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SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis

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Introduction

Preeclampsia, a multisystem syndrome that complicates about 5% of pregnancies, is one of the leading causes of maternal mortality worldwide,

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OBJECTIVE: To examine the relationship between SARS-CoV-2 infection during pregnancy and the risk for preeclampsia.

DATA SOURCES: MEDLINE, Embase, POPLINE, CINAHL, LILACS, and the World Health Organization COVID-19, Chinese, and preprint databases (all from December 1, 2019, to May 31, 2021). Google Scholar, bibliographies, and conference proceedings were also searched.

STUDY ELIGIBILITY CRITERIA: Observational studies that assessed the association between SARS-CoV-2 infection during pregnancy and preeclampsia and that reported unadjusted and/or adjusted risk estimates and 95% confidence intervals or data to calculate them.

STUDY APPRAISAL AND SYNTHESIS METHODS: The primary outcome was preeclampsia. Secondary outcomes included preeclampsia with severe features, preeclampsia without severe features, eclampsia, and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Two reviewers independently reviewed studies for inclusion, assessed their risk of bias, and extracted data. Pooled unadjusted and adjusted odds ratios with 95% confidence intervals, and 95% prediction interval were calculated. Heterogeneity was quantified using the I^2 statistic, for which $I^2 \geq 30\%$ indicated substantial heterogeneity. Subgroup and sensitivity analyses were performed to test the robustness of the overall findings.

RESULTS: A total of 28 studies comprising 790,954 pregnant women, among which 15,524 were diagnosed with SARS-CoV-2 infection, met the inclusion criteria. The meta-analysis of unadjusted odds ratios showed that the odds of developing preeclampsia were significantly higher among pregnant women with SARS-CoV-2 infection than among those without SARS-CoV-2 infection (7.0% vs 4.8%; pooled odds ratio, 1.62; 95% confidence interval, 1.45–1.82; $P<.00001$; $I^2=17\%$; 26 studies; 95% prediction interval of the odds ratio, 1.28–2.05). The meta-analysis of adjusted odds ratios also showed that SARS-CoV-2 infection during pregnancy was associated with a significant increase in the odds of preeclampsia (pooled odds ratio, 1.58; 95% confidence interval, 1.39–1.80; $P<.0001$; $I^2=0\%$; 11 studies). There was a statistically significant increase in the odds of preeclampsia with severe features (odds ratio, 1.76; 95% confidence interval, 1.18–2.63; $I^2=58\%$; 7 studies), eclampsia (odds ratio, 1.97; 95% confidence interval, 1.01–3.84; $I^2=0\%$, 3 studies), and HELLP syndrome (odds ratio, 2.10; 95% confidence interval, 1.48–2.97; 1 study) among pregnant women with SARS-CoV-2 infection when compared to those without the infection. Overall, the direction and magnitude of the effect of SARS-CoV-2 infection during pregnancy on preeclampsia was consistent across most prespecified subgroup and sensitivity analyses. Both asymptomatic and symptomatic SARS-CoV-2 infections significantly increased the odds of developing preeclampsial; however, it was higher among patients with symptomatic illness (odds ratio, 2.11; 95% confidence interval, 1.59–2.81) than among those with asymptomatic illness (odds ratio, 1.59; 95% confidence interval, 1.21–2.10).

CONCLUSION: SARS-CoV-2 during pregnancy is associated with higher odds of preeclampsia.

Key words: coronavirus, COVID-19, eclampsia, HELLP syndrome, hepatic damage, hypertension, hypertensive disorders of pregnancy, liver enzymes, maternal morbidity, preeclampsia with severe features, preeclampsia without severe features, proteinuria, thrombocytopenia, viral infection

AJOG at a Glance

Why was this study conducted?

Current evidence indicates that urinary tract infections and periodontal disease during pregnancy are associated with an increased risk for preeclampsia. We performed a systematic review and meta-analysis to assess whether SARS-CoV-2 infection during pregnancy also increases the risk for preeclampsia.

Key findings

Pregnant women with a SARS-CoV-2 infection had significantly increased odds of developing preeclampsia when compared to those without the infection (pooled odds ratio, 1.62; 95% confidence interval, 1.45-1.82). Moreover, SARS-CoV-2 infection during pregnancy was associated with increased odds of developing preeclampsia with severe features, eclampsia, and hemolysis, elevated liver enzymes, low platelet count syndrome. Both asymptomatic and symptomatic SARS-CoV-2 infections significantly increased the risk for preeclampsia.

What does this add to what is known?

Pregnant women with a SARS-CoV-2 infection are more likely to develop preeclampsia. Healthcare professionals should be aware of this association and closely monitor pregnant women with SARS-CoV-2 infection for early detection of preeclampsia.

accounting for approximately 14% of all maternal deaths.[1,2] In 2018, preeclampsia was responsible for 5.3% of maternal deaths in the United States.[3] Preeclampsia is also associated with an increased risk for maternal morbidity and perinatal morbidity and mortality worldwide, mainly in low- and middle-income countries.[4−12] In addition, women with preeclampsia are at a greater risk for developing cardiovascular disease later in life.[7,11−13] Although the etiology of preeclampsia remains unclear, it is currently believed that abnormal placentation leading to later placental malperfusion and dysfunction, syncytiotrophoblast stress, oxidative stress, imbalances in circulating placental angiogenic factors, perturbation of the renin-angiotensin system (RAS), placental senescence, inflammation, endothelial dysfunction, and immune abnormalities influenced by maternal genetics, epigenetics, lifestyle, and environmental factors are involved in the pathophysiology of this disorder.[14−29]

In 2008, our group published a systematic review and meta-analysis that demonstrated that urinary tract infection and periodontal disease during pregnancy were associated with a significantly increased risk of preeclampsia.[30] Similar findings were reported in more recent meta-analyses.[31−37] Several studies have assessed the relationship between viral infections during pregnancy, such as those caused by HIV,[38,39] human papillomavirus,[40,41] cytomegalovirus,[42−44] hepatitis B virus,[45−49] herpes simplex virus,[50,51] Epstein-Barr virus,[52] and influenza A (H1N1),[53] and the risk for preeclampsia. The results of these studies have been conflicting. The mechanisms that have been proposed to explain the association between infection during pregnancy and preeclampsia include (1) direct effects of the infectious agents on trophoblast function and the arterial wall, including endothelial injury or dysfunction; (2) acute atherosis; (3) local inflammation that might cause relative uteroplacental ischemia; and (4) indirect effects through exaggerated maternal systemic inflammatory response.[54−59]

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in China in December 2019.[60] Individuals of all ages are at risk for infection and severe disease. Current evidence suggests that pregnancy does not increase susceptibility to SARS-CoV-2 infection, but it appears to worsen the clinical course of COVID-19 when compared to nonpregnant females of the same age.[61,62] Overall, pregnant women with COVID-19 were at higher risk for intensive care unit (ICU) admission, invasive mechanical ventilation use, need for extra corporeal membrane oxygenation, and maternal death than nonpregnant women with COVID-19.[61−74]

Three meta-analyses have compared the risk for adverse maternal and perinatal outcomes between pregnant women with and without SARS-CoV-2 infection.[62,75,76] Results from these studies indicate that pregnant women with SARS-CoV-2 infection have a significant increase in the risk for maternal death, admission to the ICU, preterm birth, and stillbirth when compared to those without SARS-CoV-2 infection. Moreover, infants born to mothers with SARS-CoV-2 infection were more likely to be admitted to the neonatal ICU than those born to mothers without the disease. The relationship between SARS-CoV-2 infection during pregnancy and the risk for preeclampsia has received less attention. This topic is relevant for public health and clinical practice. Hence, we performed a systematic review with the primary aim of compiling and critically assessing the existing evidence about the relationship between SARS-CoV-2 infection during pregnancy and the risk for preeclampsia by using formal methods of systematic review and meta-analytic techniques.

Material and Methods

This systematic review was conducted in accordance with a prospectively registered protocol (PROSPERO number CRD42021239092) and reported in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for meta-analyses of observational studies.[77] Both authors independently reviewed studies for inclusion, assessed their risk of bias, and extracted data. Disagreements were resolved through consensus.

Literature search

To identify potentially eligible studies, we searched MEDLINE, Embase,

CINAHL, LILACS, the World Health Organization COVID-19 database, China National Knowledge Infrastructure, Wanfang, and preprint databases such as medRxiv, bioRxiv, and search.bioPreprint (all from December 1, 2019, to May 31, 2021). Our search terms included a combination of keywords and text words related to *SARS-CoV-2* ("SARS-CoV-2," "COVID-19," "2019-nCoV," "nCov-2019," "SARS-CoV-19," "coronavirus," "betacoronavirus," and "severe acute respiratory syndrome"), *preeclampsia* ("preeclampsia," "eclampsia," "gestosis, EPH," "pregnancy toxemia," "pregnancy-induced hypertension," "hypertensive disorders of pregnancy," "gestational hypertension," "pregnancy-associated hypertension," and "pregnancy hypertension"), and *pregnancy* ("pregnancy," "gestation," and "gravidity"). Google Scholar, proceedings of congresses on obstetrics, maternal-fetal medicine, pediatrics, and neonatology, reference lists of identified studies, previously published systematic reviews, and review articles were also searched. No language restrictions were applied.

