PROGNOSIS AND OUTCOMES OF PREGNANT WOMEN WITH COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT: Objective: This systematic review aimed to analyze whether COVID-19 represents a risk factor for preeclampsia, preterm birth, maternal death, neonatal death, and admission of neonates to the Intensive Care Unit (NICU). Data Sources: Searches were performed in Embase, PubMed, and CENTRAL. Study Selection: Analytical observational studies whose subjects were pregnant women with confirmed COVID-19 were included. Data Extraction: Three reviewers extracted all relevant data from the studies selected for inclusion using a standardized form previously agreed upon by the team. Data pertaining to the studies and clinical outcomes were collected. Results: Twenty studies were included in the systematic review and the meta-analysis. Over 125.000 subjects were included, among them, over 5.000 positive for COVID-19. The meta-analysis showed a significant association between COVID-19 and preterm delivery and maternal death. It was also associated with cesarean delivery,

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preeclampsia/eclampsia, and emergency cesarean. Conclusion: Patients who are present with COVID-19 infection warrant careful clinical and obstetrical vigilance due to their higher risk of adverse outcomes and measures to reduce the risk for patients and fetuses.
KEYWORDS: Pregnancy outcome; Communicable Diseases; SARS-CoV-2; COVID-19; Maternal death; Neonate.

PROGNÓSTICO E RESULTADOS DE GESTANTES COM COVID-19: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

RESUMO: Objetivo: analisar se a COVID-19 representa um fator de risco para pré-eclâmpsia, parto prematuro, morte materna, morte neonatal e admissão de neonatos na Unidade de Terapia Intensiva (UTI). Fontes de dados: As buscas foram realizadas no Embase, PubMed e CENTRAL. Seleção de estudos: estudos observacionais analíticos, cujos sujeitos eram gestantes com COVID-19 confirmado, foram incluídos. Extração de dados: Três revisores extraíram todos os dados relevantes dos estudos selecionados para inclusão usando um formulário padronizado previamente acordado pela equipe. Dados relativos aos estudos e desfechos clínicos foram coletados. Resultados: Vinte estudos foram incluídos na revisão sistemática e na meta-análise. Mais de 125.000 sujeitos foram incluídos, entre eles, mais de 5.000 positivos para COVID-19. A meta-análise evidenciou uma associação significativa entre COVID-19 e parto prematuro e morte materna. Também foi associada a parto cesáreo, pré-eclâmpsia/eclâmpsia e cesárea de emergência. Conclusão: Pacientes com COVID-19 justificam vigilância clínica e obstétrica cuidadosa devido ao seu maior risco de resultados adversos, bem como necessitam de medidas para reduzir o risco para as mães e para os fetos.
PALAVRAS-CHAVE: Desfechos na gestação; Doenças transmissíveis; SARS-CoV-2; COVID-19; Morte materna; Neonato.

PRONÓSTICO Y RESULTADOS DE LAS MUJERES EMBARAZADAS CON COVID-19: UNA REVISIÓN SISTEMÁTICA Y UN METANÁLISIS

RESUMEN: Objetivo Esta revisión sistemática tuvo como objetivo analizar si la COVID-19 representa un factor de riesgo para la preeclampsia, el parto prematuro, la muerte materna, la muerte neonatal y la admisión de neonatos en la Unidade de Terapia Intensiva (UTI). Fuentes de datos: Se realizaron búsquedas en Embase, PubMed y CENTRAL. Selección de estudios: Se incluyeron estudios observacionales analíticos cuyos sujetos fueron mujeres embarazadas con COVID-19 confirmado. Extracción de datos: Tres revisores extrajeron todos los datos relevantes de los estudios seleccionados para su inclusión utilizando un formulario estandarizado previamente acordado por el equipo. Se recopilaron los datos pertenecientes a los estudios y los resultados clínicos. Resultados: Se incluyeron 20 estudios en la revisión sistemática y el metanálisis. Se incluyeron más de 125.000 sujetos, entre ellos, más de 5.000 positivos para COVID-19. El metanálisis mostró una asociación significativa entre COVID-19 y parto prematuro y muerte materna. También se asoció con parto por cesárea, preeclampsia/eclampsia y cesárea de emergencia. Conclusión: Las pacientes que presentan infección por COVID-19 requieren una vigilancia clínica y obstétrica cuidadosa debido a su mayor riesgo de resultados adversos y medidas para reducir el riesgo para las pacientes y los fetos.
PALABRAS CLAVE: Desfechos en la gestación; Enfermedades transmisibles; SARS-CoV-2; COVID-19; Muerte materna; Neonato.

