i>p</i> -value
		Yes (N = 17)	No (N = 141)	
Male gender	52/77 (67.5 %)	8/12 (66.7 %)	44/65 (67.7 %)	1
Gestational age (weeks)	38 [36–39.1]	40 [35.35–40]	38 [36–39]	0.111
Birthweight (g)	3120 [2692–3370]	3228 [2852–3278]	3100 [2692–3400]	0.906
Small-for-gestational age	10/127 (7.9 %)	2/12 (16.7 %)	8/114 (7 %)	0.243
1-minute Apgar score	9 [8,9]	8 [6.5–9]	9 [8,9]	0.077
5-minute Apgar score	10 [9,10]	9 [8.5–10]	10 [9,10]	0.111
Stillbirth	3/158 (1.9 %)	1/17 (6.25 %)	2/141 (1.4 %)	0.291
Neonatal death	2/158 (1.3 %)	0/17 (0 %)	2/141 (1.4 %)	1

**Table 3**  
Clinical outcomes of neonates infected by SARS-CoV-2.

Author; Country	Gestational age (w)	Birthweight (g)	Delivery	Symptoms	Pneumonia	Lymphopenia/ Thrombocytopenia	Increased CRP/PCT	Treatment	NICU admission	Mechanical ventilation	CPAP/ NIPPV	Duration of respiratory support (days)	Sepsis	Shock	Inotropes	Neonatal death	Follow- up (days)
Yu N.; China	40	3250	Cesarean	SOB	Yes	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	40
Zamaniyan M; Iran	30.7	2350	Cesarean	Fever	No	NR/NR	NR/NR	Ampicillin, gentamicin	Yes	No	No	–	No	No	No	No	7+
Alzamora MC; Peru	33	2970	Cesarean	Cough, SOB	No	NR/NR	NR/NR	No	Yes	Yes	CPAP	0.5	No	No	No	No	6+
Wang S; China	40	3205	Cesarean	No	Yes	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	15
Dong L; China	37.7	3120	Cesarean	No	No	No/No	No/NR	No	Yes	No	No	–	No	No	No	No	25
Zeng L; China	40	3250	Cesarean	Fever	Yes	No/No	No/Yes	NR	Yes	No	No	–	No	No	No	No	6+
	40.6	3360	Cesarean	Fever	Yes	Yes/No	NR/NR	NR	No	No	No	–	No	No	No	No	6+
	31.3	1580	Cesarean	SOB	Yes	Yes/No	NR/NR	NR	Yes	No	NIPPV	14	Yes	No	No	No	14+
Aghdam MK; Iran	NR	3460	Cesarean	Fever, cough	No	No/No	No/NR	Vancomycin, amikacin, oseltamivir	Yes	No	No	–	Yes	No	No	No	14+
Zhang ZJ; China	40	NR	Cesarean	SOB	Yes	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	NR
	NR	NR	Cesarean	Fever, cough, vomiting	Yes	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	23
	NR	NR	Cesarean	Fever	No	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	30
Coronado Munoz; USA	40.1	NR	Cesarean	No	Yes	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	16
	36	NR	NR	Nasal congestion, SOB, feeding intolerance	Yes	No/No	Yes/Yes	Ampicillin, gentamycin, vancomycin, cefepime, hydroxychloroquine, azithromycin	Yes	Yes	No	5	Yes	Yes	Yes	No	9
Khan S; China	40.6	3360	Cesarean	NR	No	NR/NR	NR/NR	NR	NR	NR	NR	NR	NR	NR	NR	No	NR
	39.1	3570	Cesarean	NR	Yes	NR/NR	NR/NR	NR	NR	NR	NR	NR	NR	NR	NR	No	NR
Hu X; China	40	3250	Cesarean	No	No	No/No	No/No	No	No	No	No	–	No	No	No	No	NR
Salvatori G; Italy	41.3	4440	NR	No	No	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	NR
	39	3120	NR	Cough, diarrhea	No	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	5+
Alonso Diaz C; Spain	38.6	2500	Cesarean	SOB	Yes	NR/NR	No/NR	No	Yes	No	No	–	No	No	No	No	13
Zeng LK; China	39	NR	NR	Fever, SOB, vomiting	Yes	No/No	No/Yes	No	No	No	No	–	No	No	No	No	7
Wang J; China	38.6	3030	Vaginal	Fever, cough, vomiting	Yes	No/Yes	No/No	Interferon	No	No	No	–	No	No	No	No	14
Xiaoyuan F; China	NR	NR	NR	Fever, vomiting	No	NR/NR	NR/NR	Antimicrobial	No	No	No	–	No	No	No	No	16
	NR	NR	NR	Vomiting	No	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	16
	NR	NR	NR	Diarrhea, vomiting	Yes	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	15
	NR	NR	NR	Fever	Yes	NR/NR	NR/NR	Antimicrobial	No	No	No	–	No	No	No	No	13
	NR	NR	NR	Feeding intolerance	Yes	NR/NR	NR/NR	No	No	No	No	–	No	No	No	No	7