Study selection

We included observational studies that assessed the relationship between SARS-CoV-2 infection during pregnancy and preeclampsia and reported unadjusted and/or adjusted odds ratio (OR) or relative risk (RR) estimates and 95% confidence intervals (CIs) or data to calculate these values. The exposed group were pregnant women with a current or previous diagnosis of SARS-CoV-2 infection at any stage of gestation, which was based on a positive reverse transcriptase—polymerase chain reaction (RT-PCR) test result or positive antigen test result in a sample collected from the upper respiratory tract, or a positive result for anti—SARS-CoV-2 antibodies in serum. The unexposed group were pregnant women with a negative RT-PCR or antigen test result in a sample collected from the upper respiratory tract or a negative serum antibody test result, or those who were pregnant and delivered before the pandemic. Given that no routine diagnostic testing for SARS-CoV-2 infection was available at the beginning of the pandemic, we included studies in which pregnant women were assigned to exposed or unexposed groups based on the presence or absence of clinical signs or symptoms and/or computed tomography or radiography images of the chest.

Studies were excluded from the review if they (1) were case series or reports, editorials, comments, reviews, or letters without original data; (2) examined only the relationship between SARS-CoV-2 infection and gestational hypertension (new onset hypertension at $\geq$20 weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction); or (3) did not report risk estimates or CIs and sufficient information to calculate these values could not be retrieved. Studies published only as abstracts were excluded if information on methodological issues and results were not clearly reported. If a study included women with preeclampsia and gestational hypertension, it was not considered for inclusion in the review unless the data for women with preeclampsia were extractable or obtainable separately. For multiple or duplicate publications of the same dataset, we included only the most recent or complete study and supplemented it if additional information appeared in other publications.

Outcome measures

The primary outcome was preeclampsia, defined as hypertension (at or after 20 weeks of gestation in a previously normotensive woman, or that precedes pregnancy or is present before 20 weeks of gestation in a woman with preexisting chronic hypertension) accompanied by one or more of the following features at or after 20 weeks of gestation: proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, neurologic complications,[78,79] or fetal growth restriction.[79] Secondary outcomes included preeclampsia with severe features, preeclampsia without severe features, eclampsia, and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.

Risk of bias assessment

The risk of bias in each included study was assessed by the judgement of 6 domains that were deemed by the authors to be important for the quality of observational studies evaluating the association between SARS-CoV-2 infection during pregnancy and preeclampsia. Each domain was judged as a "low," "high," or "unclear" risk of bias. The domains that were evaluated and how they were interpreted were as follows:

1. *Selection of participants* — "low risk of bias": women, both with and without SARS-CoV-2 infection, were recruited from the same population and during the same time period; "high risk of bias": women, both with and without SARS-CoV-2 infection, were not recruited from the same population or during the same time period.
2. *Inclusion in the exposed cohort* — "low risk of bias": $\geq$90% of included women had a positive RT-PCR or antigen test result or tested positive for the presence of serum SARS-CoV-2 antibodies; "high risk of bias": <90% of included women had a positive RT-PCR or antigen test result or tested positive for serum SARS-CoV-2 antibodies.
3. *Inclusion in the non-exposed cohort* — "low risk of bias": $\geq$90% of included women had a negative RT-PCR or antigen test result or tested negative for the presence of serum SARS-CoV-2 antibodies, or women were drawn from a historical control group who delivered before the beginning of the COVID-19 pandemic; "high risk of bias": <90% of included women had a negative RT-PCR or antigen test result or tested negative for serum SARS-CoV-2 antibodies.
4. *Loss to follow-up or exclusions* — "low risk of bias": losses to follow-up or nonvalid exclusions <10%; "high risk of bias": losses to follow-up or nonvalid exclusions $\geq$10%.
5. *Control for confounding factors* — "low risk of bias": the study controlled for potential confounding factors related to both SARS-CoV-2

infection and preeclampsia; "high risk of bias": the study did not control for potential confounding factors related to both SARS-CoV-2 infection and preeclampsia.

6. *Temporality between the exposure and outcome* — "low risk of bias": the study reported the time elapsed between SARS-CoV-2 infection diagnosis and preeclampsia diagnosis; "high risk of bias": the study did not report the time elapsed between SARS-CoV-2 infection diagnosis and preeclampsia diagnosis.

If there was insufficient information available to make a judgment about the bias of a domain, the domain was scored as having an "unclear risk of bias."

Data extraction

Data were extracted by using a standardized data collection form. The following information was extracted from each study: first author's name, date of publication, geographic location of the study, study design, inclusion and exclusion criteria, characteristics of the study population, sample size, case definition, tests used for diagnosing SARS-CoV-2 infection, gestational age at diagnosis of SARS-CoV-2 infection, severity of SARS-CoV-2 infection, criteria used to include women in the unexposed group, mean or median time elapsed between SARS-CoV-2 infection diagnosis and preeclampsia diagnosis, definition and severity of preeclampsia, confounding factors controlled for by matching or adjustment, report of dose-response gradient, and unadjusted and/or adjusted RRs or ORs with 95% CIs. The corresponding authors of primary studies were contacted to obtain additional information on methods used and/or unpublished relevant data.

Statistical analysis

The exposure (independent) variable was the presence or absence of a current or previous SARS-CoV-2 infection, and the outcome (dependent) variable was the presence or absence of preeclampsia. We estimated pooled unadjusted and adjusted ORs with 95% CIs as the measure of the association between SARS-CoV-2 infection during pregnancy and preeclampsia. The basic data used in the unadjusted analyses consisted of a series of 2×2 tables defined by the dichotomous SARS-CoV-2 infection/non–SARS-CoV-2 infection and preeclampsia/nonpreeclampsia for each study. The results from individual studies were then combined to produce the pooled unadjusted OR with 95% CI by using a random-effects model. This analysis model was chosen because of the high likelihood of between-study variance in observational studies. We also calculated the pooled adjusted OR with 95% CI by only taking into consideration studies that provided an adjusted estimate, either using appropriate methods of analysis or through matching of variables in the study design. The data needed from each study were the estimated adjusted effect (either the adjusted RR or the adjusted OR, the latter being a good approximation of the adjusted RR if the prevalence of the disease is low) and its estimated standard error (often obtained indirectly from the CI reported in the study).

The heterogeneity of the results among studies was evaluated by visually inspecting forest plots and by estimating the quantity I^2.[80] A significant level of heterogeneity was defined as $I^2 \geq 30\%$.[80] Subgroup analyses were performed to test the robustness of the overall findings and to explore potential sources of heterogeneity. We also addressed heterogeneity by calculating the 95% prediction interval for the pooled unadjusted OR, which gives an estimate of the point at which the true effects are to be expected for 95% of similar studies that might be conducted in the future.[81–83] Prespecified subgroup analyses were carried out according to the severity of SARS-CoV-2 infection (asymptomatic illness vs symptomatic illness), study design (retrospective cohort vs prospective cohort vs cross-sectional), study of the association (as primary aim vs as secondary aim), control for confounding factors (yes vs no), geographic location (North America vs Europe vs Asia vs Latin America vs Multiregion), sample size (<200 vs 200–999 vs 1000–5000 vs >5000), test used for diagnosing SARS-CoV-2 infection (RT-PCR vs RT-PCR or antigens vs antibodies in serum vs mixed or unclear), and timing of the diagnosis of SARS-CoV-2 infection (at any time during pregnancy vs at admission for delivery).

The impact of the risk of bias on the results was examined by performing a sensitivity analysis that included only studies with a low risk of bias in at least 5 of the 6 domains evaluated. We assessed publication and related biases visually by examining the symmetry of the funnel plots and statistically by measuring the degree of asymmetry with the Egger[84] and Begg-Mazumdar[85] tests, with $P<.10$ indicating significant asymmetry. In the presence of funnel plot asymmetry, we assessed the potential impact of publication bias on the overall effect size obtained in the meta-analysis by using the "Trim and Fill" method developed by Duval and Tweedie.[86,87]

Statistical analyses were performed by using Review Manager (RevMan, version 5.4.1, The Cochrane Collaboration, London, United Kingdom) and StatsDirect (version 3.3.5; StatsDirect Ltd, Merseyside, United Kingdom).

Results

Selection, characteristics, and risk of bias of studies

Figure 1 shows the process of the literature search and selection of studies. The searches produced 3659 records of which 107 were considered relevant. Of these, 79 were excluded, the main reason being a lack of data on the relationship between SARS-CoV-2 infection and preeclampsia. A total of 28 studies (14 prospective cohort, 12 retrospective cohort, and 2 cross-sectional) including 790,954 pregnant women, among which 15,524 were diagnosed with SARS-CoV-2 infection, met the inclusion criteria.[88–115] Four studies were specifically designed to evaluate the association between SARS-CoV-2 infection during pregnancy and preeclampsia.[98,108,112,115] The remaining 24 studies compared the maternal and perinatal outcomes for pregnant women with and those without SARS-CoV-2 infection and reported on the risk of preeclampsia. The corresponding authors

of 8 studies supplied additional data.[90,93,96,107–109,111,113]

The main characteristics of the studies included in the systematic review are presented in Table 1. A total of 14 studies were conducted in North American countries (13 in the United States and 1 in Canada), 6 in European countries, 5 in Asian countries, and 2 in Latin America. The remaining study was performed across 18 countries. The sample size ranged from 24[99] to 406,446[104] (median, 907). Two cross-sectional studies, 1 from the United States and 1 from the United Kingdom, included a total of 748,526 pregnant women.[104,114] An RT-PCR test was used to diagnose SARS-CoV-2 infection in 18 studies, an RT-PCR or antigen test was used in 3 studies, and a serum antibody test was used in 3 studies. In the remaining 4 studies, SARS-CoV-2 infection was diagnosed based on laboratory tests and/or clinical signs and symptoms of COVID-19 and/or chest imaging suggestive of the disease. Among the 22 studies that reported on the severity of SARS-CoV-2 infection, 16 had a higher proportion of patients with asymptomatic illness, 5 had a higher proportion of patients with symptomatic illness, and 1 had the same proportion of patients with asymptomatic and symptomatic illness. Fifteen studies included women among whom SARS-CoV-2 infection was diagnosed at any time during pregnancy and 13 studies included women among whom SARS-CoV-2 infection was diagnosed at admission for delivery. Most patients were diagnosed with SARS-CoV-2 infection during the third trimester. In 25 studies, women with and without SARS-CoV-2 infection were recruited from the same population and during the same time period. In the remaining 3 studies, the comparison group without SARS-CoV-2 infection were pregnant women who delivered before the beginning of the COVID-19 pandemic.