1. INTRODUCTION

In December of 2019, at the city of Wuhan, Hubei Province, in China, it was announced to the world an outbreak of pneumonia of uncertain identity 2020). Rapidly spreading to the rest of the world in 2020, according to the WHO, there has been over 700 million cases reported since the outbreak worldwide, alongside over 7 millions of deaths. (COVID-19 cases | WHO COVID-19 dashboard, 2025) The pandemic also ellicited a major response of over 13 billions vacines applied worldwide, avoding about 2 million deaths (Ioannidis *et al.*, 2025).

The COVID-19 pandemic has brought several impacts to health care worldwide including severe acute respiratory syndrome, which is one of the outcomes with the highest mortality in pregnant women. The gestational state produces a unique environment that makes mothers more vulnerable to viral infections. Physiologic changes in pregnancy increase susceptibility to infections in general, particularly when the cardiorespiratory system is affected, possibly leading, when severe, to respiratory failure.

The gestational modifications of the respiratory system include physiological dyspnea, altered functional residual capacity, and an early decrease of end-respiratory volume and residual volume due to diaphragmatic compression, resulting in reduced total lung capacity. This puts pregnant women at an increased risk for diffuse pneumonia and respiratory failure associated with infection. In pregnancy, the changes in the immune system leading to Th2 preponderance provide more susceptibility to overall infections, including viruses that are intracellular pathogens, thus contributing to morbidity and mortality. Cytokines produced by Th1 cells are bactericidal and induce an inflammatory state. However, the Th2 type produces an anti-inflammatory response (Dashraath *et al*., 2020).

The quality and scope of the current systematic reviews evaluating pregnancy and COVID-19 infection is often variable. Some studies have offered valuable insight into the similar clinical presentation of the infection that pregnant women generally have in relation to non- pregnant adults, as seen in Yang (2022), and regarding outcomes, Wei (2021) suggests association with preeclampsia, stillbirth, and low birth-weight in severe disease, while Allotey (2020) also makes an association with preterm birth, albeit does not report an increased risk of preeclampsia. It is of due note that vaccination was associated with decreased risk of adverse outcomes in pregnant patients as reported in (Watanabe, 2022). Vertical transmission has been show to be a very rare phenomena,

though decidely possible, such as in Vivanti *et al*. (2020). It is important, therefore, to better assess the maternal, obstetrical and feto-neonatal outcomes due to the fact that such knowledge may readily enable practitioners to better manage patients in such scenarios. Being able to accurately predict adverse outcomes is key to preventive and effective medical pratice, and it may also provide evidence and rational for the justification of public health campaigns such as vaccinations targetting pregnant women as priority groups. This review purports, then, to evalute the association of COVID-19 infection with such outcomes and place it among the current literature.

2. MATERIALS AND METHODS

The review was early registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol CRD42021283789. The study was carried out following the recommendations of the Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins; Green, 2011), allowing the optimization of the systematic review report.

The elaboration of the guiding research question was determined following the acronym PECO (Population, Exposure, Comparator, and Outcome). Thus, the question is: "*Given the population of pregnant women (P) diagnosed with COVID-19 (E), in comparison to pregnant without such diagnosis (C), what are the outcomes after SARS-CoV-2 infection during and after pregnancy, notably delivery? Are infected patients more likely to have preterm births, to need cesarean delivery, or to have other obstetrical complications? Are there any relevant neonatal outcomes associated with COVID-19 disease (O)*?".

2.1 Eligibility criteria

For a study to be included in this review, the study would need to be an observational analytical study (case-control, cohort, cross-sectional) (Higgins; Green, 2011; Mueller *et al.*, 2018; Stroup *et al.*, 2000) that contains the pertinent population for this review: pregnant women with completed pregnancies and a COVID-19 confirmed diagnosis, either through an RT-PCR SARS-CoV-2 positive test or a characteristic clinical presentation associated with thorax CT findings diagnostic of COVID-19. Studies that would be case reports or case series would be excluded. Any study that featured

pregnant women without completed pregnancies would also be excluded, alongside studies that didn't feature the criteria cited above for confirmed COVID-19 diagnosis.

