Obstetric and perinatal outcomes of pregnancies with COVID 19: a systematic review and meta-analysis

Faustino R. Pérez-López, Ricardo Savirón-Cornudella, Peter Chedraui, María T. López-Baena, Gonzalo Pérez-Roncero, Ana Sanz-Arenal, Marta Narváez-Salazar, Peña Dieste-Pérez & Mauricio Tajada

View supplementary material

Published online: 13 Mar 2022.

Submit your article to this journal

Article views: 307

View related articles

View Crossmark data

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Check for updates

Obstetric and perinatal outcomes of pregnancies with COVID 19: a systematic review and meta-analysis

Faustino R. Pérez-López[a,b] , Ricardo Savirón-Cornudella[c] , Peter Chedraui[d] ,
María T. López-Baena[a] , Gonzalo Pérez-Roncero[a] , Ana Sanz-Arenal[e] , Marta Narváez-Salazar[e] ,
Peña Dieste-Pérez[a,e] and Mauricio Tajada[a,b,e]

[a]Instituto de Investigaciones Sanitarias de Aragón, Zaragoza, Spain; [b]Faculty of Medicine, University of Zaragoza, Zaragoza, Spain;
[c]Department of Obstetrics and Gynecology, Hospital Clínico San Carlos, Madrid, Spain; [d]Instituto de Investigación e Innovación en
Salud Integral & Laboratorio de Biomedicina, Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador; [e]Department of
Obstetrics and Gynecology, Hospital Universitario Miguel Servet, Zaragoza, Spain

ABSTRACT

Objective: This meta-analysis aimed at comparing obstetric and perinatal outcomes in laboratory-tested pregnant women for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection before delivering.
Method: We performed a comprehensive systematic review of electronic databases for studies reporting pregnant women with and without SARS-CoV-2 infection, as determined by polymerase chain reaction (PCR) before delivery, during the pandemic period published up to June 25, 2021. Results are reported as mean difference (MD) or odds ratio (OR) and their 95% confidence interval (CI).
Results: Seventeen observational studies with low to moderate risk of bias, reported on 2,769 pregnant women with a positive SARS-CoV-2 PCR test and 13,807 with a negative test. Pregnant women with a positive PCR test delivered at an earlier gestational age (MD -0.19; 95% CI -0.36 to -0.02 weeks), smoked less (OR 0.75; 95% CI 0.61–0.94) and were associated with higher odds for preeclampsia (OR 1.30; 95% CI 1.09–1.54), NICU admissions (OR 2.37; 95% CI 1.18–4.76), stillbirths (OR 2.70; 95% CI, 1.38–5.29), and perinatal mortality (OR 3.23; 95% CI 1.23–8.52). There were no significant differences between positive and negative tested women in terms of nulliparity, multiple pregnancies, gestational diabetes, route of delivery, labor induction, preterm birth, infant birth weight, 5 min Apgar scores < 7, small-for-gestational-age infants and fetal malformations. Eleven studies included neonatal PCR SARS-CoV-2 testing which was performed on 129 infants, of which 20 were positive.
Conclusion: Positive SARS-CoV-2 tested pregnant women had higher odds for preeclampsia/hypertensive disorders of pregnancy, NICU admissions, stillbirths and perinatal mortality.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused more than 185 million cases and more than 4,200,000 deaths up to July 30, 2021 [1]. The clinical characteristics of the severe infection occurring during pregnancy are similar to those observed among non-pregnant subjects: dyspnea, cough, fever, pneumonia, respiratory failure, leukocytosis, and lymphopenia [2]. The prevalence of severe forms of SARS-CoV-2 infections is higher among pregnant women than in non-pregnant. Compared to asymptomatic pregnant women, those with the more severe forms of SARS-CoV-2 present higher rates of critical respiratory disease, thromboembolism, hypertensive disorders, intensive care unit admission (NICU), severe sepsis, correlating to adverse maternal and perinatal outcomes, including higher rates of cesarean deliveries and preterm births as compared to asymptomatic infected pregnant women. At the beginning of the pandemic, many studies included mostly hospitalized pregnant women with severe symptoms and complications; whereas those with mild or no symptoms were not specifically reported. Indeed, universal polymerase chain reaction (PCR) testing was not the case. However, to determine the real impact of the SARS-CoV-2 infection on pregnancy outcomes it seems relevant to include oligosymptomatic and asymptomatic cases.

CONTACT Faustino R. Pérez-López ✉ faustino.perez@unizar.es 🖃 Faculty of Medicine, University of Zaragoza, Zaragoza, 50009, Spain

⊕ Supplemental data for this article can be accessed here.

During the last year, obstetric recommendations for pregnant women with SARS-CoV-2 infection were based mainly on the initial reports from China fatalities and some Western cohorts of pregnant women, and meta-analyses of case reports or comparisons with pre-pandemic pregnant women. Universal screening of pregnant women before or during labor and delivery has been proposed to identify positive cases, even if they are asymptomatic, in order to prevent infection from spreading and monitor pregnant women more closely and organize clinical assistance during labor and delivery. The objective of this systematic review and meta-analysis is to compare obstetric and perinatal outcomes in delivering pregnant women with and without SARS-CoV-2 infection as demonstrated by PCR testing.

Methods

Protocol, study design and search strategy

This investigation is a systematic review and meta-analysis of observational (cohort, case-control and cross-sectional) clinical studies comparing the impact of SARS-CoV-2 infection on maternal and perinatal outcomes in delivering pregnant women. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [3]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021235782). A formal institutional review board approval was not required since this analysis consisted of the pooling of published studies.

We searched the PubMed, Embase, and LILACS online databases for relevant articles published up to June 25 2021, using the keywords and related MeSH terms as follows: "COVID-19," "SARS-CoV-2," "Coronavirus 2019" AND "polymerase chain reaction" OR "PCR" AND "Pregnant women" OR "gravida" OR "obstetric delivery" OR "obstetric outcomes" OR "labor" OR "maternal outcomes" OR "neonatal outcomes" OR "perinatal outcomes" OR "preeclampsia" OR "preterm" OR "neonate" OR "infant" OR "stillbirth." There was no restriction regarding the language or status of the publication. Detailed search strategies are described in Supplemental Table 1. Found abstracts were pooled into the EndNote X9 (Clarivate Analytics, Philadelphia, Pennsylvania, United States) to identify and remove duplicate records. A further manual search of bibliographic references was carried out in selected references and in existing reviews to identify potential studies that were not captured by the electronic database searches. Also, information related to the topic was periodically screened on Twitter and Google Scholar for additional potential publications.

Selection criteria, data extraction and risk of bias

Eligible studies included cohort, case-control and cross-sectional designs without language limitations. The studied population was composed of pregnant women delivering during the second half of pregnancy, the exposure was a positive SARS-CoV-2 PCR test reported in at least three pregnant women. The comparative group was composed of negative SARS-CoV-2 PCR tested pregnant women of the same community and study period. This systematic review was not designed to evaluate outcomes of only those pregnancies affected by SARS-CoV-2 infection nor compare outcomes of pandemic versus pre-pandemic cohorts.

Principal outcomes included maternal characteristics and obstetric and perinatal/neonatal outcomes. The study set up the outcomes to evaluate the relationships between SARS-CoV-2 infection and maternal or perinatal/neonatal outcomes: maternal co-comorbidity, mode of delivery, gestational age and birth weight at delivery, Apgar score < 7 at 5 min, maternal and/or NICU admissions, and the rates of preeclampsia, preterm birth, small-for-gestational age infants, stillbirths, and perinatal mortality. Any study that described at least one of the outcomes was included for assessment and analysis. The following types of articles were excluded: review articles, hypotheses, case reports, articles focusing on pediatric populations, articles providing inadequate information or not relevant to the study goal. Four investigators independently performed a systematic review using the same criteria and included studies on the basis of agreement. Upon disagreement, all authors joined and helped make the final decision. Five investigators independently extracted data from the included studies using an established data collection form. Collected variables included the first author's surname, year of publication, country of the study, study design, sample size, study period, demographics of participants, follow-up duration, method of SARS-CoV-2 testing, study quality and outcomes. When required, corresponding authors were contacted to gather missing data.

The Newcastle-Ottawa Scale (NOS) risk of bias tool [4] was used to appraise the quality of the studies. This instrument consists of eight items covering three broad perspectives: the selection of the study groups, the comparability of the groups and the ascertainment

of either the exposure or outcome of interest. The total maximum score of these three perspectives is nine. A study that scores equal to or higher than seven is considered high-quality research, and moderate-quality is considered for those scoring 4–6. Articles with a NOS score of 4 or less were excluded.

Data synthesis and statistical analyses

We used the DerSimonian-Laird generic inverse variance method to perform meta-analysis since some of the enrolled studies reported results with an inverse design [5]. We conservatively chose random effect modeling for analysis since differences were found in relation to the study populations and study designs. We calculated mean differences (MDs) for continuous variables and the odds ratios (ORs) and 95% confidence interval (95% CI) to present the overall estimated effects represented in forest plots. The heterogeneity of analyses was tested by I^2 analysis. An I^2 60% indicated the existence of substantial heterogeneity [6,7]. In addition, small studies effects were estimated with funnel plots and Egger's tests. All meta-analyses were conducted by Review Manager version 5.3 software (Cochrane Collaboration, Oxford, UK).

Subgroup analyses and sensitive analyses

Tentative subgroup analyses were planned considering obstetric and perinatal outcomes (i) different paradigmatic infection clinical approached forms: comparison of results from universal SARS-CoV-2 maternal screening cohorts versus case-control and cross-sectional studies aside of universal population screening programs; (ii) comparison of pregnant women living in high-income countries (HICs) (United States and Europe) and low- to middle-income countries (LMICs) (Latin America, the Caribbean region and India) [8,9]. Sub-analysis by symptomatic and asymptomatic SARS-CoV2 infections was also considered if articles separately report both asymptomatic and symptomatic infected pregnant women. Sensitivity analyses were planned, including the removal of studies one by one [10], for gestational age at delivery, preeclampsia, preterm birth (<37 weeks), stillbirth and perinatal mortality.

Results

General characteristics of included studies

We found 187 records through database searching, and after the removal of duplicates, 157 abstracts were evaluated along with seven articles found from other sources. Forty-four full-text articles were evaluated for eligibility. Seven papers included duplicate information, eight did not report individualized information of control groups, and 12 did not report the outcomes of interest (Figure 1). Finally, a total of 17 observational studies were evaluated for qualitative and quantitative assessment [11–27]. These studies reported on 2,769 delivering women with a positive SARS-CoV-2 PCR test and 13,807 with negative results.