A total of 14 studies controlled for potential confounding factors related to both SARS-CoV-2 infection and preeclampsia. Most of them adjusted their results for maternal age, body mass index, preexisting comorbidities, and race or ethnicity. Twenty-six studies provided data on the relationship between SARS-CoV-2 infection and preeclampsia (with and without severe features), 7 on the relationship with preeclampsia with severe features, 5 on the relationship with preeclampsia without severe features, 3 on the relationship with eclampsia, and 1 on the relationship with HELLP syndrome.

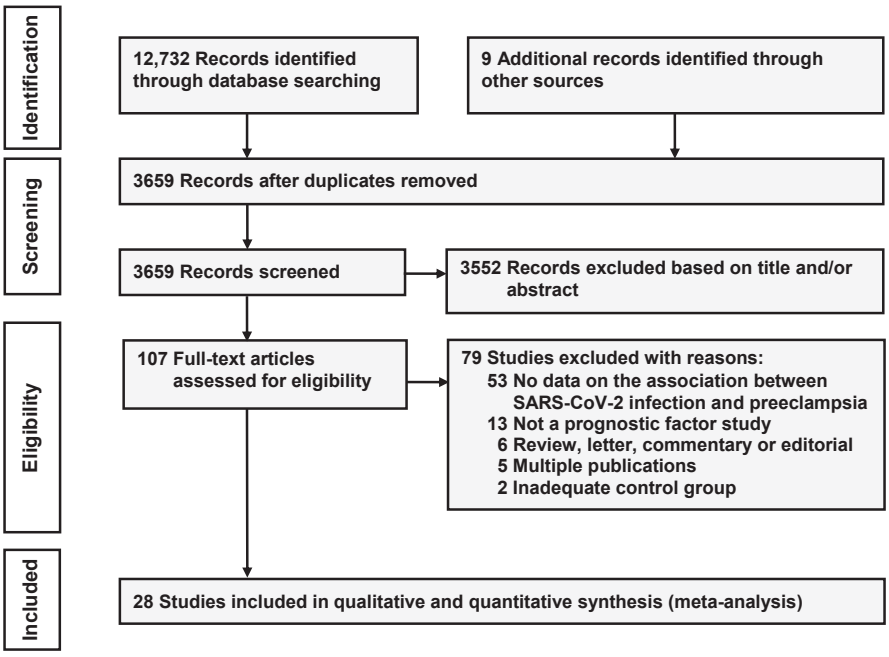
The risk of bias in each included study is shown in Supplemental Figure 1. No study was judged to be at low risk of bias for all 6 domains. Six studies were deemed to be at low risk of bias for 5 domains and 13 were judged to be at low risk of bias for 4 domains. The remaining 9 studies were judged to be at low risk of bias for ≤3 domains. The most common shortcomings were the failure to report temporality of the association between SARS-CoV-2 infection and preeclampsia and the lack of adjustment for confounding factors.

Association between SARS-CoV-2 infection during pregnancy and preeclampsia

A total of 26 studies,[88–91,93,95–115] comprising 786,861 women, reported on the association between SARS-CoV-2 infection during pregnancy and the risk of preeclampsia (with and without severe features). All but 1 study[95] found that the frequency of preeclampsia was higher among pregnant women with a diagnosis of SARS-CoV-2 infection than among those without a diagnosis of SARS-CoV-2 infection. The meta-analysis of unadjusted ORs showed that the odds of developing preeclampsia were significantly higher among pregnant women with SARS-CoV-2 infection than among those without SARS-CoV-2 infection (7.0% vs 4.8%; pooled unadjusted OR, 1.62; 95% CI, 1.45–1.82; $P<.00001$; 95% prediction interval of the OR, 1.28–2.05) (Figure 2).

There was evidence of low statistical heterogeneity ($I^2=17\%$), which indicates little variability among studies. This degree of heterogeneity was primarily due to the study by Jering et al[104] since the exclusion of this study from the meta-analysis produced a pooled OR of 1.70 (95% CI, 1.52–1.89) without statistical heterogeneity ($I^2=0\%$). Visual examination of the funnel plot suggested the presence of asymmetry

FIGURE 1
Flow diagram of the study selection process



Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

TABLE 1
Main characteristics of studies included in the systematic review

First author, y (country)	Design (sample size)	Group with SARS-CoV-2 infection	Timing of the diagnosis of SARS-CoV-2 infection	Group without SARS-CoV-2 infection	Adjustment for confounders or matching of variables	Outcome
Ahlberg,[88] 2020 (Sweden)	Retrospective cohort (759)	n=155; women with a positive RT-PCR test result (98%) or positive for antibodies against SARS-CoV-2 (2%); 65% asymptomatic and 35% symptomatic	Admission for delivery (91%) and antepartum period (9%); ~90% during the third trimester	n=604; women in labor with a negative RT-PCR test result (100%)	Maternal age, parity, body mass index, country of birth, living with partner, and prepregnancy comorbidity	Preeclampsia
Yang,[89] 2020 (China)	Retrospective cohort (11,078)	n=65; women with a positive RT-PCR test result (100%)	"During late pregnancy"	n=11,013; women with a negative RT-PCR test result (57%) or without signs or symptoms of COVID-19 (43%)	Maternal age, occupation, education, gravidity, parity, gestational hypertension, preeclampsia, gestational diabetes mellitus, and premature rupture of membranes	Preeclampsia
Prabhu,[90] 2020 (United States)	Prospective cohort (675)	n=70; women with a positive RT-PCR test result (100%); 79% asymptomatic and 21% symptomatic	Admission for delivery (100%); median gestational age, 39.0 wk	n=605; women admitted for delivery with a negative RT-PCR test result (100%)	No	Preeclampsia
Grechukhina,[91] 2020 (United States)	Retrospective cohort (8768)	n=77; women with a positive RT-PCR test result (100%); 53% asymptomatic and 47% symptomatic	Admission for delivery (67%), antepartum period (24%), and postpartum period (9%); most during the third trimester	n=8691; prepandemic (2018–2019) control group of pregnant women	No	Preeclampsia
Adhikari,[92] 2020 (United States)	Retrospective cohort (3280)	n=245; women with a positive RT-PCR test result (100%); 39% asymptomatic, 56% with mild or moderate illness and 5% with severe or critical illness	Admission for delivery (68%), antepartum period (30%), and unclear (2%); 93% during the third trimester and 7% during the second trimester	n=3035; women with a negative RT-PCR test result (100%)	No	Preeclampsia with severe features
Pirjani,[93] 2020 (Iran)	Prospective cohort (199)	n=66; women with a positive RT-PCR test result, or signs or symptoms of COVID-19 plus a chest CT scan suggestive of the disease; 100% symptomatic	During the second (24%) and third (74%) trimester; mean gestational age, 32.6 wk	n=133; healthy women without signs or symptoms of COVID-19 (100%)	Maternal age, body mass index, previous delivery type, gestational age, previous pregnancy problems, and preexisting medical problems	Preeclampsia

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

(continued)

TABLE 1
Main characteristics of studies included in the systematic review *(continued)*