NR: not reported; CRP: C-reactive protein; PCT: procalcitonin; NICU: neonatal intensive care unit; CPAP: continuous positive airway pressure; NIPPV: noninvasive positive pressure ventilation; SOB: shortness of breath.



**Fig. 2.** Comparison of outcomes between case reports/series and observational studies. SOB: shortness of breath; PTB: preterm birth.

delivery was significantly higher in studies in China (88 % vs. 30 %). The outcomes of the meta-analysis of case reports/series compared to those of observational studies are depicted in Fig. 2.

## Discussion

Worldwide, SARS-CoV-2 is taking its toll on health systems and has caused hospitals and healthcare providers to rearrange facilities and habits to ensure the highest degree of safety to patients and workers. The shortage of data regarding COVID-19 in the neonatal age represents a further challenge for obstetricians and neonatologists, who are called to face a rather unknown enemy. Moreover, perinatal care to the mother-neonate dyad requires special considerations due to the peculiarity of their condition, since bonding and close interaction between the mother and her baby are crucial for their well-being. Unfortunately, the paucity of supporting data impedes to draw conclusions at this point. To date, the vast majority of neonatal information is scattered and fragmented, since it is derived from case reports or small case series. To the best of our knowledge, the present meta-analysis is the largest one to date, providing pooled outcomes from 11 observational studies and 44 case reports/case series.

### Maternal outcomes

The clinical course of Covid-19 is typically mild during pregnancy, with 15 % of infections being asymptomatic. The reported rates of severe disease were significantly higher in studies conducted in countries other than China, probably reflecting publication bias during the first wave of SARS-CoV-2. The most common symptoms were fever and cough, followed by shortness of breath, while gastrointestinal symptoms were rare. Radiological signs of pneumonia were almost ubiquitously present. Cesarean section rates were high, mainly due to concerns about perinatal transmission. The incidence of preterm birth was remarkable (29.7 % in case reports – 16 % in observational studies), although the risk of preeclampsia and placental previa were estimated to be low (5.4 % and 2.7 %, respectively).

### Transmission

Symptomatic patients with COVID-19 are regarded as the main disseminators, but asymptomatic individuals should not be

underestimated. The main transmission routes are droplets, contact, and aerosol transmission, although fecal-oral transmission should be also considered since SARS-CoV-2 RNA has been detected in fecal samples. [85] Our results confirm that horizontal spread from caregivers (primarily the mother) to the neonate is the most likely way of transmission in this population. Hence, it is recommended that in case of asymptomatic or mildly symptomatic SARS-CoV-2 positive mothers, general hygienic measures should be taken. Specifically, the neonate's crib should be distanced from the mother's bed by at least two meters and the mother should wear a surgical face mask when breastfeeding or looking after the neonate [86].

Vertical spread remains doubtful, in keeping with the absence of reported cases of intrauterine transmission for SARS-CoV-1 and MERS. [87] Vertical transmission was suspected in 4 cases due to positive placental/amniotic fluid SARS-CoV-2 PCR testing or detection of neonatal IgM antibodies against the virus shortly after delivery [43,68,73,74]. Alzamora et al. [68] reported a severe presentation of maternal COVID-19 during pregnancy, followed by the finding of positive RT-PCR in nasopharyngeal swab of the neonate at 16 h of life, despite immediate isolation from the mother. Moreover, Dong and coll [61] described the case of a newborn with early elevated IgM antibodies to SARS-CoV-2 born to a mother with COVID-19.