Table 1 details (i) Main general characteristics (study location, study period, type of study, total pregnant women at delivery); (ii) number of SARS-CoV-2 pregnant women tested positive, and the number of infants tested positive for SARS-CoV-2; and (iii) number of women tested negative for SARS-CoV-2 and maternal mortality. Positive SARS-CoV-2 pregnant women included asymptomatic and symptomatic ones. Supplemental Table 2 details objectives of the studies, clinical characteristics of pregnant women and main findings, neonates with positive PCR testing and maternal mortality. The studies included pregnant women living in the United States [11,13,15,18,21–24], India [19,27], Spain [16,25], Canada [26], Chile [17], French Guiana [20], Mexico [14], and Sweden [12] (Table 1). There were 8 cohort studies [11,13,15,19,20,22,23,25], three matched case-control studies [12,24,26] and, and 6 cross-sectional studies [14,16–18,21,27]. Positive SARS-CoV-2 PCR tested women ranged from 8 to 1,347 pregnant women gravida [13,16] (Table 1 and Supplemental Table 2).

The objectives of the authors and main maternal, obstetrical and perinatal characteristics of meta-analyzed studies are displayed in Supplemental Table 2. The research objectives of the meta-analyzed papers were (i) in eight studies aimed at performing universal screening of SARS-CoV-2 infection before or during labor and delivery [13–15,19,20,22,23,25], (ii) to compare clinical characteristics and perinatal outcomes among positive and negative SARS-CoV-2 tested pregnant women [11,12,16,17,19,20,26,27], (iii) to study preeclampsia/hypertensive disorders of pregnancy [24], (iv) early characteristics of infants [18,21], or (v) analyze placental characteristics [21] There were no separate subgroup reports to differentiate by the severity of clinical symptoms and obstetric and perinatal outcomes.

All publications identified the characteristics of the study population, pregnant women representative of the average of symptomatic SARS-CoV-2 clinical cases and local health care services. In addition, there was a large proportion of asymptomatic pregnant women,
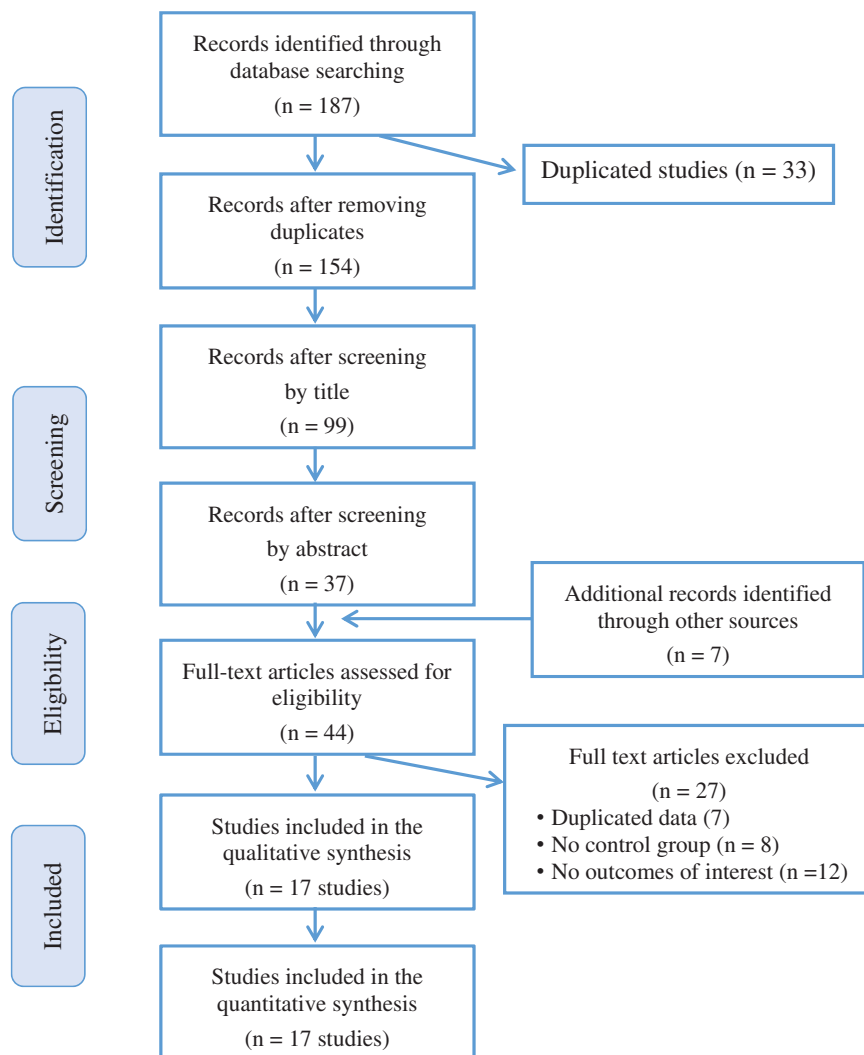
Figure 1. Flowchart of study selection.

and controls that were derived from the same population as cases (Table 1, Supplemental Table 2). All studies reported a population of pregnant women representative of the average in their respective social context during the observation period (Table 1). The cohort studies [11,13,15,19,20,22,23,25] corresponded to universal SARS-CoV-2 screening protocol near or prior to labor and delivery. Prospective cohort screening studies of SARS-CoV-2 reported prevalences of positive pregnant women ranging from 1.9% in Madrid and Zaragoza, Spain [25] to 11.6% in New York, USA [23]. Retrospective analysis of screening studies reported prevalences ranging between 2.5% in New York [13] and 37.0% in the French Guiana [20] during different pandemic phases and variable duration of the studies. Case control and cross-sectional studies included subgroups with sample sizes according to their corresponding scientific objectives (Supplemental Table 1). The Cruz-Melguizo et al. [16] cross-sectional study reported mixed results from an

initial PCR testing approach of suspicious infected pregnant women ($n = 1,347$) and the second sample of universal PCR screening.

The NOS was used for the quality assessment of studies (Supplemental Table 3). It was determined that 3 studies had a moderate risk of bias [16,18,27], and 14 had a low risk of bias [11–15,17,19–26] (Table 1 and Supplemental Table 2).

Meta-analysis results

According to Figure 2, pregnant women with a positive PCR testing were significantly younger (MD $= -0.75$; 95% CI -1.26 to -0.24 years; Figure 2A) yet with similar odds for nulliparity (Figure 2B). Positive SARS-CoV-2 pregnant women were at higher risk of delivering at an earlier gestational age (MD $= -0.19$; 95% CI -0.36 to -0.02 weeks, Figure 2C), and developing preeclampsia/hypertensive disorders of pregnancy (OR $= 1.30$, 95% CI $1.09 - 1.54$,

Table 1. General characteristics of studies comparing maternal and perinatal outcomes in women positive or negative to the SARS-CoV-2 as determined by laboratory testing.

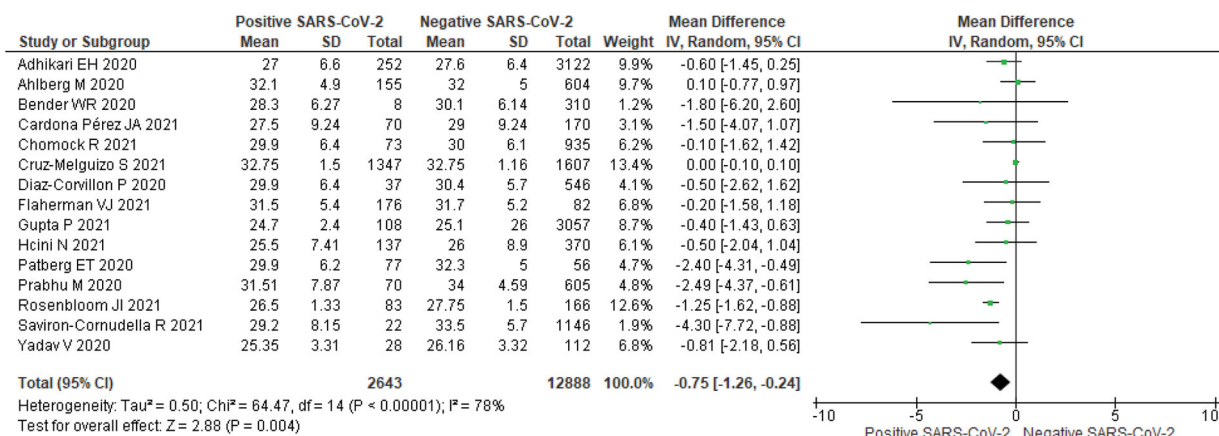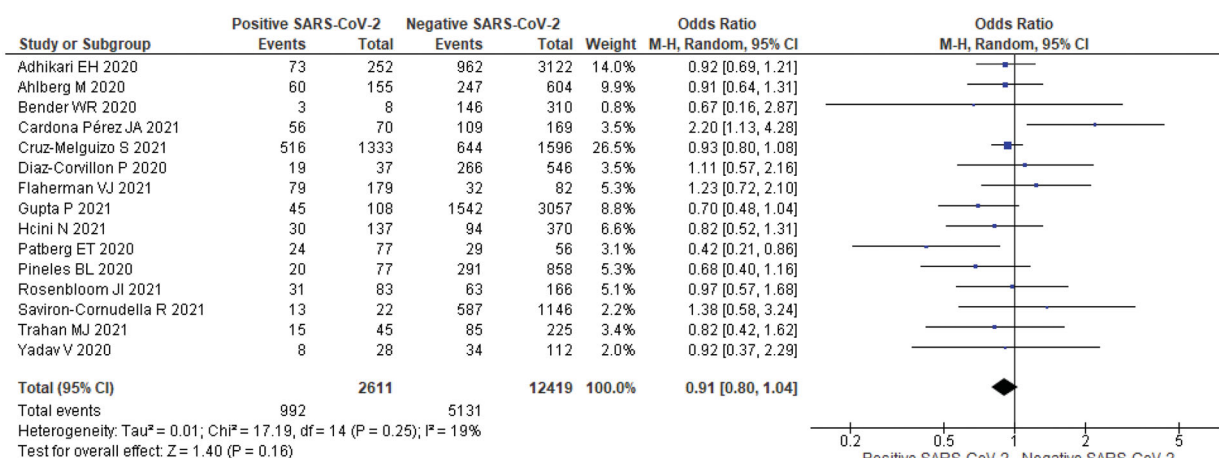| Authors [Reference]	General characteristics			Positive SARS-CoV-2 gravida		Infants positive to SARS-CoV2 testing	Negative SARS-CoV-2 gravida
	Study location	Study period	Type of study. Total gravida at delivery	Positive SARS-CoV-2 testing (n). Maternal Mortality (MM)	Clinical symptoms of gravida		Negative SARS-CoV-2 testing gravida (n). Maternal mortality (MM)
Adhikari et al. [11]	Dallas, Texas, USA	March 18 to August 22, 2020.	Cohort study. $n = 3,374$	$n = 252$. MM: no	8 mild symptoms; 6 severe or critical symptoms.	6/188	$n = 3,122$. MM: no
Ahlberg et al. [12]	Stockholm, Sweden	March 25 to July 24, 2020.	Matched case-control study. $n = 760$	$n = 156$. MM: no	35% of PCR positive women were symptomatic.	No reported	$n = 604$. MM: no
Bender et al. [13]	Philadelphia, PA, USAs.	April 13 to April 26, 2020	Cohort study. $n = 318$	$n = 8$. MM: no	3 women had mild symptoms in the 2 weeks after a positive test results.	No reported	$n = 310$. MM: no
Cardona- Pérez et al. [14]	Mexico City, Mexico	April 22 to May 25, 2020	Cross-sectional study. $n = 240$	$n = 70$. MM: no	9 women mild symptoms and 1 moderate symptoms. Women with severe symptoms were treated in another center.	9/70	$n = 170$. MM: no
Chornock et al. [15]	Washington DC, USA	April 8 to July 31, 2020	Retrospective cohort study. $n = 1,008$	$n = 73$. MM: none	Three gravida had mild symptoms acutely worsened, needing admission at the ICU for respiratory support. One patient was directly admitted to the ICU and required cesarean delivery due to cardiopulmonary arrest.	No reported.	$n = 935$. MM: no
Cruz-Melguizo et al. [16]	78 Hospitals of Spain	February 26 to November 5, 2020	Cross-sectional study. $n = 2954$	$n = 1,347$. MM: 2	659 women had symptoms: 70.9% showed mild to moderate symptoms, 25.2% pneumonia and 3.9% complicated pneumonia/shock (ICU admission and/or mechanical ventilation and/or septic shock).	No reported.	$n = 1,607$. MM: no
Diaz-Corvillon et al. [17]	Santiago, Chile	April 27 to June 7, 2020	Cross-sectional study. $n = 583$	$n = 37$. MM: no	18 mild symptoms, and 3 had severe symptoms requiring admission to ICU.	2/37	$n = 546$. MM: no
Flaherman et al. [18]	PRIORITY Study, 100 US Hospitals	March 22 to June 22, 2020	Cross-sectional study. $n = 263$	$n = 179$. MM: no	18 women hospitalized and 6 in the ICU at the time of enrollment.	2/179	$n = 84$. MM: no