First author, y (country)	Design (sample size)	Group with SARS-CoV-2 infection	Timing of the diagnosis of SARS-CoV-2 infection	Group without SARS-CoV-2 infection	Adjustment for confounders or matching of variables	Outcome
Wang,[94] 2020 (United States)	Retrospective cohort (813)	n=53; women with a positive RT-PCR or antigen test result (100%); 85% with asymptomatic or mild illness and 15% with moderate, severe, or critical illness	Admission to the hospital (100%); mean gestational age, 38.1 wk	n=760; women with a negative RT-PCR or antigen test result, or without signs or symptoms of COVID-19	No	Preeclampsia with severe features
Egerup,[95] 2021 (Denmark)	Prospective cohort (1313)	n=28; women with a positive result for anti–SARS-CoV-2 IgM or IgG antibodies in serum (100%); no woman had a positive RT-PCR test result; 50% asymptomatic and 50% symptomatic	Admission for delivery (100%); median gestational age, 40.1 wk	n=1285; women with a negative result for anti–SARS-CoV-2 IgM and IgG antibodies in serum (100%); one woman had a positive RT-PCR test result	No	Preeclampsia
Hcini,[96] 2021 (French Guiana)	Prospective cohort (507)	n=137; women with a positive RT-PCR test result (100%); 63% asymptomatic, 33% with mild illness, and 4% with severe illness	Admission for delivery (100%); most during the third trimester	n=370; women admitted for delivery with a negative RT-PCR test result (100%)	"Unbalanced maternal characteristics"	Preeclampsia
Mahajan,[97] 2021 (India)	Retrospective cohort (73)	n=10; women with multiple gestation and a positive RT-PCR test result (100%); 80% asymptomatic and 20% symptomatic	During the second (25%) and third (75%) trimesters; median gestational age, 34.5 wk	n=63; prepandemic (2019–2020) control group of pregnant women with multiple gestation	No	Preeclampsia and eclampsia
Madden,[98] 2021 (United States)	Retrospective cohort (1715)	n=167; women with a positive RT-PCR test result (100%)	Admission to the hospital (100%)	n=1548; women with a negative RT-PCR test result (100%)	No	Preeclampsia, preeclampsia with severe features, and preeclampsia without severe features
Colon-Aponte,[99] 2021 (United States)	Prospective cohort (24)	n=12; women with a positive RT-PCR test result (100%)	Admission for delivery (100%); mean gestational age, 39.0 wk	n=12; women with a negative RT-PCR test result (100%)	No	Preeclampsia

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

TABLE 1
Main characteristics of studies included in the systematic review *(continued)*

First author, y (country)	Design (sample size)	Group with SARS-CoV-2 infection	Timing of the diagnosis of SARS-CoV-2 infection	Group without SARS-CoV-2 infection	Adjustment for confounders or matching of variables	Outcome
Yazihan,[100] 2021 (Turkey)	Prospective cohort (187)	n=95; women with a positive RT-PCR test result (100%); 74% with mild illness, 24% with moderate illness, and 2% with severe illness	During the first (34%), second (34%) and third (33%) trimesters	n=92; healthy women without signs or symptoms of COVID-19	No	Preeclampsia
Brandt,[101] 2021 (United States)	Prospective cohort (183)	n=61; women with a positive RT-PCR test result (100%); 89% with asymptomatic or mild illness, and 11% with severe or critical illness	Mean gestational age, 38.8 wk for women with asymptomatic or mild illness and 33.6 wk for those with severe or critical illness	n=122; women with a negative RT-PCR test result or those without signs or symptoms of COVID-19	Maternal age, obesity, maternal race, and comorbid medical problems (chronic hypertension, diabetes mellitus, renal disease, asthma, immunocompromised state, and anemia)	Preeclampsia
Cardona-Pérez,[102] 2021 (Mexico)	Retrospective cohort (231)	n=67; women with a positive RT-PCR test result (100%); 86% asymptomatic and 14% symptomatic	Admission for delivery (100%); <28 wk, 10%; 28–36 wk, 24%, ≥37 wk, 66%	n=164; women with a negative RT-PCR test result (100%)	Maternal age, body mass index, preexisting comorbidities, and gestational age at admission	Preeclampsia
Steffen,[103] 2021 (United States)	Prospective cohort (1000)	n=61; women with a positive result for anti–SARS-CoV-2 IgG antibodies in serum (84%) or RT-PCR test (5%) or both tests (11%); 51% asymptomatic and 49% symptomatic	Admission for delivery (100%); median gestational age, 39.0 wk	n=939; women with a negative result for anti–SARS-CoV-2 IgG antibodies in serum or RT-PCR test (100%)	No	Preeclampsia, preeclampsia with severe features, preeclampsia without severe features, and eclampsia

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

TABLE 1
Main characteristics of studies included in the systematic review *(continued)*

First author, y (country)	Design (sample size)	Group with SARS-CoV-2 infection	Timing of the diagnosis of SARS-CoV-2 infection	Group without SARS-CoV-2 infection	Adjustment for confounders or matching of variables	Outcome
Jering,[104] 2021 (United States)	Cross-sectional (406,446)	n=6380; women giving birth with a diagnosis of COVID-19 at discharge (ICD-10 code U07.1). Diagnostic criteria for SARS-CoV-2 infection were not reported	At birth; 98% in the third trimester	n=400,066; women giving birth without a diagnosis of COVID-19 at discharge (ICD-10 code U07.1)	Adjusted for propensity score, which included the following covariates: maternal age, race and ethnicity, geographic region, urban population, teaching hospital, discharge month, trimester of pregnancy, obesity, smoking, hypertension, gestational hypertension, diabetes, gestational diabetes, kidney disease, pulmonary disease	Preeclampsia, eclampsia, and HELLP syndrome
Vousden,[105] 2021 (United Kingdom)	Prospective cohort (1842)	n=1148; women with a positive RT-PCR test result within 7 days of admission to hospital (99%) or chest imaging suggestive of COVID-19 (1%); 37% asymptomatic and 63% symptomatic	<22 wk, 7%; 22–27 wk, 7%; ≥28 wk, 86%	n=694; prepandemic (2017–2018) control group of pregnant women	Maternal age, ethnicity, body mass index, any relevant previous medical problem, cigarette smoking	Preeclampsia
Abedzadeh-Kalahroudi,[106] 2021 (Iran)	Prospective cohort (149)	n=55; women with a positive RT-PCR test result, signs or symptoms of COVID-19, or laboratory tests and a chest CT scan suggestive of the disease; >90% symptomatic	During the first (7%), second (14%), and third (79%) trimesters; mean gestational age, 31.9 wk	n=94; healthy women without clinical signs or symptoms of COVID-19 (100%)	No	Preeclampsia
Crovetto,[107] 2021 (Spain)	Prospective cohort (1304)	n=176; women with a positive result for anti–SARS-CoV-2 IgG or IgM or IgA antibodies in serum (~99%) and/or RT-PCR test; 60% asymptomatic and 40% symptomatic	Admission for delivery (100%); 24–42 wk	n=1128; women with a negative result for anti–SARS-CoV-2 IgG and IgM or IgA antibodies in serum or negative RT-PCR test (100%)	No	Preeclampsia

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

TABLE 1
Main characteristics of studies included in the systematic review *(continued)*

First author, y (country)	Design (sample size)	Group with SARS-CoV-2 infection	Timing of the diagnosis of SARS-CoV-2 infection	Group without SARS-CoV-2 infection	Adjustment for confounders or matching of variables	Outcome
Rosenbloom,[108] 2021 (United States)	Retrospective cohort (249)	n=83; women with a positive RT-PCR or antigen test result (100%); 58% asymptomatic and 42% symptomatic	Any time during pregnancy	n=166; women with a negative RT-PCR test result (100%)	Race, parity	Preeclampsia, preeclampsia with severe features, and preeclampsia without severe features
Trahan,[109] 2021 (Canada)	Retrospective cohort (270)	n=45; women with a positive RT-PCR test result (100%); 27% asymptomatic and 73% symptomatic	Any time during pregnancy; 98% in the third trimester	n=225; women with a negative RT-PCR test result (100%)	No	Preeclampsia
Soto-Torres,[110] 2021 (United States)	Retrospective cohort (209)	n=106; women with a positive RT-PCR or antigen test result (100%); 54% asymptomatic and 46% symptomatic (28% with mild illness and 18% with severe illness)	Any time during pregnancy; median gestational age, 32.9 wk (range, 10.9–40.4 wk);	n=103; women with a negative RT-PCR or antigen test result (100%)	Maternal age, body mass index, parity, gestational age	Preeclampsia
Katz,[111] 2021 (United States)	Prospective cohort (1454)	n=490; women with a positive RT-PCR test result within 14 d of delivery (100%); 64% asymptomatic and 36% symptomatic	Within 14 d of delivery; most in the third trimester	n=964; women with a negative RT-PCR test result (84%) or without signs or symptoms of COVID-19 (16%)	Maternal age, race, ethnicity, body mass index, and maternal comorbidities (including diabetes, preexisting hypertension, cardiac, pulmonary, or autoimmune disease)	Preeclampsia
Chornock,[112] 2021 (United States)	Retrospective cohort (1008)	n=73; women with a positive RT-PCR test result (100%); 84% asymptomatic and 16% symptomatic	Admission for delivery (99.2%) and antepartum period (0.8%); mean gestational age, 40.1 wk	n=935; women with a negative RT-PCR test result at admission for delivery (100%)	Race, body mass index, aspirin use, and chronic hypertension	Preeclampsia, preeclampsia with severe features, and preeclampsia without severe features

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022. *(continued)*

TABLE 1
Main characteristics of studies included in the systematic review *(continued)*