2.2. Type of outcome measure

The relative risk (RR) and 95% confidence interval were used as analysis measures (Higgins; Green, 2011). The primary outcomes of interest regarding the exposure studied in this review, which is COVID-19 infections, are whether SARS-CoV-2 infection is a risk factor for preterm delivery, termination of pregnancy, and maternal death. Primary outcomes for neonates included NICU admission and neonatal death. Secondary outcomes for the women population included pre-eclampsia/eclampsia, gestational diabetes, elective cesarean delivery, and emergency cesarean delivery.

2.3. Search methods for identification of studies

2.3.1. Electronic searches

The searches were done through the databases Embase (Elsevier), MEDLINE (PubMed), Cochrane Library (Central Register of Controlled Trials), and the Virtual Health Library (VHL) Regional Portal. The searches were done on the 29th of December 2024. No restrictions on language or publication period were applied. The research strategy used for searching in MEDLINE via PubMed combined terms related to **pregnant women** and **COVID-19**. For the population, it included both MeSH terms and free-text variations such as *"Pregnant Women"*, *"Pregnant Woman"*, and *"Women, Pregnant"*. For the exposure, it used an extensive set of synonyms and MeSH terms for COVID-19, SARS-CoV-2, and related infections (e.g., *"COVID-19 Virus Infection"*, *"2019-nCoV Infection"*, *"Coronavirus Disease 2019"*, *"SARS-CoV-2"*). Boolean operators **OR** and **AND** were applied to ensure comprehensive retrieval, with the final search combining the pregnancy-related terms (#1) AND the COVID-19 terms (#2) AND additional virus-specific descriptors (#3). This approach maximizes sensitivity by capturing all relevant studies involving COVID-19 in pregnant women. Supplementary table exposes the search strategy in more detail.

2.4 Data collection and analysis

Three reviewers extracted all relevant data from the studies selected for inclusion using a standardized form previously agreed upon by the team.

The data to be extracted included authorship and paper relevant data, subjects and relevant results related to the clinical outcomes reviewed in our work. Furthermore, information relevant to the risk of bias was extracted and detailed in the section below.

2.5 Assessment of risk of bias and certainty of evidence in included studies

Three authors (VRNM MLLPFC and MSC) independently assessed the risk of bias of included studies using the Newcastle-Ottawa scale for cohort, case-control, and cross-sectional studies. All studies were given a quantitative grade from 0 to 9, following such criteria. Disagreements between the authors regarding the risk of bias assessment were resolved through discussion, with the involvement of a fourth review author (GRVB) when necessary. We contacted the study authors to request missing data.

After analyzing the risk of bias and conducting the meta-analysis, the GRADE tool (Grades of Recommendations, Assessment, Development, and Evaluation Working Group) was used to analyze the certainty of the evidence.

2.6. Analysis of results and summary measures

Data cleaning and preparation for analysis were done in Microsoft Office 365. The meta package (version 6.5-0) implemented in R language was used to perform the meta-analyses. The effect size, Relative Risk (RR), and 95% confidence interval (95% CI) were calculated to estimate the strength of the association between exposure to the risk factor (diagnosis of COVID-19) and outcomes (pregnant women are likely to have premature births, require a cesarean section or have other obstetric complications, as well as having relevant neonatal outcomes associated with COVID-19 disease). Random effects models were used to estimate pooled effects (Higgins; Green, 2011).

Furthermore, the I2 statistic was used to assess heterogeneity between studies (Domingues de Freitas *et al.*, 2020; Higgins; Green, 2011), and high heterogeneity was characterized as I2 > 50%. Considering statistical heterogeneity, the "baujat" argument was used for graphical analysis of heterogeneity. After identifying the studies that most contributed to making the data set heterogeneous, the "subset" argument was used to

exclude these studies, and a new meta-analysis was performed to verify heterogeneity (Mueller *et al.*, 2018; Stroup *et al.*, 2000).

Two-tailed statistics and a significance level of less than 0.05 were considered for all analyses.

3. RESULTS

3.1. Results of the search

The searches in the mentioned databases resulted in 2481 studies, and 2066 after removal of duplicates. These 2066 articles were fully read and assessed for eligibility, after which 2046 were excluded due to not having the appropriate exposition, population, or searched outcomes described in the methodology. Thus, twenty studies were included in the review, all included in the meta-analysis (Figure 1).