(continued)

Table 1. Continued.

Authors [Reference]	General characteristics			Positive SARS-CoV-2 gravida			Negative SARS-CoV-2 gravida
	Study location	Study period	Type of study. Total gravida at delivery	Positive SARS-CoV-2 testing (n). Maternal Mortality (MM)	Clinical symptoms of gravida.	Infants positive to SARS-CoV2 testing	Negative SARS-CoV-2 testing gravida (n). Maternal mortality (MM)
Gupta et al. [19]	Jammu and Kashmir, India	September 1 to November 30, 2020	Reprospective cohort study. $n = 3,165$	$n = 108$. MM: 1	297 gravida were symptomatic at admission.	0/108	$n = 3,057$. MM: 7
Hcini et al. [20]	Saint-Laurent-du-Maroni, French Guiana	June 16 to August 16, 2020	Prospective cohort study. $n = 507$	$n = 137$. MM: no	34/137 women had clinical symptoms at admission, 16/103 asymptomatic became symptomatic, 5/137 developed severe infection.	No reported	$n = 370$. MM: no
Patberg [21]	New York, NY, US	31 March to 17 June 2020	Cross-sectional study. $n = 133$	$n = 77$. MM: no	10 women had mild symptoms.	0/77	$n = 56$. MM: no
Pineles BL [22]	Houston, Texas, USA	April 22 to July 22, 2020	Retrospective cohort study. $n = 935$	$n = 77$. MM: no	11 patients had clinical symptoms, including 3 needing respiratory support.	1/77	$n = 858$. MM: no
Prabhu [23]	New York, New York, USA	March to April, 2021	Prospective cohort study. $n = 675$	$n = 70$. MM: no	13 women had mild symptoms before admission, and 7 developed symptoms after admission. Two women developed symptoms on postpartum day 3.	0/70	$n = 605$. MM: no
Rosenbloom [24]	Saint Louis, Missouri, USA	June 1 to November 30, 2020	Matched case-control study. $n = 249$	$n = 83$. MM: no	There was no difference in baseline characteristics between SARS-CoV-2 infected women and controls.	No reported.	$n = 166$. MM: no
Savirón-Cornudella [25]	Madrid and Zaragoza, Spain	March 31 to September 30, 2020	Prospective cohort study. $n = 1,168$	$n = 22$. MM: no	2 women had mild symptoms.	0/22	$n = 1,146$. MM: no
Trahan [26]	Montréal, Canada	March 22 to July 31, 2020.	Matched case-control study. $n = 270$	$n = 45$ gravida. MM: no	The majority of patients with SARS-CoV-2 had symptoms (32 of 44), with 6 of 45 requiring antepartum hospital admission due to infection. One patient required mechanical ventilation.	No reported.	$n = 225$. MM: no
Yadav V [27]	Greater Noida, Uttar Pradesh, India	March 23 to July 23, 2020	Cross-sectional study. $n = 140$	$n = 28$. MM: no	6 women had mild symptoms.	0/28	$n = 112$. MM: no

ICU: Intensive Care Unit; MM: Maternal Mortality.

A. Maternal age

Study or Subgroup	Positive SARS-CoV-2 Mean	SD	Total	Negative SARS-CoV-2 Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Adhikari EH 2020	27	6.6	252	27.6	6.4	3122	9.9%	-0.60 [-1.45, 0.25]
Ahlberg M 2020	32.1	4.9	155	32	5	604	9.7%	0.10 [-0.77, 0.97]
Bender WR 2020	28.3	6.27	8	30.1	6.14	310	1.2%	-1.80 [-6.20, 2.60]
Cardona Pérez JA 2021	27.5	9.24	70	29	9.24	170	3.1%	-1.50 [-4.07, 1.07]
Chomock R 2021	29.9	6.4	73	30	6.1	935	6.2%	-0.10 [-1.62, 1.42]
Cruz-Melguizo S 2021	32.75	1.5	1347	32.75	1.16	1607	13.4%	0.00 [-0.10, 0.10]
Diaz-Corvillon P 2020	29.9	6.4	37	30.4	5.7	546	4.1%	-0.50 [-2.62, 1.62]
Flaherman VJ 2021	31.5	5.4	176	31.7	5.2	82	6.8%	-0.20 [-1.58, 1.18]
Gupta P 2021	24.7	2.4	108	25.1	26	3057	8.7%	-0.40 [-1.43, 0.63]
Hcini N 2021	25.5	7.41	137	26	8.9	370	6.1%	-0.50 [-2.04, 1.04]
Patberg ET 2020	29.9	6.2	77	32.3	5	56	4.7%	-2.40 [-4.31, -0.49]
Prabhu M 2020	31.51	7.87	70	34	4.59	605	4.8%	-2.49 [-4.37, -0.61]
Rosenbloom JI 2021	26.5	1.33	83	27.75	1.5	166	12.6%	-1.25 [-1.62, -0.88]
Saviron-Cornudella R 2021	29.2	8.15	22	33.5	5.7	1146	1.9%	-4.30 [-7.72, -0.88]
Yadav V 2020	25.35	3.31	28	26.16	3.32	112	6.8%	-0.81 [-2.18, 0.56]
Total (95% CI)			**2643**			**12888**	**100.0%**	**-0.75 [-1.26, -0.24]**

Heterogeneity: Tau² = 0.50; Chi² = 64.47, df = 14 (P < 0.00001); I² = 78%
Test for overall effect: Z = 2.88 (P = 0.004)

B. Nulliparous women

Study or Subgroup	Positive SARS-CoV-2 Events	Total	Negative SARS-CoV-2 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Adhikari EH 2020	73	252	962	3122	14.0%	0.92 [0.69, 1.21]
Ahlberg M 2020	60	155	247	604	9.9%	0.91 [0.64, 1.31]
Bender WR 2020	3	8	146	310	0.8%	0.67 [0.16, 2.87]
Cardona Pérez JA 2021	56	70	109	169	3.5%	2.20 [1.13, 4.28]
Cruz-Melguizo S 2021	516	1333	644	1596	26.5%	0.93 [0.80, 1.08]
Diaz-Corvillon P 2020	19	37	266	546	3.5%	1.11 [0.57, 2.16]
Flaherman VJ 2021	79	179	32	82	5.3%	1.23 [0.72, 2.10]
Gupta P 2021	45	108	1542	3057	8.8%	0.70 [0.48, 1.04]
Hcini N 2021	30	137	94	370	6.6%	0.82 [0.52, 1.31]
Patberg ET 2020	24	77	29	56	3.1%	0.42 [0.21, 0.86]
Pineles BL 2020	20	77	291	858	5.3%	0.68 [0.40, 1.16]
Rosenbloom JI 2021	31	83	63	166	5.1%	0.97 [0.57, 1.68]
Saviron-Cornudella R 2021	13	22	587	1146	2.2%	1.38 [0.58, 3.24]
Trahan MJ 2021	15	45	85	225	3.4%	0.82 [0.42, 1.62]
Yadav V 2020	8	28	34	112	2.0%	0.92 [0.37, 2.29]
Total (95% CI)		**2611**		**12419**	**100.0%**	**0.91 [0.80, 1.04]**
Total events	992		5131			

Heterogeneity: Tau² = 0.01; Chi² = 17.19, df = 14 (P = 0.25); I² = 19%
Test for overall effect: Z = 1.40 (P = 0.16)