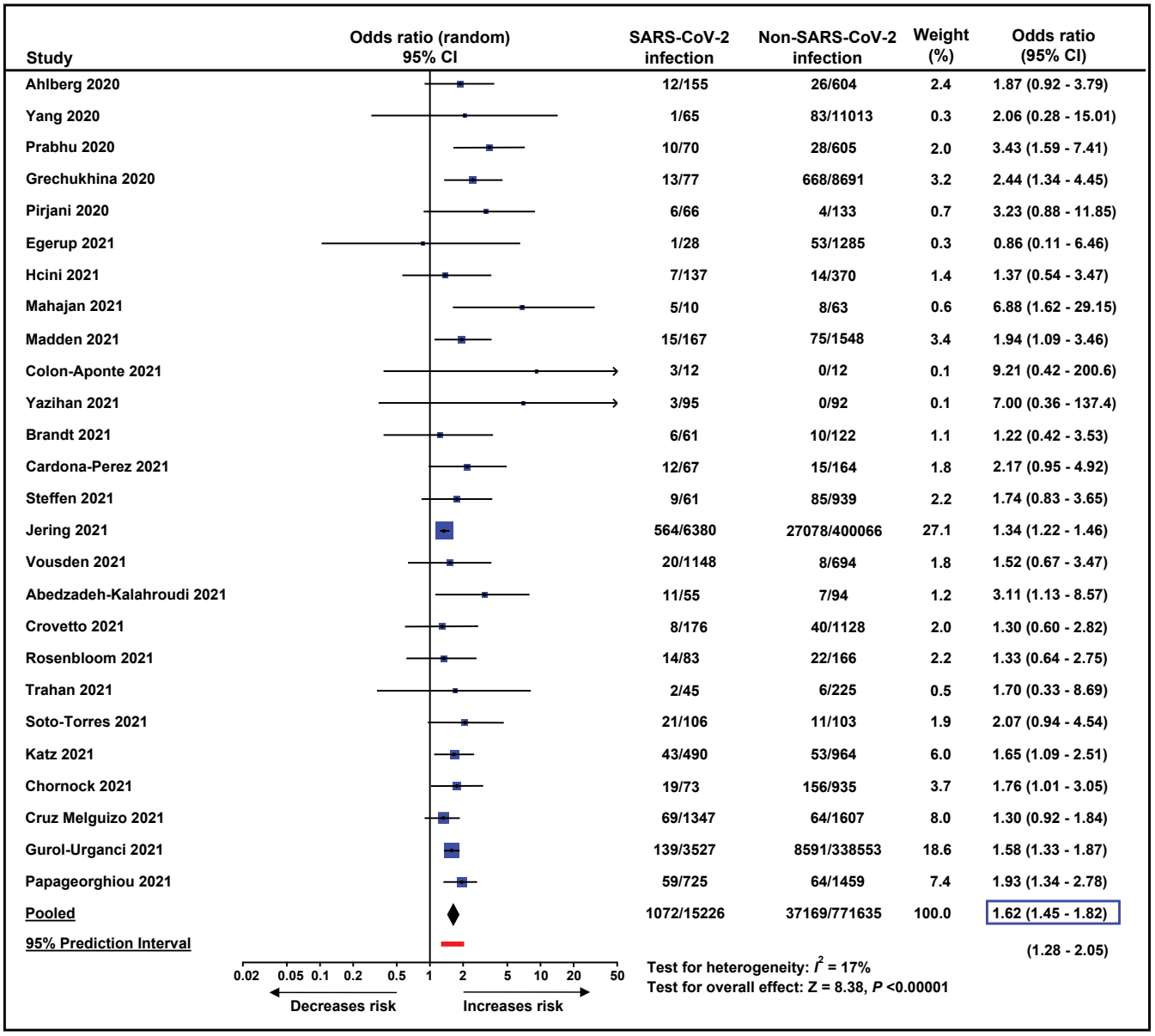
First author, y (country)	Design (sample size)	Group with SARS-CoV-2 infection	Timing of the diagnosis of SARS-CoV-2 infection	Group without SARS-CoV-2 infection	Adjustment for confounders or matching of variables	Outcome
Cruz Melguizo,[113] 2021 (Spain)	Prospective cohort (2954)	n=1347; women with a positive RT-PCR test result (100%); 51% asymptomatic and 49% symptomatic (35% with mild or moderate illness and 14% with severe or critical illness)	Any time during pregnancy; most in the third trimester	n=1607; women with a negative RT-PCR test result at admission for delivery (100%)	No	Preeclampsia, preeclampsia with severe features, and preeclampsia without severe features
Gurol-Urganci,[114] 2021 (United Kingdom)	Cross-sectional (342,080)	n=3527; women with a positive RT-PCR test result (100%)	At the time of birth (100%)	n=338,553; women without laboratory-confirmed SARS-CoV-2 infection (ICD-10 code U07.1)	Maternal age, ethnicity, parity, preexisting diabetes, preexisting hypertension, and socioeconomic deprivation	Preeclampsia
Papageorghiou,[115] 2021 (Multicountry)[a]	Prospective cohort (2184)	n=725; women with a positive RT-PCR test result (92.7%), clinical signs or symptoms of COVID-19 (6.8%), or chest imaging suggestive of COVID-19 (0.6%); 40% asymptomatic and 60% symptomatic	≤26 wk, 5%; >26 wk, 95%; median gestational age, 37.6 wk (IQR 34.3–39.1); 71% of women were diagnosed <10 d before giving birth	n=1459; women with a negative RT-PCR or antigen test result (50%) or women without signs or symptoms of COVID-19 (50%)	Maternal age, parity, cigarette smoking, overweight or obesity, history of diabetes, cardiac disease, hypertension, or renal disease, and history of adverse pregnancy outcomes	Preeclampsia

CT, computed tomography; *HELLP*, hemolysis, elevated liver enzymes, low platelet count; *ICD*, International Classification of Diseases; *IgM*, immunoglobulin M; *IQR*, interquartile range; *RT-PCR*, reverse transcription polymerase chain reaction.

[a] Includes cases from Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland, the United Kingdom, and the United States.

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

FIGURE 2
Meta-analysis of unadjusted odds ratios for the association between SARS-CoV-2 infection during pregnancy and preeclampsia



Data are n/N.
***CI*, confidence interval; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.**

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

(Supplemental Figure 2), which was statistically significant according to the Egger's test ($P<.002$) but not according to the Begg and Mazumdar's test ($P=.63$). After applying the "Trim and Fill" method (Supplemental Figure 3), the pooled unadjusted estimate reduced slightly but remained statistically significant (OR, 1.53; 95% CI, 1.30−1.81).

The meta-analysis of adjusted ORs also showed that, compared to pregnant women without SARS-CoV-2 infection, those with the disease had increased odds of developing preeclampsia (pooled adjusted OR, 1.58; 95% CI, 1.39−1.80; $P<.0001$; $I^2=0\%$; 11 studies, 756,661 women) (Figure 3).

The results of the pooled unadjusted ORs for the association between SARS-CoV-2 infection and preeclampsia-related disorders are depicted in Table 2. There was a statistically significant increase in the odds of preeclampsia with severe features (OR, 1.76; 95% CI, 1.18−2.63; $I^2=58\%$; 7 studies, 11,019 women), eclampsia (OR, 1.97; 95% CI,

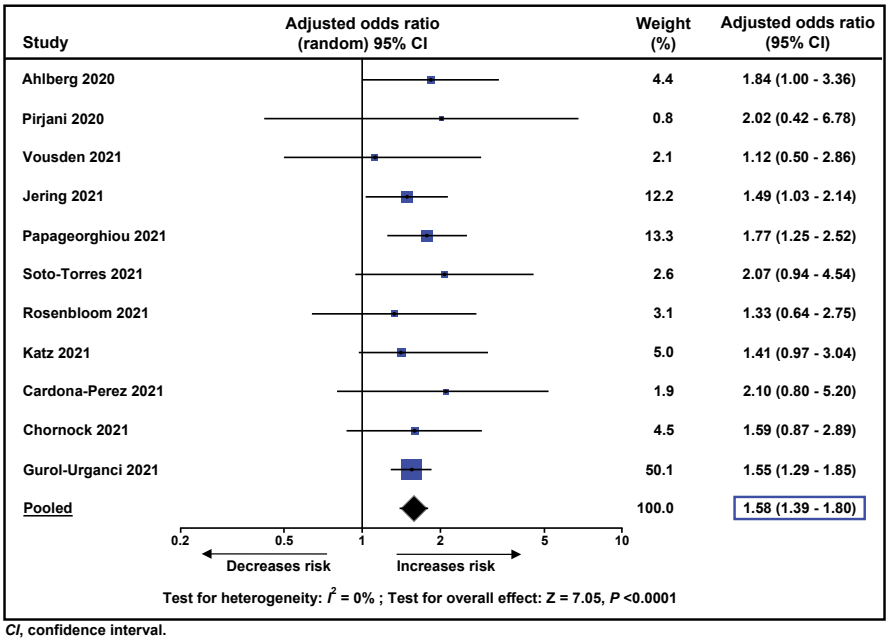
1.01−3.84; I^2=0%; 3 studies, 407,519 women), and HELLP syndrome (OR, 2.10; 95% CI, 1.48−2.97; 1 study, 406,446 women) among pregnant women with SARS-CoV-2 infection, as compared to those without the infection. There was no significant difference in the odds of preeclampsia without severe features between pregnant women with and those without SARS-CoV-2 infection (OR, 1.25; 95% CI, 0.81−1.93; I^2=29%; 5 studies, 6926 women).

Subgroup and sensitivity analyses

The results of the subgroup analyses for the association between SARS-CoV-2 infection and preeclampsia are shown in Table 3. Overall, the direction and magnitude of the effect of SARS-CoV-2 infection during pregnancy on preeclampsia were consistent across most prespecified subgroup analyses. However, studies with a retrospective cohort design, those that did not adjust for confounding factors, those that were conducted in Asia, or those that had a sample size <200 were associated with higher pooled ORs. On the other hand, studies with a cross-sectional design, those that controlled for confounding factors, or those that used serum antibody tests for diagnosing SARS-CoV-2 infection were associated with a slight reduction in the pooled ORs. Both asymptomatic and symptomatic SARS-CoV-2 infections significantly increased the odds of preeclampsia; however, the odds were higher among patients with symptomatic illness (OR, 2.11; 95% CI, 1.59−2.81) than among those with asymptomatic illness (OR, 1.59; 95% CI, 1.21−2.10).