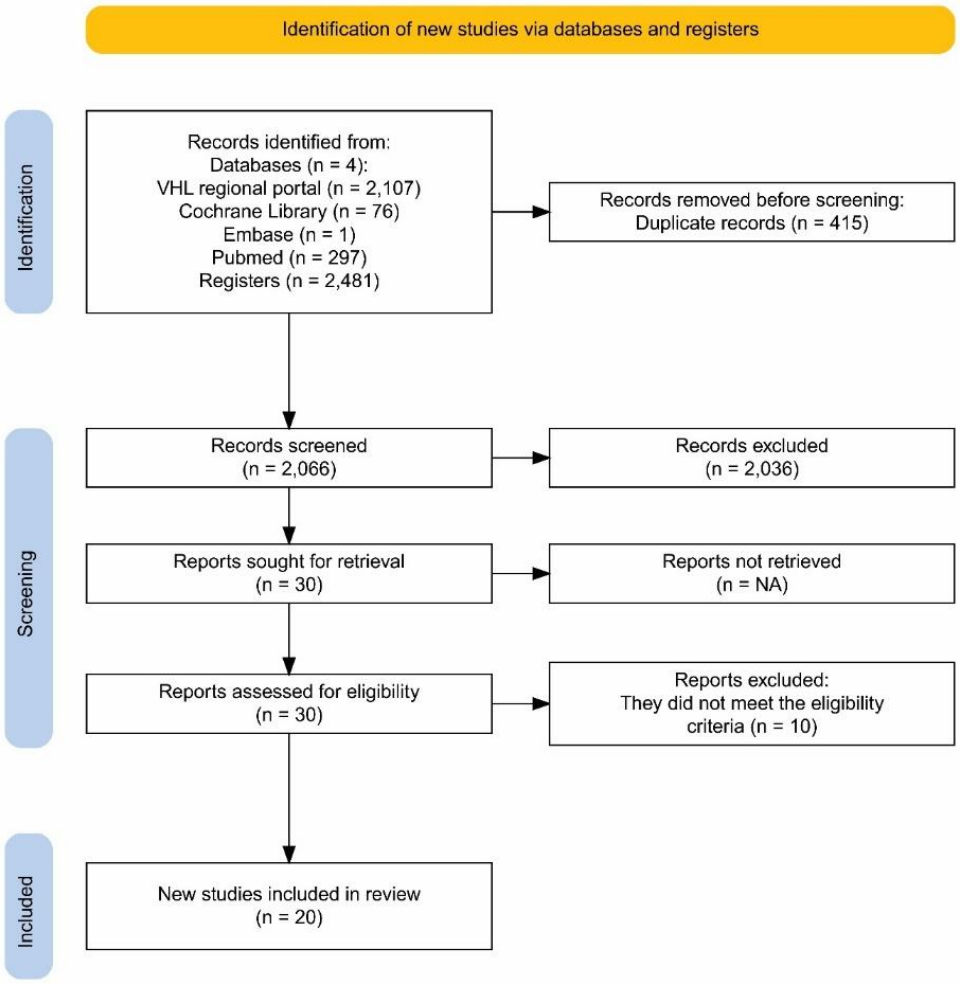

Figure 1. Diagram of the study selection steps for the SR.
After removing duplicates, the studies were selected according to the methodology described. The studies that were excluded did not meet the eligibility criteria. The reasons for excluding studies were: i) the studies did not assess for at least the primary outcomes; ii) the studies were only focused on neonatal outcomes; and iii) there were inadequate criteria for inclusion of the subjects.

3.2. Included studies

Most studies included were retrospective or prospective cohorts, with a single case-control study included. Most of the studies that described a mean age or range of age of the population usually had a 20-35 age range, with one study including women up to 49 years old. Every single study included cases with a positive RT-PCR test. Notably, 4 of the 20 studies that were included had no statistically significant findings, either from maternal, obstetrical or neonatal outcomes (Adhikari *et al.*, 2020; Crovetto *et al.*, 2021; Nayak *et al.*, 2020; Vielma *et al.*, 2020). Another four studies reported only 1 or 2 statistically significant findings; these included increased maternal mortality, decreased weeks of gestation at birth, and a higher rate of c-sections, which were, overall, the most consistent findings among studies (Akbar *et al.*, 2022; Cruz-Lemini *et al.*, 2021; Katz *et al.*, 2021; Prabhu *et al.*, 2020). Cruz-Lemini and colleagues (2021) prospective cohort is of due note because it is the only study included in this review that solely included asymptomatic cases as their subject; their only positive findings were a significantly higher PROM at term in the case group and higher NICU admission for newborns from the infected group. Adhikari and colleagues (2020) was also the single study that reported a possible vertical transmission, with confirmed viral particles found in placental tissue via electron microscopy. It is worth considering that, as many writers noted, preterm birth was often increased in case groups due to iatrogenic indications (CRUZ MELGUIZO *et al.*, 2021; YANG *et al.*, 2020). However, other studies did report higher preterm labor overall among the infected. (Akbar *et al.*, 2022; Cruz Melguizo *et al.*, 2021) reported that only nearly half of the preterm deliveries were iatrogenic. See Table 1 for a summary of all results from the studies.