C. Gestational age at delivery

Study or Subgroup	Positive SARS-CoV-2 Mean	SD	Total	Negative SARS-CoV-2 Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bender WR 2020	38.57	1.28	8	39.14	1.27	310	3.0%	-0.57 [-1.47, 0.33]
Cardona Pérez JA 2021	34.17	5.62	66	34.62	3.65	156	1.2%	-0.45 [-1.92, 1.02]
Chomock R 2021	40.1	3.5	73	40.7	2.9	935	3.4%	-0.60 [-1.42, 0.22]
Cruz-Melguizo S 2021	39.24	0.35	1347	39.5	0.3	1607	20.3%	-0.26 [-0.28, -0.24]
Diaz-Corvillon P 2020	38.6	1.9	37	38.8	1.7	549	5.3%	-0.20 [-0.83, 0.43]
Gupta P 2021	36.6	3.3	108	37.5	2.2	3057	5.3%	-0.90 [-1.53, -0.27]
Patberg ET 2020	39.1	1	77	39.3	1.1	56	10.4%	-0.20 [-0.56, 0.16]
Prabhu M 2020	38.84	1.55	70	39.08	0.96	605	10.2%	-0.24 [-0.61, 0.13]
Rosenbloom JI 2021	38.5	0.33	83	38.5	0.33	166	19.3%	0.00 [-0.09, 0.09]
Saviron-Cornudella R 2021	39.62	0.53	22	39.42	0.07	1146	15.0%	0.20 [-0.02, 0.42]
Trahan MJ 2021	38.9	2.2	45	38.8	2.5	225	4.3%	0.10 [-0.62, 0.82]
Yadav V 2020	36.8	2.49	28	37.95	2.31	112	2.4%	-1.15 [-2.17, -0.13]
Total (95% CI)			**1964**			**8924**	**100.0%**	**-0.19 [-0.36, -0.02]**

Heterogeneity: Tau² = 0.04; Chi² = 56.71, df = 11 (P < 0.00001); I² = 81%
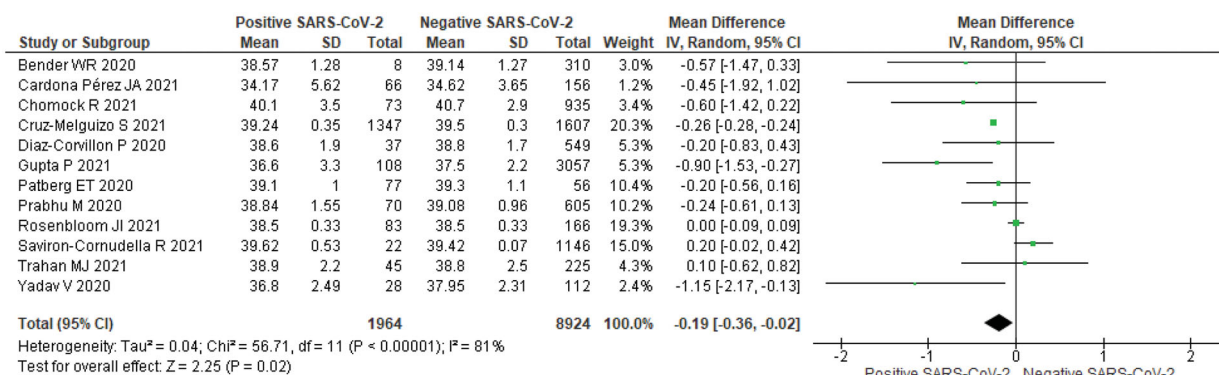Test for overall effect: Z = 2.25 (P = 0.02)

Figure 2. Forest plots comparing positive and negative PCR tested pregnant women. Results are presented as mean difference or odds ratio (OR) and their 95% confidence interval (CI). From the top to the bottom: maternal age (A), nulliparity (B), gestational age at delivery (C), preeclampsia/hypertensive disorders of pregnancy (D), gestational diabetes mellitus (E), and smoking/tobacco consumption (F).

D. Preeclampsia / hypertensive disorders of pregnancy
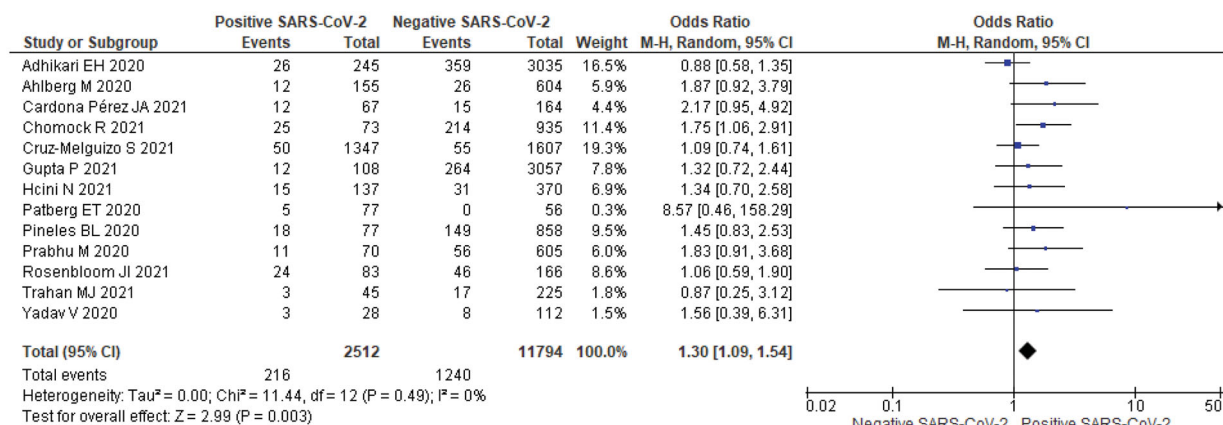
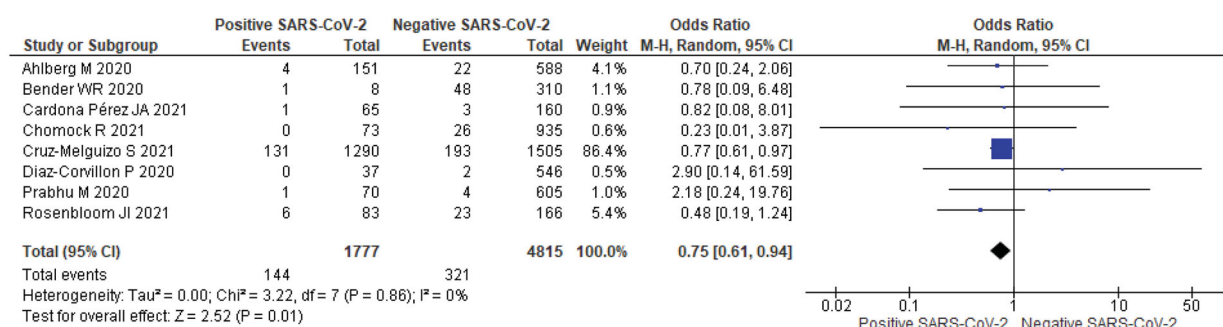## E. Gestational diabetes mellitus
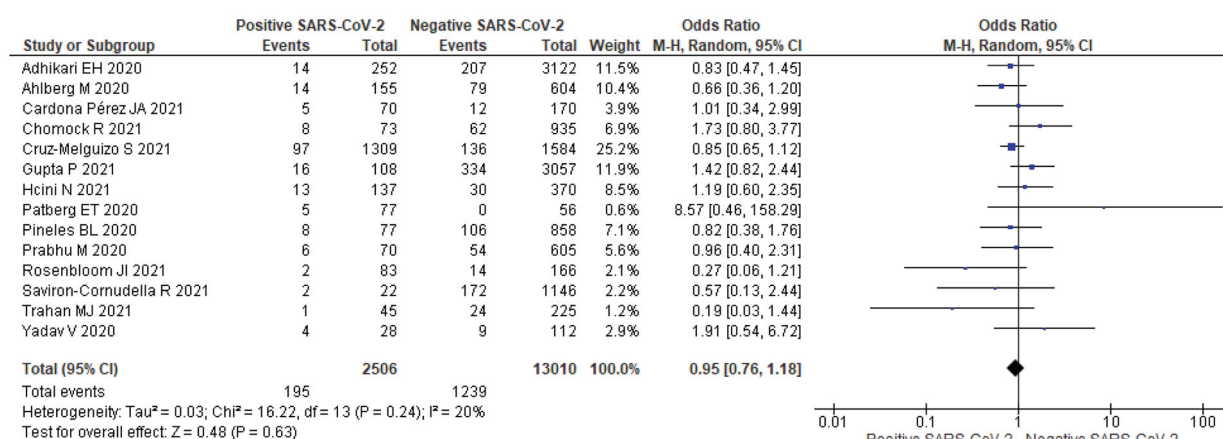
F. Smoking/tobacco use

Figure 2. Continued.

Figure 2D). The odds for presenting gestational diabetes among cases and controls were similar (Figure 2E). Lower odds for smoking were found among positive SARS-CoV-2 tested pregnant women (OR 0.75, 95% CI = 0.61 − 0.94, Figure 2F) as compared to controls. Positive tested pregnant women did not have higher odds for obesity (>30 kg/m²; Supplemental Figure 2A), pregestational diabetes mellitus (Supplemental Figure 2B), chronic hypertension (Supplemental Figure 2C), chronic cardiac disease (Supplemental Figure 2D), and asthma (Supplemental Figure 2E).

Clinical evolution of labor and delivery was not influenced by the presence of SARS-CoV-2 infection. There were similar odds for spontaneous vaginal