The effect of SARS-CoV-2 infection during pregnancy on the risk of preeclampsia did not change after a sensitivity analysis limited to the 6 studies[88,102,108,110-112] with a low risk of bias in at least 5 of the 6 domains evaluated (pooled OR, 1.74; 95% CI, 1.35−2.23; I^2=0%). The pooled OR for the subgroup of 20 studies[89−91,93,95−101,103−107,109,113−115] with a low risk of bias in less than 5 of the 6 domains evaluated was 1.65 (95% CI, 1.43−1.91) with an I^2=30%.

FIGURE 3
Meta-analysis of adjusted odds ratios for the association between SARS-CoV-2 infection during pregnancy and preeclampsia



CI, confidence interval.

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

Temporality of the association between SARS-CoV-2 infection and preeclampsia

Only the study by Rosenbloom et al[108] provided data on the time elapsed between SARS-CoV-2 infection diagnosis and preeclampsia diagnosis. In this study, the median interval from the diagnosis of SARS-CoV-2 infection to the diagnosis of preeclampsia was 3.79 weeks (interquartile range, 0.43−13.0). The hazard ratios for the association between SARS-CoV-2 infection and the development of preeclampsia were 2.88 (95% CI, 1.20−6.93) for the infection diagnosed before 32 weeks of gestation and 2.74 (95% CI, 0.98−7.71) for the infection diagnosed at or after 32 weeks of gestation.

Comment

Principal findings

This systematic review shows that women with SARS-CoV-2 infection during pregnancy had a significantly higher odds (62%) of developing preeclampsia than those without SARS-CoV-2 infection during pregnancy. This association was remarkably consistent across all predefined subgroups. Moreover, SARS-CoV-2 infection during pregnancy was associated with a significant increase in the odds of preeclampsia with severe features, eclampsia, and HELLP syndrome. Both asymptomatic and symptomatic SARS-CoV-2 infections significantly increased the risk for preeclampsia. Nevertheless, the odds of developing preeclampsia were higher among patients with symptomatic illness than among those with asymptomatic illness, which suggests a dose-response gradient effect.

Assessing the causal relationship between SARS-CoV-2 infection during pregnancy and preeclampsia

The results of this systematic review provide convincing evidence for an association between SARS-CoV-2 infection during pregnancy and the risk for preeclampsia for the following reasons: (1) there was a significant effect based on

TABLE 2
Pooled unadjusted odds ratios for the association between SARS-CoV-2 infection and preeclampsia-related disorders

Outcome	Number of studies	SARS-CoV-2 infection	No SARS-CoV-2 infection	Pooled odds ratio (95% CI)	*P* value	I^2, %
Preeclampsia (with and without severe features)	26[88–91,93,95–115]	1072/15,226	37,169/771,635	1.62 (1.45–1.82)	<.00001	17
Preeclampsia with severe features	7[92,94,98,103,108,112,113]	101/2029	629/8990	1.76 (1.18–2.63)	.006	58
Preeclampsia without severe features	5[98,103,108,112,113]	61/1731	190/5195	1.25 (0.81–1.93)	.31	29
Eclampsia	3[97,103,104]	9/6451	290/401,068	1.97 (1.01–3.84)	.048	0
HELLP syndrome	1[104]	33/6380	989/400,066	2.10 (1.48–2.97)	<.0001	NA

Data are presented as n/N.

CI, confidence interval; *HELLP*, hemolysis, elevated liver enzymes, low platelet count; *NA*, not applicable.

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

the random-effects model at $P<.00001$ and $P<.0001$ for the pooled unadjusted and adjusted effect size estimates, respectively; (2) the magnitude of the effect estimate was relatively large; (3) the CIs observed were relatively narrow, implying that the estimates of effect size are more precise; (4) the relationship was consistently present in the majority of the studies, across diverse populations worldwide, and in virtually every way the data were interrogated; (5) the large number of pregnant women with and without SARS-CoV-2 infection included in the analyses; (6) in most studies, an association between SARS-CoV-2 infection and a higher risk for preeclampsia was neither anticipated nor hypothesized when the study was carried out; (7) the low statistical heterogeneity; (8) evidence of clinical homogeneity across the included studies; (9) a statistically significant effect was reported in the largest studies; (10) the 95% prediction interval that excluded a null effect and that was in the same direction as the 95% CI; and (11) the sensitivity analysis that was restricted to studies at low risk of bias (and thus supporting the overall findings).

Additional information could support the hypothesis that SARS-CoV-2 infection during pregnancy plays a causal role in the development of preeclampsia. When assessing causality, evidence of a dose-response relationship suggests that the association is less likely to be due to confounding.[116,117] We found evidence for a dose-response gradient effect on the basis that patients with symptomatic illness were more likely to develop preeclampsia (OR=2.11) than those with asymptomatic illness (OR=1.59). Recently, a multicenter cohort study by Metz et al,[118] which did not include women without SARS-CoV-2 infection, reported that the frequency of hypertensive disorders of pregnancy among women with asymptomatic SARS-CoV-2 infection, mild or moderate disease, and severe or critical disease was 18.8%, 23.8%, and 40.4%, respectively. Compared to asymptomatic patients, those with mild or moderate and severe or critical disease were at an increased risk for hypertensive disorders of pregnancy (adjusted RR, 1.24; 95% CI, 0.98–1.58 for mild or moderate disease; and adjusted RR, 1.61; 95% CI, 1.18–2.20 for severe or critical disease). These data strongly suggest a dose-response effect.

Temporality is considered fundamental when assessing the likelihood of a causal relationship between an exposure and an outcome.[116,117] Evidence that the participants were exposed before the occurrence of the outcome strengthens a causal relationship argument. The study by Rosenbloom et al[108] provided clear evidence to support a meaningful temporal relationship between SARS-CoV-2 infection and preeclampsia. The median time interval between SARS-CoV-2 infection diagnosis and preeclampsia diagnosis was 3.79 weeks. Both cases of SARS-CoV-2 infection diagnosed before 32 weeks of gestation and cases diagnosed at or after 32 weeks of gestation were associated with a higher risk for developing preeclampsia. However, the association was only statistically significant for SARS-CoV-2 infection diagnosed before 32 weeks of gestation. Rosenbloom et al[108] hypothesized that SARS-CoV-2 infection that was diagnosed closer to term was not associated with a significant increase in the risk for preeclampsia because the time remaining to develop the clinical disorder was limited. Nevertheless, a subgroup analysis in our meta-analysis showed that SARS-CoV-2 infection diagnosed either at delivery or at any time during pregnancy was significantly associated with an increased risk for preeclampsia.

Several mechanisms could explain how SARS-CoV-2 infection during pregnancy might be involved in the pathogenesis of preeclampsia. SARS-CoV-2 enters the cell after the N-terminal portion of the viral spike protein binds to the cell membrane angiotensin-converting enzyme 2 (ACE2) receptor.[119–121] The ACE2 receptor is an important component of the RAS, which converts angiotensin II into angiotensin 1 to 7.[122] The RAS is an important regulator of placental function, because it plays a role in the control of trophoblast proliferation, angiogenesis, and blood flow. The RAS significantly modulates uteroplacental blood flow through the balance of its vasoconstrictive and

TABLE 3
Subgroup analyses for the association between SARS-CoV-2 infection and preeclampsia

Subgroup	Number of studies	SARS-CoV-2 infection	No SARS-CoV-2 infection	Pooled odds ratio (95% CI)	I^2, %
Severity of SARS-CoV-2 infection					
Asymptomatic	6[90,95,105,107,111,115]	63/1206	246/6135	1.59 (1.21–2.10)	0
Symptomatic	7[90,93,95,105,107,111,115]	84/1497	250/6268	2.11 (1.59–2.81)	0
Study design					
Prospective cohort	14[90,93,95,96,99–101,103,105–107,111,113,115]	255/4471	430/9504	1.69 (1.42–2.01)	0
Retrospective cohort	10[88,89,91,97,98,102,108-110,112]	114/848	1070/23,512	1.98 (1.56–2.52)	0
Cross- sectional	2[104,114]	703/9907	35,669/738,619	1.43 (1.22–1.67)	65
Study of the association					
As primary aim	4[98,108,112,115]	107/1048	317/4108	1.81 (1.41–2.33)	0
As secondary aim	22[88–91,93,95–97,99–107,109–111,113,114]	965/14,178	36,852/767,527	1.61 (1.41–1.83)	20
Control for confounding factors					
Yes	14[88,89,93,96,101,102,104,105,108,110–112,114,115]	923/13,083	36,135/755,346	1.43 (1.33–1.54)	0
No	12[90,91,95,97–100,103,106,107,109,113]	149/2143	1034/16,289	1.98 (1.49–2.64)	25
Geographic location					
North America	12[90,91,98,99,101,103,104,108–112]	719/7625	28,192/414,376	1.67 (1.38–2.02)	26
Europe	6[88,95,105,107,113,114]	249/6381	8782/343,871	1.52 (1.31–1.75)	0
Asia	5[89,93,97,100,106]	26/291	102/11,395	3.65 (1.92–6.96)	0
Latin America	2[96,102]	19/204	29/534	1.77 (0.96–3.28)	0
Multiple regions	1[115]	59/25	64/1459	1.93 (1.34–2.78)	NA
Sample size					
<200	6[93,97,99–101,106]	34/299	29/516	2.90 (1.65–5.09)	0
200–999	7[88,90,96,102,108–110]	78/663	122/2237	1.94 (1.42–2.65)	0
1000–5000	9[95,98,103,105,107,111–113,115]	243/4215	598/10,559	1.62 (1.36–1.92)	20
>5000	4[89,91,104,114]	717/10,049	36,420/758,323	1.50 (1.25–1.80)	53
Test used for diagnosing SARS-CoV-2 infection					
RT-PCR	17[88–91,96–102,105,109,111–113,115]	299/4744	1278/29,168	1.79 (1.53–2.10)	0
RT-PCR or antigens	2[108,110]	35/189	33/269	1.63 (0.95–2.78)	0
Antibodies in serum	3[95,103,107]	18/265	178/3352	1.46 (0.87–2.44)	0
Mixed or unclear	4[93,104,106,114]	720/10,028	35,680/738,846	1.50 (1.23–1.84)	56
Timing of the diagnosis of SARS-CoV-2 infection					
At any time during pregnancy	12[89,91,93,97,100,105,106,108–110,113,115]	224/3822	945/24,340	1.80 (1.47–2.21)	4
At admission for delivery	14[88,90,95,96,98,99,101–104,107,111,112,114]	848/11,404	36,224/747,295	1.49 (1.35–1.66)	9