Hypothyroidism was suggested as a potential predisposing factor for perinatal transmission. Overall, six women with hypothyroidism were included and neonatal SARS-Cov-2 positivity was detected in 4 of these cases. This association remained significant in multivariate regression analysis after taking into account the effects of country, maternal age, other comorbidities, symptoms and pregnancy complications. The increased incidence of neonatal transmission may be based on the effects of thyroid hormones on placental function and maturation since subclinical hypothyroidism has been linked to increased rates of placental abruption and preterm birth [88]. In this context, thyroid hormones have been proposed to affect placental development by modulating inflammatory and apoptotic processes [89], especially by altering the placental immune profile and intrauterine trophoblast migration [90]. Nonetheless, whether the potential effects of thyroid dysfunction on placental barrier may facilitate vertical SARS-CoV-2 transmission remains to be elucidated by further studies in the field.



Nonetheless, the understanding of the mechanisms related to vertical transmission remains to be determined. One could speculate that vertical transmission is more likely in case of significant viral load in maternal samples, or critically-ill patients. However, there is currently no evidence to support any conclusion in this respect, while potential answers may be expected from the INTERCOVID study group [91].

#### Neonatal clinical aspects

The present findings suggest that the clinical presentation of COVID-19 in neonates may range from asymptomatic to severe respiratory distress. The most common symptoms were fever and dyspnea, although gastrointestinal manifestations, such vomiting and milk refusal may occasionally be the only ones in neonates [58]. Sporadic cases of neonatal infections (pneumonia or sepsis) requiring mechanical ventilation have been also described [62,68,92], while Zhu et al. [41] reported on a late-preterm who died on the ninth day of life due to refractory shock, multiple organ failure, and disseminated intravascular coagulation. Some laboratory findings, such as thrombocytopenia and lymphopenia, appear rather common in neonates born to COVID-19 mothers, even when transmission to the offspring is not confirmed either on serology or nasopharyngeal swab; these findings have been proposed to resemble those of certain late-acquired TORCH (Toxoplasmosis, Other, Rubella, Cytomegalovirus, and Herpes) infections and thus have prompted some authors to suggest the inclusion of SARS-CoV-2 among TORCH complex [93].

#### Delivery

Since the beginning of COVID-19 epidemic in China, in some cases, mothers with suspected or confirmed SARS-CoV-2 infections have undergone cesarean section in the absence of other obstetrical indications with the aim to reduce the odds of intrapartum transmission [63]. Notably, currently available case series show a higher than expected number of preterm deliveries and cesarean sections. According to our data, the rate of cesarean delivery was 83.5 % and 80 % in case reports and observational studies, respectively. This can be in part explained as a consequence of obstetric decision to deliver due to the severity of the maternal infection (bilateral pneumonia with respiratory insufficiency and shock) [94].

Since cesarean deliveries entail the exposure of a greater number of health care workers compared with spontaneous vaginal delivery and are linked to an increase in neonatal morbidity, the decision to deliver *via* cesarean should be cautiously weighted. To date, clear findings on whether spontaneous vaginal delivery favors neonatal infection are lacking. Hence, for the time being, the mode of delivery and anesthesia is best advisable as per maternal and fetal indications and spontaneous vaginal delivery should generally be preferred [94].

#### Neonatal care in the delivery room

Whether skin-to-skin contact increases the risk of SARS-CoV-2 transmission is yet to be clarified [95,96]. It is advisable to share decision-making with the parents before delivery regarding the potential risks and benefits of skin-to-skin care and kangaroo mother care, taking into account also risks of exposure to both the neonate and to health care providers [94]. Delayed cord clamping is unlikely to increase the odds of vertical transmission, since the fetus has exchanged the same blood supply during the entire pregnancy. Therefore, if vertical transmission was possible, it would probably have occurred before delivery. Currently, there is no evidence supporting the abolishment of delayed cord clamping,

which is still recommended in all vigorous neonates for at least 60 s [94].