A. Spontaneous vaginal delivery
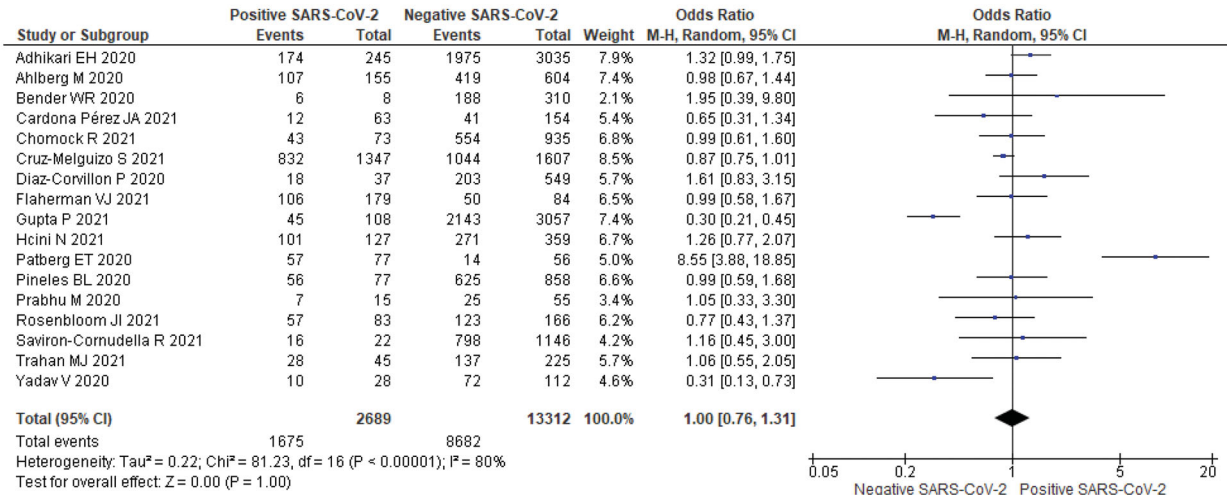
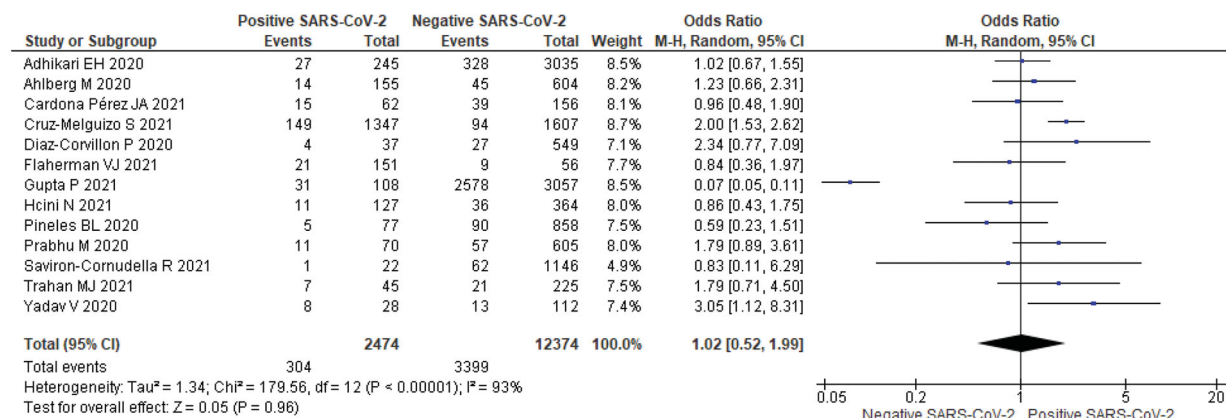## B. Instrumental / operative vaginal delivery
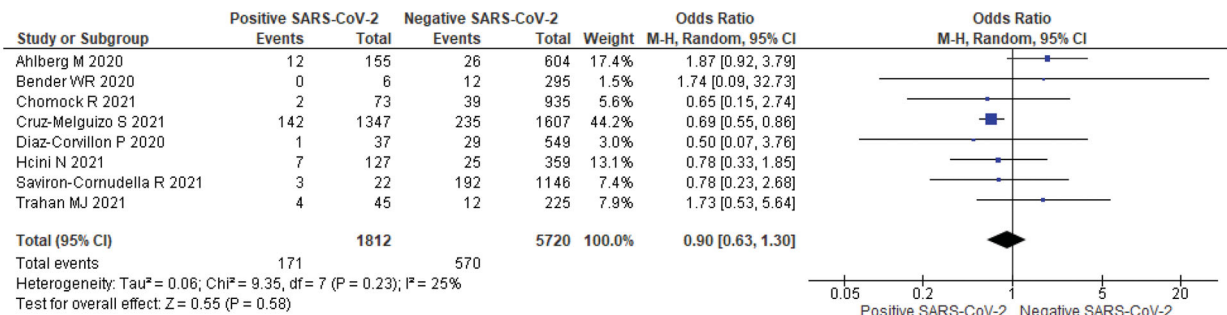
C. Cesarean delivery
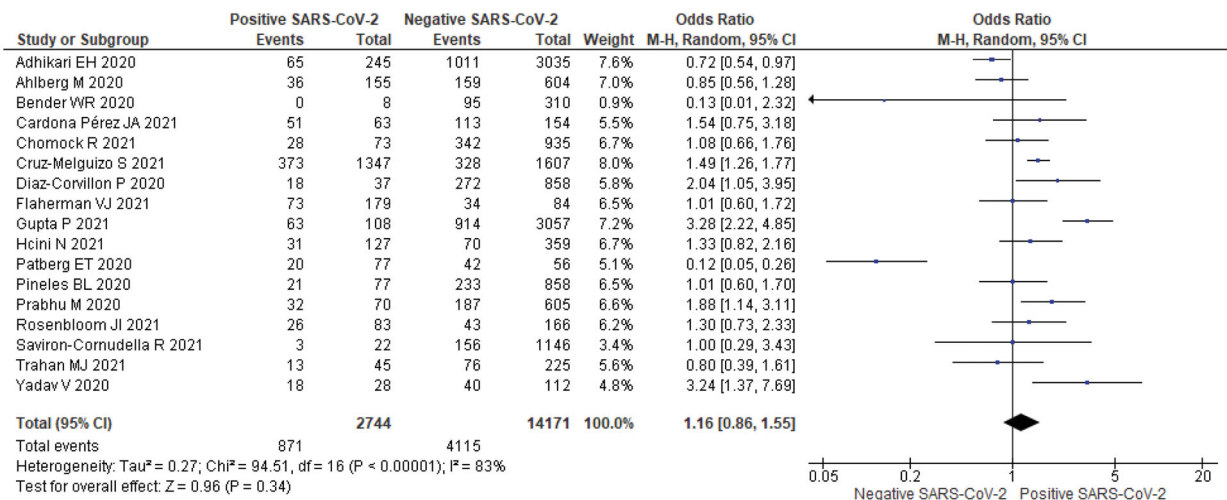
Figure 3. Forest plots comparing positive and negative PCR tested pregnant women. Results are presented as odds ratio (OR) and their 95% confidence interval (CI). From the top to the bottom: spontaneous vaginal delivery (A), instrumental/operative vaginal delivery (B), a cesarean delivery (C), labor induction (D), preterm birth (< 37 weeks, (E) and < 34 weeks, (F)), and placental abruption (G).

D. Labor induction
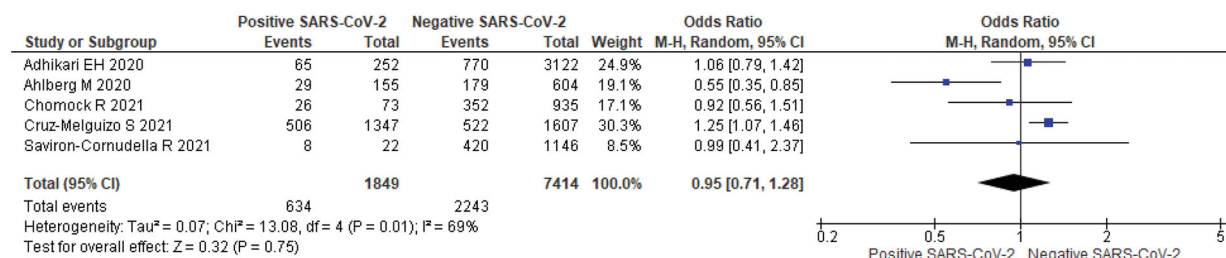
E. Preterm birth (< 37 weeks)

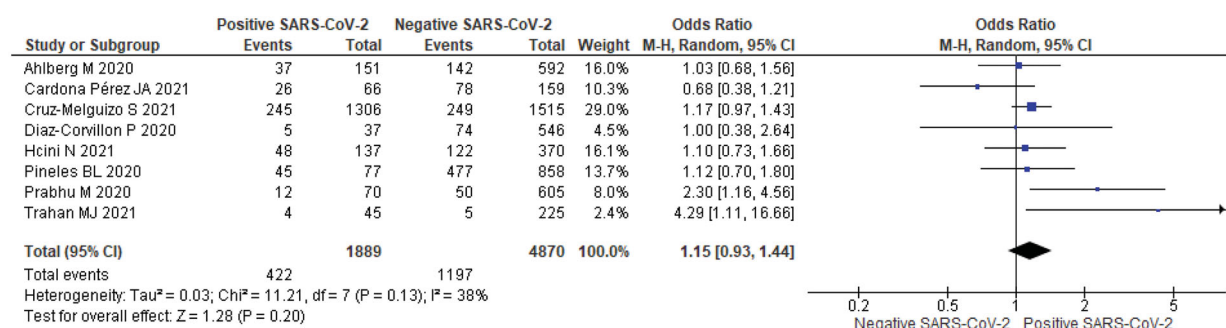## F. Preterm birth (< 34 weeks)
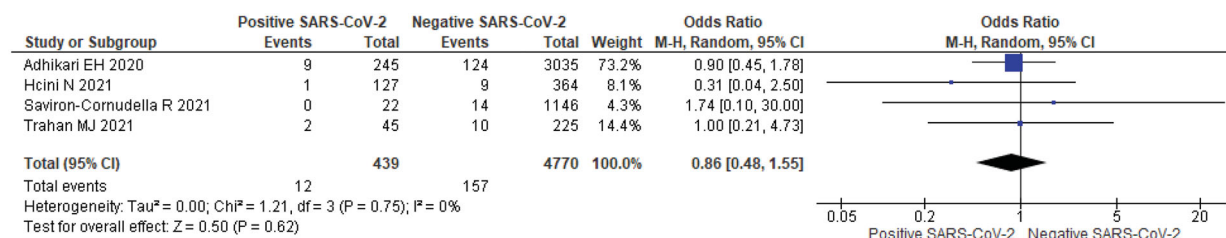
G. Placental abruption

Figure 3. Continued.

delivery (Figure 3A), instrumental/operative vaginal delivery (Figure 3B), a cesarean delivery (Figure 3C), labor induction (Figure 3D), preterm birth before 37 (Figure 3E) or before 34 weeks (Figure 3F), and placental abruption (Figure 3G). Similar odds were also observed for chorioamnionitis (Supplemental Figure 2A), intrapartum fever (Supplemental Figure 2B), meconium staining of the amniotic fluid

(Supplemental Figure 2C), and postpartum hemorrhage (>500 ml) (Supplemental Figure 2D).

Regarding perinatal outcomes, there were similar odds for 5 min Apgar scores <7 (Figure 4A), and neonatal metabolic acidosis (Figure 4B). Contrary to this, positively tested pregnant women had significant odds for NICU admissions (OR = 2.37, 95% CI 1.18 − 4.76, Figure 4C), stillbirths (OR = 2.70, 95% CI 1.38 − 5.29, Figure 4D), and perinatal mortality (OR = 3.23, 95% CI 1.23 − 8.52, Figure 4E). Odds for fetal malformations (Figure 4F), and small-for-gestational-age infants (Figure 4G) did not differ between positive and negative tested pregnant women.

There were three maternal deaths among PCR positive tested pregnant women [16,19] and seven among those tested negative [19]. Of a total of 2,769 positive tested pregnant women, only 129 neonates were tested for SARS-CoV-2 and 20 of them were positive (Table 1).

Publication bias and subgroup analysis results

According to funnel plots, there was evidence of a small study effect for gestational age at delivery (Supplemental Figure 3A), preeclampsia risk (Supplemental Figure 3B), preterm birth risk (Supplemental Figure 3C), and neonatal birth weight (Supplemental Figure 3D). Although the "trim and fill" analysis is recommended to examine the impact of potentially missed or unpublished studies on the pooled estimates, this procedure has poor performance in the presence of between-study heterogeneity [7,28,29]. Therefore, we followed the Cordero and Dans [29] recommendation of subgroup analyses (Supplemental Figure 4–9).