Table 1. Results of studies included in the review.

Author	Methodology	Subjects	Analyzed outcomes	Conclusions
(AABAKKE *et al.*, 2021)	Prospective cohort	420 positives, 82262 negatives	Maternal outcomes: admission to an ICU, pneumonia thromboembolic events, maternal mortality, termination of pregnancy.	The risk of pneumonia and termination of pregnancy was significantly higher among cases.
(ABEDZADEH-KALAHROUDI *et al.*, 2021)	Prospective cohort	56 positive, 94 negatives, mean age ranging from 20-35	Abortion, preterm labor, pre-eclampsia, type of delivery, neonatal death, and admission to the NICU.	Exposure was associated with preterm labor, fetal distress and higher rates of preeclampsia.
(ADHIKARI *et al.*, 2020)	Prospective cohort	252 positive, 3122 negative, mean age 27.6	Preterm birth, preeclampsia with severe features, cesarean delivery.	Exposure was not significantly associated with any outcome.
(CRUZ-LEMINI *et al.*, 2021)	Prospective cohort	62 positive, 79 negative (median 28yo positive, 28,5yo negative)	Maternal death, hospital length of stay, pregnancy complications, mode of delivery, preterm delivery rates, birth weight, and size, APGAR.	Maternal deaths in the positive group were significantly higher than those in the non-COVID-19 groups as well as the length of stay.
(ALIPOUR *et al.*, 2021)	Retrospective cohort	133 positives, 165 negatives, age averaging 29.4 positives, and 30.7 negatives	Preterm birth, NICU admission, fetal distress, stillbirth, neonatal death, ICU admission, maternal mortality.	Exposure was significantly associated with: cesarian delivery, ICU admission, maternal mortality, preterm birth, fetal distress and NICU admission.
(BADR *et al.*, 2021)	Retrospective cohort	393 positive, 10532 negatives	Primary outcomes of the study were preterm delivery, preeclampsia, eclampsia, cesarean delivery, PE, pregnancy loss or maternal death. NICU admission.	Infection was associated with an increase in many obstetric and neonatal outcomes, such as preeclampsia, eclampsia, or HELLP syndrome, preterm delivery, cesarean delivery and NICU admission.

(BARACY *et al.*, 2021)	Retrospective cohort	70 positive, 210 negative	Preeclampsia, gestational diabetes, IGR, preterm labor, NICU admission.	Preterm labor was associated with COVID-19 infection, alongside severe preeclampsia.
(BRANDT *et al.*, 2021)	Case-control	Sixty-one positives, 122 negatives, age averaging 30.3 among cases and 30.9 among controls.	PE, ICU admission, maternal death, preterm delivery, intrauterine fetal demise, mode of delivery, length of hospital stay, and chorioamnionitis.	Mild cases of COVID-19 did not offer increased odds for any outcome, although moderate to severe did.
(CROVETTO *et al.*, 2021)	Prospective cohort	317 positive, 1808 negative (29-37yo)	Miscarriage, preeclampsia, preterm delivery, perinatal death, NICU.	Exposure was not associated with any outcome.
(CRUZ MELGUIZO *et al.*, 2021)	Prospective cohort	1347 positive, 1607 negative (18-49)	Preterm delivery, ICU admission, obstetric complications, stillbirth, maternal mortality, NICU admission, neonatal mortality.	Infection significantly increased risk for severe preeclampsia, preterm delivery and NICU admission.
(CRUZ-LEMINI *et al.*, 2021)	Prospective cohort	174 cases, 430 negatives	Preterm delivery, type of delivery, gestational hypertension, preeclampsia, obstetric hemorrhage, and thrombotic risk. NICU admission.	Of note is that this study only included asymptomatic cases as their subject. It showed no difference in comorbidities during pregnancy among groups. The single neonatal outcome with a statistically significant difference was NICU admission.
(HCINI *et al.*, 2021)	Prospective cohort	137 positive, 370 negative (Mean age 20-25 yo)	Maternal death, ICU admission, preterm delivery, cesarean section, acute fetal distress, neonatal death, NICU admission.	Infected patients had a higher risk of having post-partum hemorrhage and needing transfusion, ICU admissions, and intra-uterine fetal demise.
(KATZ *et al.*, 2021)	Prospective Cohort	490 positive, 964 controls, mean age 30.4 among cases, 32.0 among controls	Cesarean delivery, preterm delivery, placental abruption, length of stay, prolonged neonatal stay, transfer to the NICU, neonatal respiratory support.	Increased risk for delivery at less than 37 among positives. Cesarean delivery was associated with symptomatic infection.