Data are presented as n/N.

CI, confidence interval; *NA*, not applicable; *RT-PCR*, Reverse transcription polymerase chain reaction.

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

vasodilatory pathways.[122] The binding of SARS-CoV-2 to ACE2 receptors causes down-regulation of the RAS system with reduced levels of vasodilatory angiotensin 1 to 7, thereby leaving the vasoconstrictive and proinflammatory effects of angiotensin II unopposed. These alterations in the RAS could have a role in the pathophysiology of preeclampsia.[123–138]

There is evidence that SARS-CoV-2 can infect the syncytiotrophoblast and

activate inflammatory responses in placentas of women with a positive RT-PCR test result.[139−151] Recently, Verma et al[152] showed that SARS-CoV-2 colonizes ACE2 receptor-expressing maternal and fetal cells in the placenta, which leads to alterations in the local RAS. The infected placentas had a significant reduction in the expression of ACE2 receptors, with a concomitant increase in soluble fms-like tyrosine kinase-1 (sFlt-1) production and a decrease in proangiogenic factors. In addition, the serum levels of sFlt-1 and angiotensin II type 1-receptor autoantibodies, both markers of preeclampsia, were significantly higher among women with SARS-CoV-2 infection before delivery than among uninfected women. The findings of this study provide a plausible mechanism for explaining the association between SARS-CoV-2 infection and preeclampsia.

Seethy et al[153] explored *in silico* potential interactions between SARS-CoV-2 proteins and proteins involved in the key functions of the placenta. Potential SARS-CoV-2 interactions with placental proteins such as MFGE8, PLAT, and PAR2, which may play key roles in trophoblast invasion, migration, proliferation, and differentiation processes, were identified. The authors concluded that these interactions could be involved in the development of preeclampsia. Beys-da-Silva et al[154] assessed differentially expressed genes from clinical and experimental datasets of SARS-CoV-2 infection and their potential roles in preeclampsia. It was found that SARS-CoV-2 infection upregulates sFlt-1 and endoglin, vasoconstrictive peptides, nitric oxide modulators, and prothrombotic-related molecules. Therefore, SARS-CoV-2 infection can affect different molecular pathways related to the pathogenesis of preeclampsia such as angiogenesis, hypoxia, inflammatory signaling, thrombin or platelet activation, and imbalance of vasoactive peptides. In summary, multiple mechanisms link SARS-CoV-2 infection to the subsequent development of vascular disease and preeclampsia.

Strengths and limitations

The main strength of our study is the use of the most rigorous methodology for performing a systematic review and meta-analysis of observational studies, which included the use of a prospective protocol designed to address a specific research question, the extensive literature searches without language restrictions, the risk of bias assessment in the included studies, the quantitative summarization of the evidence, the performance of multiple subgroup and sensitivity analyses, the exploration of sources of heterogeneity, the calculation of the 95% prediction interval, and the use of methods for addressing potential publication bias. Other strengths of our review are the inclusion of a relatively large number of studies and of women from different populations throughout the world and the inclusion of additional unpublished data from 29% of the included studies.

Some potential limitations of our study should be considered. First, only 1 study reported on the temporality of the association between SARS-CoV-2 infection during pregnancy and preeclampsia. Second, only one-half of the included studies controlled for potential confounding factors. However, there were no significant differences in the pooled unadjusted and adjusted ORs obtained from the subgroup analysis of studies that controlled for confounding factors and the overall estimate obtained for all included studies. Even if adjustments for potential confounding factors are made, residual confounding remains a potentially serious problem in observational research. Third, there was evidence of funnel plot asymmetry, which raises the possibility of publication bias. Nevertheless, funnel plot asymmetry may also be caused by other reporting biases (eg, selective outcome or analysis reporting), poor methodological quality of smaller studies, true heterogeneity, statistical artifact, or chance.[155−157] We assessed the potential impact of publication bias in our meta-analysis by using the "Trim and Fill" approach and the "adjusted" estimate obtained (OR, 1.53; 95% CI, 1.30−1.79) was slightly lower than that obtained in the original analysis (OR, 1.62; 95% CI, 1.45−1.82). Therefore, we concluded that the potential impact of publication bias is probably trivial. Finally, the number of studies that reported on the relationship between SARS-CoV-2 infection and preeclampsia according to the severity of the infection was limited.

Clinical implications

SARS-CoV-2 infection during pregnancy and preeclampsia are independently associated with an increased risk for adverse maternal and perinatal outcomes.[4−12,74,76] One of the studies included in our systematic review reported that SARS-CoV-2 infection during pregnancy and preeclampsia are associated in an additive fashion with an increased risk for adverse pregnancy outcomes.[115] In fact, patients diagnosed with both SARS-CoV-2 infection and preeclampsia had a higher risk for preterm birth, a small-for-gestational-age neonate, and adverse maternal and perinatal outcomes than those diagnosed with only SARS-CoV-2 infection or only preeclampsia. Healthcare professionals need to be aware of the increased risk for preeclampsia among pregnant women diagnosed with SARS-CoV-2 infection, even among those with asymptomatic illness, and the negative additive effect of SARS-CoV-2 infection and preeclampsia to plan close monitoring of the affected pregnancy and to adopt early effective interventions that can reduce risks to mothers and their fetuses or neonates.

The association between low-dose aspirin administration to prevent preeclampsia and SARS-CoV-2 infection remains unclear. Two studies included in our review reported on such an association. Papageorghiou et al[115] reported that the significant association between SARS-CoV-2 infection and preeclampsia was not modified by aspirin use during pregnancy (*P* value for interaction=.42); Chornock et al[112] reported that the frequency of aspirin use during pregnancy was higher among women with SARS-CoV-2 infection than among those without the disease; however, this difference was not statistically significant (19.2% vs 11.9%; *P*=.07). Currently,

most professional organizations recommend that low-dose aspirin administration should still be offered to pregnant women during the COVID-19 pandemic for the prevention of preeclampsia.[158−162] Some authors who believe that aspirin could increase the risk for progression of SARS-CoV-2 infection have suggested that the prescription of aspirin for the prevention of preeclampsia should be ceased immediately following a diagnosis of SARS-CoV-2 infection, that aspirin use should be avoided for the duration of the disease, and that medication use can be resumed after full recovery from the infection.[163]

Public health implications

A recent meta-analysis assessed the impact of the COVID-19 pandemic on maternal and perinatal outcomes by comparing the rates of adverse outcomes during the pandemic to those before the pandemic.[164] This study reported a significant increase in maternal mortality, stillbirth, maternal stress, and ruptured ectopic pregnancies during the pandemic, as compared to before the pandemic. Unfortunately, this review did not assess the effect of the COVID-19 pandemic on the rates of preeclampsia. We identified 3 studies conducted in high-income countries[165−167] that compared the rates of preeclampsia before and during the COVID-19 pandemic. We performed a meta-analysis of these studies and found that the rate of preeclampsia during the COVID-19 pandemic was significantly higher than before the pandemic (3.4% vs 3.0%; OR, 1.25; 95% CI, 1.03−1.51; P=.02) (Supplemental Figure 4). Another study, which provided insufficient data to be included in this meta-analysis, reported that the risk of preeclampsia was significantly higher during the COVID-19 pandemic than before the pandemic (RR, 1.53; 95% CI, 1.24−1.90 when compared to the 2018 preeclampsia rate; RR, 1.25; 95% CI, 1.02−1.52 when compared to the 2019 preeclampsia rate).[168] These data support the findings of our study.