Gestational age at delivery was lower in pregnant women living in LMICs or case-control and cross-sectional studies (without universal SARS-CoV-2 screening) in comparison to pregnant women living in HICs and to those with universal SARS-CoV-2 screening (Supplemental Figure 4A,B). Odds for preeclampsia/hypertensive disorders of pregnancy risk were significantly higher among women living in LMICs and without universal SARS-CoV-2 screening programs (Supplemental Figure 5A,B). Odds for the risk of preterm birth before 37 weeks and admissions to NICUs were not significantly different between positive and negative tested pregnant women living in LMICs (Supplemental Figure 6A,B) or those without universal SARS-CoV-2 screening programs (Supplemental Figure 7A,B).

Odds for the risk of stillbirth did not differ between women living in countries with HICs or LMICs (Supplemental Figure 8A), and the odds for stillbirths were higher in two meta-analyzed studies for mothers included in case-control and cross-sectional studies (Supplemental Figure 8B). Odds for perinatal mortality did not differ for women living in LMICs or HICs (Supplemental Figure 9A) or women included in case-control and cross-sectional studies (Supplemental Figure 9B).

Sensitivity analysis results

One-study leave-out sensitivity analyses for gestational age at delivery, preeclampsia, preterm birth, NICU admission, stillbirths and perinatal mortality are displayed in Supplemental Table 4. Preeclampsia, stillbirths and perinatal mortality had low heterogeneity (I^2) values, suggesting the robustness of results. The very high heterogeneity ($I^2 > 80\%$) for gestational age at delivery was reduced to 56% when one study was deleted [16]. A similar phenomenon was detected concerning the odds for preterm birth (37 weeks), high heterogeneity ($I^2 > 90\%$) that was reduced to $I^2 = 47\%$ by deleting one study [19]. On the contrary, the high heterogeneity ($I^2 = 86\%$) for admission to the NICU was only mildly reduced to $I^2 = 64\%$ by deleting one study [22].

Discussion

This systematic review and meta-analysis were based on observational studies that included positive PCR tested pregnant women (asymptomatic and symptomatic) matched to those with negative results before delivery. The 17 studies included a few SARS-CoV-2 cases with severe symptoms. We found that compared to negative PCR tested delivering pregnant women, those with a positive test were younger, delivered at an earlier gestational age, smoked less, and had higher odds for preeclampsia/hypertensive disorders of pregnancy, NICU admissions, stillbirths, and perinatal mortality. Sub-analyses suggest that the odds for earlier gestational age at delivery and preeclampsia were increased in both LMIC and HIC and in all types of observational studies. Odds for preterm birth (< 37 weeks), NICU admissions and stillbirths were not influenced by the level of income of the country level nor the design of the studies. The odds for perinatal mortality were increased in those living in LMIC countries. There were 3 maternal deaths among positive tested pregnant women, and 7 among those tested negative.
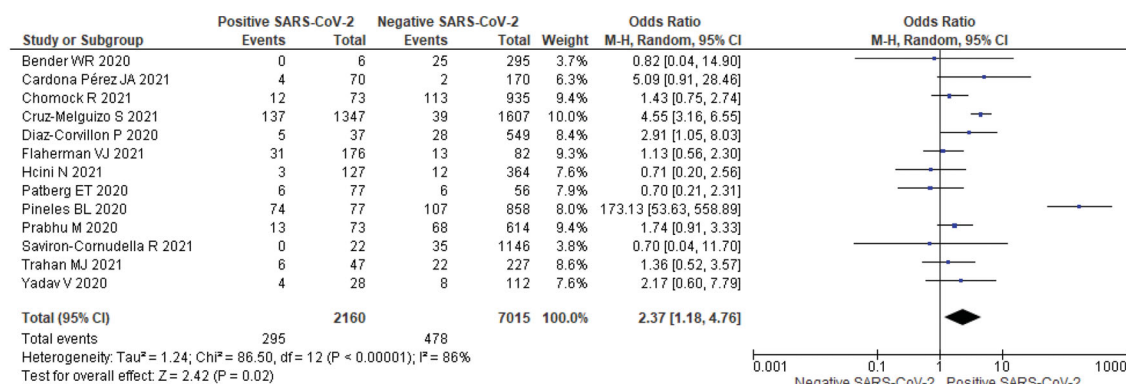
A. 5 minutes Apgar test score < 7
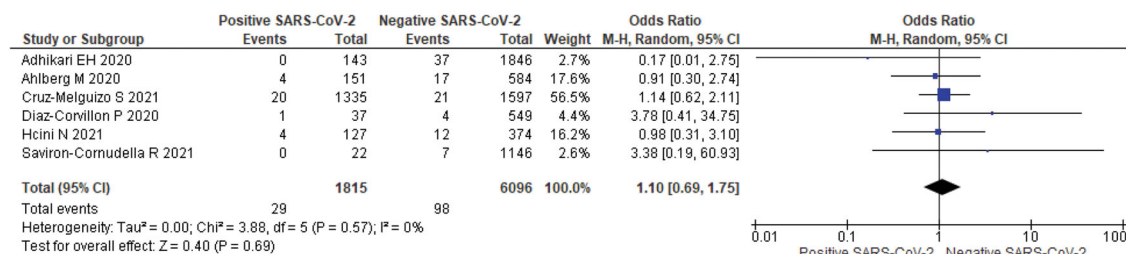
B. Neonatal metabolic acidosis
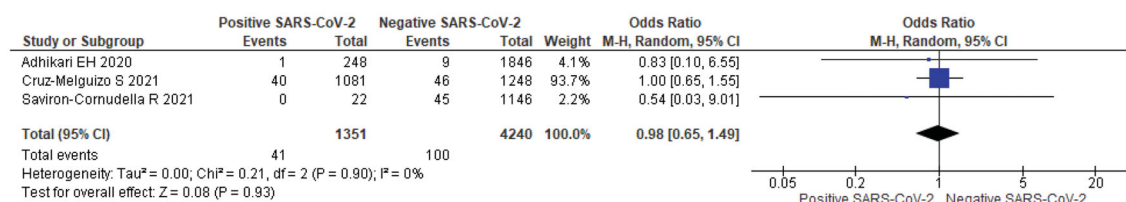
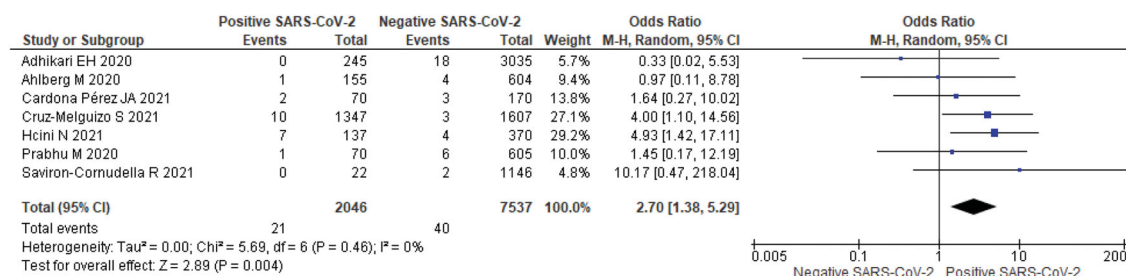## C. NICU admission

D. Stillbirth

Figure 4. Forest plots comparing positive and negative PCR tested pregnant women. Results are presented as odds ratio (OR) and their 95% confidence interval (CI). From the top to bottom: 5 min Apgar tests score < 7 (A), neonatal metabolic acidosis (B), NICU admissions (C), stillbirths (D), perinatal mortality (E), fetal malformations (F), and small-for-gestational-age infants (G).

Eleven studies reported 20 positive PCR newborns out of 129 tested ones.

Pre-gestational co-morbidity

Pregnant women with severe forms of SARS-CoV-2 infection frequently have some predisposing conditions that favor a more severe course of the disease.

Reichelt et al. [30] reported that the prevalence of obesity and hyperglycemia were increased in pregnancies complicated with severe SARS-CoV-2 infection. The pandemic confinement also increased the risk of hypothyroxinemia during the first and second trimesters of pregnancy [31]. Severe and critical forms of maternal SARS-CoV-2 infection have been previously described as well as the preexisting co-

E. Perinatal mortality
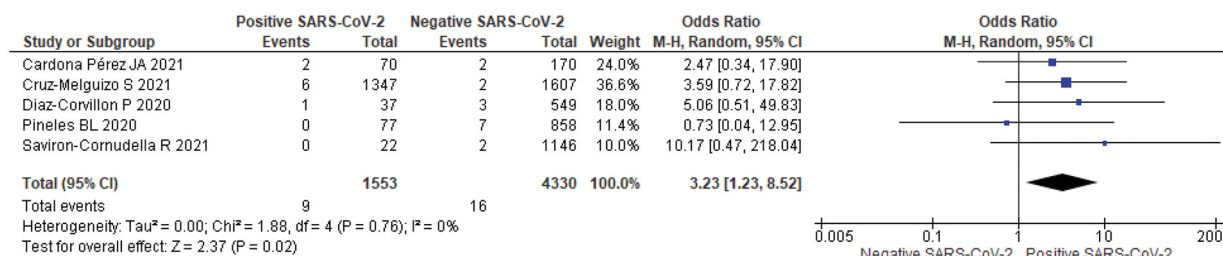
F. Fetal malformations
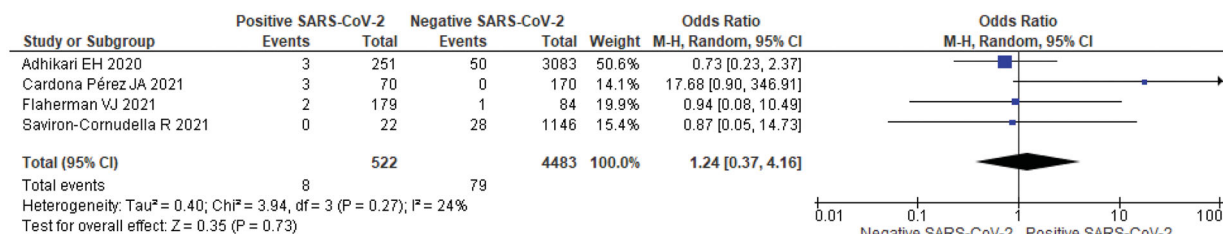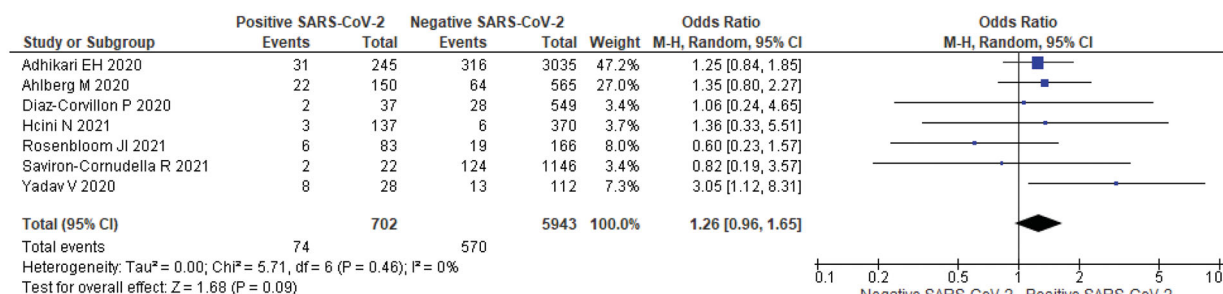