#### Breastfeeding

Despite some authors advocate for a cautious approach and recommend feeding preterm neonates on pasteurized breast milk (donor or maternal) or formula. [97] However, according to the present findings, all breast milk samples have been tested to be negative for SARS-CoV-2 and thus breast milk of a COVID-19 mother cannot be regarded as a transmission vehicle. Moreover, similarly to the 2002–2003 SARS-CoV-1 epidemic, specific SARS-CoV-2 antibodies are likely to pass *via* the breast milk from the COVID-19 mother to the infant within a few days after the onset of the disease, thus possibly modulating the clinical expression of the infant's infection [98,99]

#### Strengths and limitations of the study

The present meta-analysis gathered all the available evidence in the field, by searching 5 literature databases without applying any language restrictions. Both case reports/series and observational studies were included and separately analyzed, providing a comprehensive approach concerning the perinatal effects of SARS-CoV-2 infection. Specifically, analysis of case reports/series provided a cohort of 158 neonates with individual participant data enabling the assessment of factors potentially associated with neonatal transmission of the virus. On the other hand, the present outcomes are limited by inconsistent reporting of important clinical and laboratory characteristics leading to missing data in several variables. Moreover, inter-study heterogeneity of observational studies was estimated to be significant, reflecting potential methodological differences concerning patient selection and outcome reporting. The effects of study country was assessed by conducting meta-regression analysis; importantly, studies conducted in China reported significantly higher incidence of cesarean delivery, reflecting the remarkable variance of labor protocols among different regions. In addition, inter-study heterogeneity may be present, as different periods of evaluation may be characterized by different treatment strategies due to the rapid change of policies regarding the management of the pandemic. It should be also noted that publication bias was suspected, especially regarding the outcome of severe maternal disease, implying that its incidence may be currently overestimated by the available studies in the field.

#### Implications for future research

Many questions regarding the impact of the novel coronavirus SARS-CoV-2 are still to be addressed. Firstly, the possibility of vertical transmission in utero or at birth should be clearly demonstrated, since the sporadic cases of positive nasopharyngeal swabs or IgM testing in neonates might be due to PCR and ELISA assay differences. Greater reliability and reproducibility of assays used worldwide are strongly warranted. Moreover, it is not clear whether a neonate with positive IgM should be considered infected and, consequently, contagious even in case of negative nasopharyngeal swabs. Secondly, data regarding SARS-CoV-2 infection during the first trimester and possible embryotoxicity are still completely lacking. In this respect, a deeper investigation regarding the capacity of SARS-CoV-2 to infect the placenta is also needed. In the present study, hypothyroidism was identified as a potential predisposing factor for perinatal transmission; however, the sample size was small and thus further research is warranted in order to reach firm conclusions about the causality of this relationship. Lastly, preliminary evidence is reassuring about

breastfeeding, however more confirmatory data are needed on breast milk and viral load. Importantly, the implementation of point-of-care immune assays and virologic assays would help early identify infected but asymptomatic women who present in labor, aiming to improve perinatal management.

## Conclusions

Maternal and neonatal COVID-19 infection is linked to a variety of clinical manifestations, although asymptomatic and mild cases are most commonly seen during the third trimester. The incidence of neonatal transmission is suggested to be low and independent of maternal disease severity. Currently, most of the approaches in the management of suspected or confirmed COVID-19 mothers and their offspring are based on little evidence and experts' opinions. Future large-scale studies are needed in order to clarify the risk of vertical transmission and identify the factors that may predispose for the development of severe neonatal infection.

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## Ethical approval

Not required. The present study is a meta-analysis and is solely based on aggregated data of already published studies.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Author contributions

*Conception and design:* I. Bellos, A. Pandita.

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*Critical revision for important intellectual content:* I. Bellos, R. Panza.

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*Statistical expertise:* I. Bellos.

*Collection and assembly of data:* I. Bellos, A. Pandita.

## Declaration of Competing Interest

The authors report no declarations of interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2020.11.038>.

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