The observations from this meta-analysis can be indirectly tested in clinical trials that evaluate the effects of administering COVID-19 vaccines to pregnant women or antiviral therapies to pregnant women with SARS-CoV-2 infection or in studies assessing the impact of COVID-19 mitigation measures on the incidence of preeclampsia. We located a nonrandomized study in the medRxiv database that compared the outcomes between pregnant women who received the COVID-19 vaccine during pregnancy (n=140) and those who did not (n=1862).[169] Women vaccinated during pregnancy were less likely than unvaccinated women to be diagnosed with SARS-CoV-2 infection before delivery (1.4% vs 11.3%; RR, 0.13; 95% CI, 0.03−0.50; P=.003). Moreover, pregnant women who received COVID-19 vaccines during pregnancy had a nonsignificant decrease in the risk for preeclampsia when compared to unvaccinated pregnant women (0.7% vs 1.2%; RR, 0.58; 95% CI, 0.08−4.25; P=.59). Evidence from ongoing randomized controlled trials comparing COVID-19 vaccines to placebo in pregnant women will help to determine whether vaccines prevent SARS-CoV-2 infection in this population and reduce the risk of preeclampsia and/or other pregnancy complications. If administration of COVID-19 vaccines to pregnant women or the use of antiviral therapies among pregnant women with SARS-CoV-2 infection, or if the implementation of COVID-19 mitigation measures decreases the risk of preeclampsia, it would strongly support the causal relationship between SARS-CoV-2 infection during pregnancy and preeclampsia.

Research implications

Further research is required to elucidate (1) the mechanisms underlying the association between SARS-CoV-2 infection and preeclampsia; (2) the effects of SARS-CoV-2 infection during the first and second trimesters of pregnancy on the risk of preeclampsia; (3) the interrelationships between low-dose aspirin use, SARS-CoV-2 infection, and preeclampsia; (4) the effects of administering COVID-19 vaccines to pregnant women and antiviral therapies to pregnant women with SARS-CoV-2 infection on the risk of preeclampsia; (5) the impact of implementing COVID-19 mitigation measures on the incidence of preeclampsia; (6) effective interventions to prevent preeclampsia in pregnant women with SARS-CoV-2 infection; and (7) effective interventions in pregnant women with both SARS-CoV-2 infection and preeclampsia to prevent adverse maternal and perinatal outcomes.

Conclusion

This systematic review and meta-analysis indicates that there is an association between SARS-CoV-2 infection during pregnancy and preeclampsia and suggests that this relationship may be causal. ■

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SUPPLEMENTAL FIGURE 1
Risk of bias for each included study

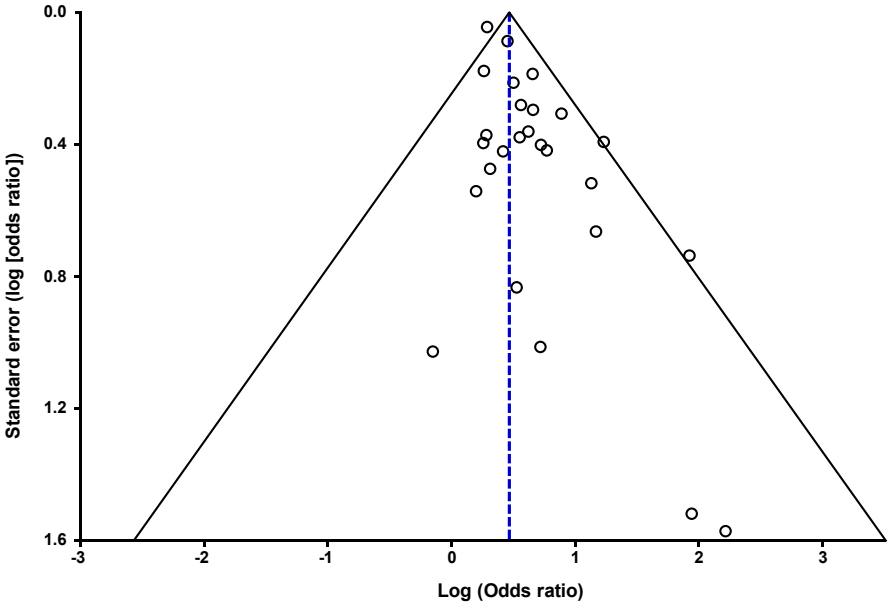
Study	Selection of participants	Inclusion in the exposed cohort	Inclusion in the non-exposed cohort	Loss to follow-up/exclusions	Control for confounding factors	Temporality between the exposure and outcome
Ahlberg 2020	+	+	+	+	+	−
Yang 2020	+	+	−	+	+	−
Prabhu 2020	+	+	+	+	−	−
Grechukhina 2020	−	+	+	+	−	−
Adhikari 2020	+	+	+	+	−	−
Pirjani 2020	+	?	−	+	+	−
Wang 2020	+	+	?	+	−	−
Egerup 2020	+	+	+	?	−	−
Hcini 2021	+	+	+	+	?	−
Mahajan 2021	−	+	+	+	−	−
Madden 2021	+	+	+	+	−	−
Colon-Aponte 2021	+	+	+	?	−	−
Yazihan 2021	+	+	−	+	−	−
Brandt 2021	+	+	?	+	+	−
Cardona-Perez 2021	+	+	+	+	+	−
Steffen 2021	+	+	+	+	−	−
Jering 2021	+	?	?	+	+	−
Vousden 2021	−	+	+	+	+	−
Crovetto 2021	+	+	+	+	−	−
Abedzadeh-Kalahroudi 2021	+	?	−	?	−	−
Rosenbloom 2021	+	+	+	+	?	+
Trahan 2021	+	+	+	+	−	−
Soto-Torres 2021	+	+	+	+	+	−
Katz 2020	+	+	+	+	+	−
Papageorghiou 2021	+	+	−	+	+	−
Cruz-Melguizo 2020	+	+	+	+	−	−
Chornock 2021	+	+	+	+	+	−
Gurol-Urganci 2021	+	+	?	+	+	−

+ Low risk of bias ? Unclear risk of bias − High risk of bias

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 2

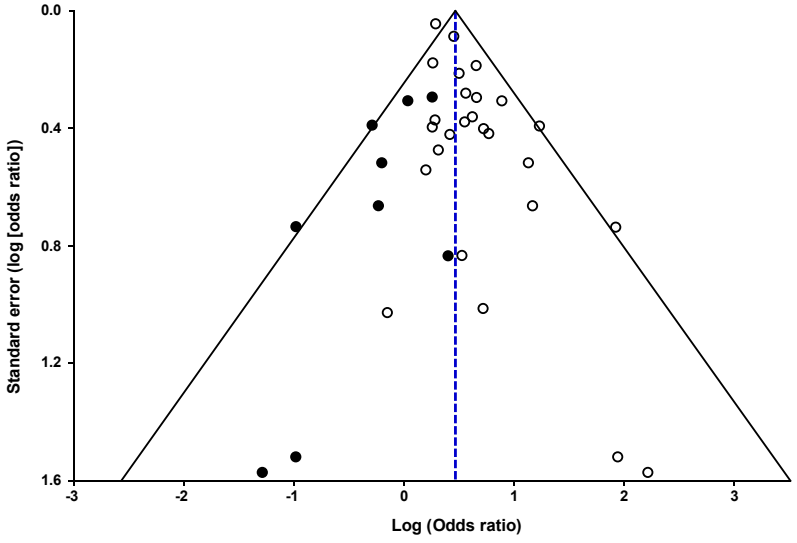
Funnel plot of the meta-analysis on the association between SARS-CoV-2 infection during pregnancy and preeclampsia



Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 3

Funnel plot of the meta-analysis on the association between SARS-CoV-2 infection during pregnancy and preeclampsia after applying the "Trim and Fill" method*

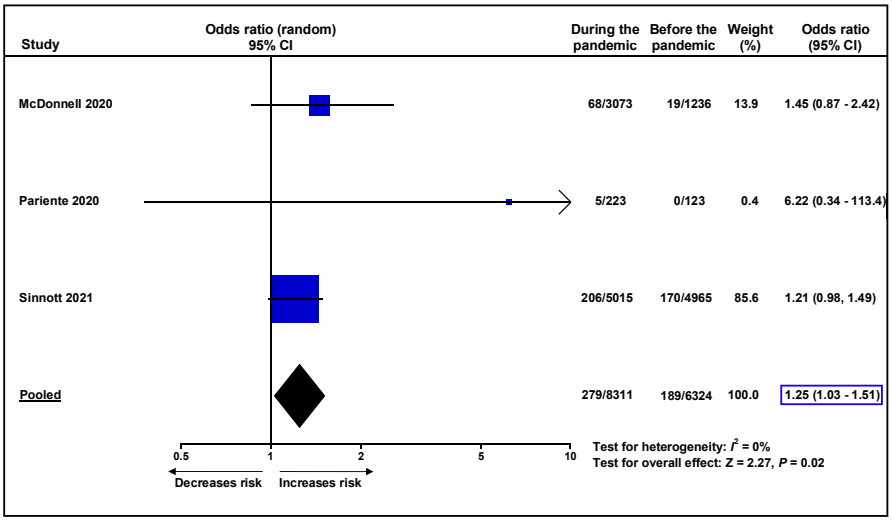


* The open circles indicate the observed studies, and the filled circles indicate the missing studies imputed by the "Trim and Fill" method.

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 4

Meta-analysis of unadjusted odds ratios for the risk of preeclampsia during the COVID-19 pandemic in comparison to before the pandemic



CI, confidence interval.

Conde-Agudelo. Association between SARS-CoV-2 infection during pregnancy and preeclampsia. Am J Obstet Gynecol 2022.