G. Small for gestational age

Figure 4. Continued.

morbid conditions, including pulmonary complications, cardiac disease, obesity and smoking [32]. When comparing positive and negative PCR tested pregnant women, our meta-analyses did not find significant differences in the prevalence of the following co-morbid conditions: obesity (BMI > 30 kg/m^2), pre-gestational diabetes mellitus, chronic hypertension, chronic cardiac disease, and asthma. The previous suggestion that some pre-gestational conditions may increase the risk of SARS-CoV-2 may be biased due to the selection of certain populations that appeared during the beginning of the pandemic or to a mixture of cultural, ethnical and socio-economical factors [33]. Furthermore, initial studies were mostly based on severe cases, many of them requiring the admission to adult ICUs, the use of anti-coagulation, and/or ventilatory assistance, whereas the spectrum of symptoms among SARS-CoV-2 infected pregnant women may vary from none, mild or severe, as we have meta-analyzed herein.

The present meta-analysis included studies based on universal PCR SARS-CoV-2 screening. However, we must take into consideration the limited value of PCR screening, since some pregnant women may display negative results despite being previously exposed to the SARS-CoV-2; as can be demonstrated by serological testing [34]. Therefore, some SARS-CoV-2 exposed pregnant women may be underdiagnosed if based on PCR testing yet be diagnosed through serological testing. These maternal antibodies can be demonstrated in the fetal circulation when maternal infections were more than 2 months before delivery, thus promoting passive immunity that may protect infants for up to six months [35]. Due to the possible transfer of maternal antibodies to the fetus, there is a need to be cautious when it comes to interpreting PCR testing in the infant.

Preeclampsia and SARS-CoV-2 infection

Preeclampsia is a highly specific pregnancy-associated syndrome causing adverse outcomes in pregnant women with SARS-CoV-2, including maternal and fetal morbidity and mortality [36]. An increased risk of preeclampsia and hypertensive disorders of pregnancy may be considered a central complication of severe maternal SARS-CoV-2 infection; as found in the present meta-analysis that included both pregnant women who were symptomatic (mild ore severe) or asymptomatic. Our results show that compared to negative PCR tested pregnant women, those positive displayed higher odds for preeclampsia/hypertensive disorders of pregnancy; even if asymptomatic SARS-CoV-2 exposed pregnant women are included in the analysis.

Preeclampsia may probably be the initial manifestation of pro-inflammatory and/or metabolic responses to viral products, and if co-existing, pregnancy may present later obstetrical complications [37], like the ones described in our study. If the infection is sustained during pregnancy, placental mal-perfusion and inflammatory products might contribute to negative clinical consequences for both the mother and the neonate. Despite this, there is evidence questioning the role of inflammation in the development of preeclampsia, giving preference to cardiovascular and metabolic alterations as the initiators of the placental disorder found among preeclampsia patients [38]. In general, future studies of SARS-CoV-2 pregnant women should include the early evaluation of inflammatory and metabolic markers related to the risk of developing preeclampsia/hypertensive disorders of pregnancy in order to provide early medical intervention.

Other neonatal and maternal outcomes

Previous meta-analyses of studies that included pregnant women with confirmed SARS-CoV-2 infection have found a higher risk of preterm birth, low birth weight neonates, NICU admissions, stillbirths with a small percentage of neonates being positive for SARS-CoV-2 [36]. Some studies have even reported that the risk of preterm birth is two-fold among pregnant women with severe symptomatic SARS-CoV-2 infections [39]. Despite this, the Yang et al. [40] meta-analysis found that preterm birth risk was reduced during the SARS-CoV-2 pandemic while the rate of stillbirth and perinatal mortality were similar to the pre-pandemic period. The present meta-analysis found no differences between positive and negative tested pregnant women in terms of preterm birth, mode of delivery, chorioamnionitis, intrapartum fever, placental abruption and postpartum hemorrhage. Several of these outcomes were reported only in some studies, hence, our results should be interpreted with caution until more studies with larger samples are available. All the above-mentioned adverse outcomes, including preeclampsia, inflammation and fibrin deposition are key pathophysiological factors. Despite this, there are different degrees of placental damage associated with the SARS-CoV-2 infection [41], and it is possible that in mild maternal infections (with mild or nil symptoms) placental function is not sufficiently altered or has a minimal lesion, hence retaining its protective barrier function without compromising fetal growth or life especially when the screening is during delivery.

Some studies, but not all, have reported a higher risk of preterm birth associated with critical cases or severe forms of maternal SARS-CoV-2 infection. In the present meta-analysis, some pregnant women with severe or critical symptoms were assisted at different hospitals [14]; therefore, the results of earlier pandemic studies are not comparable to those reported here. Our meta-analysis did not find a higher risk of preterm birth before 34 or 37 weeks. This may be due to the inclusion of asymptomatic or mild cases. Nevertheless, one meta-analysis compared preterm birth rates before and during the pandemic, finding no differences [42]. Preterm birth among critically infected pregnant women deserves a separate analysis since the earlier interruption of gestation may probably be related to avoiding maternal or fetal intrauterine death. Furthermore, these types of cases were a minority among the meta-analyzed articles herein.

The higher odds found for stillbirths and perinatal mortality among positive pregnant women as compared to negative ones are important issues for obstetrical care. The placentas of term SARS-CoV-2 infected pregnant women display villous trophoblast necrosis and inflammatory infiltration and fibrinoid deposition even in the absence of local viral placental infection [43] and also a significant increase of placental angiotensin-converting enzyme, that is associated with complications such as preeclampsia and robust immune responses even in the absence of local viral infection [44]. These placental protective mechanisms against infection may also contribute to the appearance of poor pregnancy outcomes such as stillbirths and perinatal mortality. It is likely that those outcomes are consequences or part of a spectrum of causes expressed during pregnancy or early after birth. A recent meta-analysis of a small sample suggested that intrauterine death rates were not significantly different

between positive and negatively tested pregnant women [45]. Some previous studies have suggested that critical maternal cases may be associated with higher rates of stillbirths and perinatal mortality [46]. In our study, the direct comparison of a large sample of positive and negative SARS-CoV-2 pregnant women indicates that those risks are also present in non-critically infected pregnant women.

In the present study, 20 infants were positive for SARS-CoV-2 out of only 129 positive tested infants. It seems that the risk of vertical viral transmission is very low, even among severe infections, and mostly due to in-utero hematogenous dissemination [47]. Maternal mortality was very low in our study (two deaths in positive cases and seven among negatives). All previous reports of maternal deaths were found in pregnant women with pre-gestational morbid conditions or severe/critical SARS-CoV-2 pneumonia [48]. It is likely that the severity of maternal SARS-CoV-2 infection may correlate with maternal and neonatal risks.

Strength and limitations

The main strength of the present meta-analysis is the comparison of positive and negative pregnant women tested through PCR near or during labor and delivery. Positive tested pregnant women included those with clinical symptoms (mild to severe) and those asymptomatic. Previous meta-analyses had limitations regarding the diagnosis of controls who were not tested with PCR or controls were selected from pre-pandemic populations. A second strength is the inclusion of pregnant women with a wide spectrum of clinical symptoms, whereas previous studies have been based on severe cases. Another strength was that the search had no language restrictions and we made an effort not to include duplicated publications. Indeed, some studies have periodically published updates or included information in different cooperative studies. The results of our meta-analysis should be considered robust, as it includes 2,769 positive laboratory-tested pregnant women and 13,807 tested negatives.

Despite the aforementioned strengths, our meta-analysis has several limitations, including clinical diversity (types of observational studies), types of populations along with the pandemic duration, mixing pregnant women with and without symptoms. In addition, some studies included a small number of SARS-CoV-2 positive pregnant women and clinical diversity and reporting on a small number of outcomes. Contrary to this, one cross-sectional study [16] contributed with a large sample of both positive and negative pregnant women that might have exaggeratedly influenced both the MD and OR of some of the measured outcomes. A second limitation is a fact that negative PCR results near delivery may include pregnant women that may have had a SARS-CoV-2 infection early during pregnancy without maternal or neonatal adverse outcomes [34]. Therefore, they might be diagnosed as PCR negative before delivery (non-infected) which may erroneously be categorized as non-exposed to the virus [49].

One also needs to take into account the heterogeneity of several of the outcomes mainly related to study design. For instance, the study of Cruz-Melguizo et al. [16] was found upon the sensitivity analysis to be causing heterogeneity ($I^2 = 81\%$) for gestational age at delivery, probably because a large proportion of pregnant women had no controls during the initial pandemic period while posteriorly there was a change to a close universal screening. When this study has deleted the difference for gestational age upon delivery disappeared. The study of Gupta et al. [19] was found to be causing heterogeneity for preterm birth < 37 weeks; when the study was eliminated upon sensitivity analysis, the odds became significant.

Conclusions

Seventeen observational studies from eight countries, with low to moderate risk of bias, reported 2,769 pregnant women with a positive SARS-CoV-2 PCR test and 13,807 with a negative test. Pregnant women with a positive PCR test were younger, delivered at an earlier gestational age, smoked less and associated with higher odds for preeclampsia/hypertensive disorders of pregnancy, NICU admissions, stillbirths and perinatal mortality. There were no significant differences between positive and negative tested women in terms of nulliparity, multiple pregnancies, gestational diabetes, route of delivery, labor induction, preterm birth, birth weight, and 5 min Apgar scores < 7, small-for-gestational-age infants and fetal malformations. Eleven studies reported on 129 SARS-CoV-2 PCR tested infants from positive PCR pregnant women, of which 20 were PCR positive. There were three maternal deaths among positive PCR tested pregnant women and seven among negatives. Better-designed studies should be planned to overcome the heterogeneity of results in order to provide more precise information regarding maternal and perinatal outcomes.

Acknowledgement

Ethics approval

None required. The present meta-analysis was based on published articles. All summary data generated during this study are included in this published article. Raw data used for the analyses are available in the original reviewed articles

Disclosure statement

The authors have no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Faustino R. Pérez-López (iD) http://orcid.org/0000-0002-2801-416X
Ricardo Savirón-Cornudella (iD) http://orcid.org/0000-0001-9585-0187
Peter Chedraui (iD) http://orcid.org/0000-0002-1556-3979
María T. López-Baena (iD) http://orcid.org/0000-0002-9890-8003
Gonzalo Pérez-Roncero (iD) http://orcid.org/0000-0001-8137-4837
Ana Sanz-Arenal (iD) http://orcid.org/0000-0002-5523-1637
Marta Narváez-Salazar (iD) http://orcid.org/0000-0002-6403-6585
Peña Dieste-Pérez (iD) http://orcid.org/0000-0002-0488-1832
Mauricio Tajada (iD) http://orcid.org/0000-0003-4720-8231

References

[1] WHO scientific brief. Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2, 2021. [updated 2021 February 8; cited 2021 July 30]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-mother-to-child-transmission-2021.1.

[2] Salem D, Katranji F, Bakdash T. COVID-19 infection in pregnant women: review of maternal and fetal outcomes. Int J Gynecol Obstet. 2021;152(3):291–298.

[3] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–341.

[4] Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[5] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7(3):177–188.

[6] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414): 557–560.

[7] von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Methodol. 2015;15:35.

[8] The World's Richest and Poorest Countries 2021. [cited 2021 July 20]. Available from: https://www.gfmag.com/global-data/economic-data/worlds-richest-and-poorest-countries.

[9] Schellekens P, Sourrouille D. 2020. COVID-19 mortality in rich and poor countries: a tale of two pandemics? Policy research working paper; No. 9260. World Bank, Washington, DC. [cited 2021 July 20]. Available from: https://openknowledge.worldbank.org/handle/10986/33844.

[10] Cochrane Handbook. Part 2: General methods for Cochrane reviews > 9 Analysing data and undertaking meta-analyses > 9.7 Sensitivity analyses. [cited 2021 July 20]. Available from: https://handbook-5-1.cochrane.org/chapter_9/9_7_sensitivity_analyses.htm.

[11] Adhikari EH, Moreno W, Zofkie AC, et al. Pregnancy outcomes among women with and without severe acute respiratory syndrome coronavirus 2 infection. JAMA Netw Open. 2020;3(11):e2029256.

[12] Ahlberg M, Neovius M, Saltvedt S, et al. Association of SARS-CoV-2 test status and pregnancy outcomes. JAMA. 2020;324(17):1782–1785.

[13] Bender WR, Hirshberg A, Coutifaris P, et al. Universal testing for severe acute respiratory syndrome coronavirus 2 in 2 philadelphia hospitals: carrier prevalence and symptom development over 2 weeks. Am J Obstet Gynecol Mfm. 2020;2(4):100226.

[14] Cardona-Pérez JA, Villegas-Mota I, Helguera-Repetto AC, et al. Prevalence, clinical features, and outcomes of SARS-CoV-2 infection in pregnant women with or without mild/moderate symptoms: results from universal screening in a tertiary care center in Mexico city, Mexico. PLOS One. 2021;16(4):e0249584.

[15] Chornock R, Iqbal SA, Wang T, et al. Incidence of hypertensive disorders of pregnancy in women with COVID-19. Am J Perinatol. 2021;38(8):766–762.

[16] Cruz Melguizo S, de la Cruz Conty ML, Carmona Payán P, et al. Pregnancy outcomes and SARS-CoV-2 infection: the Spanish obstetric emergency group study. Viruses. 2021;13(5):853.

[17] Díaz-Corvillón P, Mönckeberg M, Barros A, et al. Routine screening for SARS CoV-2 in unselected pregnant women at delivery. PLOS One. 2020;15(9):e0239887.

[18] Flaherman VJ, Afshar Y, Boscardin J, et al. Infant outcomes following maternal infection with SARS-CoV-2: First report from the PRIORITY study. Clin Infect Dis. 2021;73(9):e2810–e2813.

[19] Gupta P, Kumar S, Sharma SS. SARS-CoV-2 prevalence and maternal-perinatal outcomes among pregnant women admitted for delivery: experience from COVID-19-dedicated maternity hospital in Jammu, Jammu And Kashmir (India). J Med Virol. 2021;93(9):5505–5514.

[20] Hcini N, Maamri F, Picone O, et al. Maternal, fetal and neonatal outcomes of large series of SARS-CoV-2 positive pregnancies in peripartum period: a single-center prospective comparative study. Eur J Obstet Gynecol Reprod Biol. 2021;257:11–18.

[21] Patberg ET, Adams T, Rekawek P, et al. Coronavirus disease 2019 infection and placental histopathology

in women delivering at term. Am J Obstet Gynecol. 2021;224(4):382.e1–382.e18.

[22] Pineles BL, Alamo IC, Farooq N, et al. Racial-ethnic disparities and pregnancy outcomes in SARS-CoV-2 infection in a universally-tested cohort in Houston, Texas. Eur J Obstet Gynecol Reprod Biol. 2020;254: 329–330.

[23] Prabhu M, Cagino K, Matthews KC, et al. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York city: a prospective cohort study. BJOG: Int J Obstet Gy. 2020; 127(12):1548–1556.

[24] Rosenbloom JI, Raghuraman N, Carter EB, et al. Coronavirus disease 2019 infection and hypertensive disorders of pregnancy. Am J Obstet Gynecol. 2021; 224(6):623–624.

[25] Savirón-Cornudella R, Villalba A, Esteban LM, et al. Screening of severe acute respiratory syndrome coronavirus-2 infection during labor and delivery using polymerase chain reaction and immunoglobulin testing. Life Sci. 2021;271:119200.

[26] Trahan MJ, Malhamé I, O'Farrell P, et al. Obstetrical and newborn outcomes among patients with SARS-CoV-2 during pregnancy. J Obstet Gynaecol Can. 2021;43(7):888–892.e1.

[27] Yadav V, Goel N, Afreen N, et al. COVID 19 in pregnancy; obstetrical and neonatal outcomes: a retrospective comparative study. IJOGR. 2020;7(4):584–589.

[28] Shi L, Lin L. The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. Medicine. 2019; 98(23):e15987.

[29] Cordero CP, Dans AL. Key concepts in clinical epidemiology: detecting and dealing with heterogeneity in meta-analyses. J Clin Epidemiol. 2021;130:149–151.

[30] Reichelt AJ, Hirakata VN, Genro VK, et al. A snapshot of the prevalence of endocrine disorders in pregnancies complicated by coronavirus disease 2019: a narrative review with meta-analysis. Int J Gynaecol Obstet. 2021;154(2):204–211.

[31] Hua J, Shen J, Zhang J, et al. The association between COVID-19 pandemic and maternal isolated hypothyroxinemia in first and second trimesters. Psychoneuroendocrinology. 2021;128:105210.

[32] Pierce-Williams RAM, Burd J, Felder L, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. Am J Obstet Gynecol MFM. 2020;2(3):100134.

[33] Aabakke A, Krebs L, Petersen TG, et al. SARS-CoV-2 infection in pregnancy in Denmark – characteristics and outcomes after confirmed infection in pregnancy: a nationwide, prospective, population-based cohort study. Acta Obstet Gynecol Scand. 2021;100(11):2097–2110.

[34] Molenaar NM, Rommel AS, de Witte L, et al. Seroprevalence of SARS-CoV-2 during pregnancy and associated outcomes: results from an ongoing prospective cohort study. Paediatr Perinat Epidemiol. 2021. In press.

[35] Flannery DD, Gouma S, Dhudasia MB, et al. Transplacental Transfer of SARS-CoV-2 Antibodies. JAMA Pediatr. 2021;175(6):594–600.

[36] Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020; 370:m3320.

[37] Chappell LC, Cluver CA, Kingdom J, et al. Pre-eclampsia. Lancet. 2021;398(10297):341–354.

[38] Stepan H, Hund M, Andraczek T. Combining biomarkers to predict pregnancy complications and redefine preeclampsia: the angiogenic-placental syndrome. Hypertension. 2020;75(4):918–926.

[39] Lassi ZS, Ana A, Das JK, et al. A systematic review and meta-analysis of data on pregnant women with confirmed COVID-19: clinical presentation, and pregnancy and perinatal outcomes based on COVID-19 severity. J Glob Health. 2021;11:05018.

[40] Yang J, D'Souza R, Kharrat A, et al. COVID-19 pandemic and population-level pregnancy and neonatal outcomes: a living systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2021;100(10): 1756–1770.

[41] Bouachba A, Allias F, Nadaud B, et al. Placental lesions and SARS-Cov-2 infection: diffuse placenta damage associated to poor fetal outcome. Placenta. 2021;112:97–104.

[42] Chmielewska B, Barratt I, Townsend R, et al. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. Lancet Glob Health. 2021;9(6):e759–e772.

[43] Garrido-Pontnou M, Navarro A, Camacho J, et al. Diffuse trophoblast damage is the hallmark of SARS-CoV-2-associated fetal demise. Mod Pathol. 2021; 34(9):1704–1709.

[44] Hecht JL, Quade B, Deshpande V, et al. SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology: a series of 19 placentas from COVID-19-positive mothers. Mod Pathol. 2020;33(11):2092–2103.

[45] Huntley BJF, Mulder IA, Di Mascio D, et al. Adverse pregnancy outcomes among individuals with and without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a systematic review and meta-analysis. Obstet Gynecol. 2021;137(4):585–596.

[46] Gajbhiye RK, Sawant MS, Kuppusamy P, et al. Differential impact of COVID-19 in pregnant women from high-income countries and low- to middle-income countries: a systematic review and meta-analysis. Int J Gynaecol Obstet. 2021;155(1):48–56.

[47] Edlow AG, Li JZ, Collier AY, et al. Assessment of maternal and neonatal SARS-CoV-2 viral load, transplacental antibody transfer, and placental pathology in pregnancies during the COVID-19 pandemic. JAMA Netw Open. 2020;3(12):e2030455.

[48] Hessami K, Homayoon N, Hashemi A, et al. COVID-19 and maternal, fetal and neonatal mortality: a systematic review. J Matern Fetal Neonatal Med. 2020:1–6. In press.

[49] Yasa B, Memur S, Ozturk DY, et al. Severity of maternal SARS-CoV-2 infection in pregnancy predicts neonatal outcomes. Am J Perinatol. 2021. In press. DOI: 10.1055/s-0041-1733783