(NAYAK *et al.*, 2020)	Retrospective cohort	141 positive, 836 negative	Maternal and neonatal outcomes include gestational age, mode of delivery, Apgar score, and treatment.	This study showed no statistically significant differences regarding maternal or fetal outcomes relating to COVID-19 infection.
(PRABHU *et al.*, 2020)	Prospective cohort	70 positive, 605 negative (26.1-37.2)	ICU care, readmissions, placental pathology, obstetric outcomes, and neonatal outcomes.	Infection was associated with an increased risk for cesarean delivery.
(GUPTA; KUMAR; SHARMA, 2021)	Retrospective cohort	108 positive, 3057 negative (Mean age 24.9, 17-42 yo)	Cesarian delivery, vaginal delivery, preterm delivery, birth weight, Apgar scores; fetal distress, neonatal ICU admission, neonatal deaths	Pre-term deliveries, cesarean delivery and fetal distress were associated with COVID-19 infection.
(TIMIRCAN *et al.*, 2021)	Prospective cohort	38 positive, 101 negative (Over 70% 25-35 years old)	Trimester of COVID-19 diagnosis, type of actual birth, appearance, pulse, grimace, activity, and respiration (APGAR), postpartum maternal complication, and neonatal outcomes.	Exposure was associated with cesarean delivery and preterm birth.
(VIELMA *et al.*, 2020)	Retrospective cohort	59 positive, 538 negative (Average 28,5 +- 1,3 years old)	Preterm labor, neonatal resuscitation, Apgar scores.	Preterm labor was associated with symptomatic COVID-19 infection.
(VILLAR *et al.*, 2021)	Prospective cohort	706 positive, 1424 negatives	Third-trimester vaginal bleeding, pregnancy-induced hypertension, preeclampsia/eclampsia/hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, preterm labor, infections, death, fetal death, admission to the neonatal ICU (NICU).	Exposure was significantly associated with preeclampsia, admission to the ICU, maternal death, caesarean delivery, and adverse neonatal outcomes.
(YANG *et al.*, 2020)	Retrospective cohort	65 positive, 11.013 negative (78% ranging 25-34)	PROM, gestational week, preterm birth, birth weight, neonatal asphyxia, Apgar, umbilical arterial blood gas pH < 7.15.	COVID-19 offered higher risk for cesarean delivery and preterm births.

Note: all positive diagnosis among all studies was confirmed by SARS-CoV-2 R

3.3. Risk of bias in included studies

Regarding the risk of bias (see Table 2), most of the studies were of good quality, while the rest were of fair quality. Most studies were considered not to have appropriate representability of exposed cohorts since not only did they not have a randomized set of subjects, but often they were from a somewhat restricted set of patients hospitalized in a single service. Regarding absent outcomes, in the beginning, a minority of the studies did not mention whether positive subjects were infected before or after data extraction.

3.4. Meta-analysis

The meta-analysis included exposure data (COVID-19 diagnosis) on primary outcomes (preterm birth, pregnancy termination, and maternal death), as well as having relevant neonatal outcomes (NICU admission and death) associated with COVID-19 disease because this information was standard in the twenty studies where such outcomes were observed. Besides, exposure data (diagnosis of COVID-19) on some secondary outcomes related to pregnant women were meta-analyzed, information present in all included studies, including elective cesarean delivery, emergency cesarean delivery, preeclampsia/eclampsia, and gestational diabetes mellitus.

As seen in Figures 2a and 2c, exposure to COVID-19 significantly increases the relative risk of preterm delivery and maternal death, respectively. Furthermore, the data showed that there wasn't an increase in the relative risk for the pregnancy termination outcome. (Figure 2b).

Table 2. Risk of bias summary: reviewers' judgments on each risk of bias item for each included study.

Author	COHORT								Total score	Study quality
	Selection				Comparability	Exposure				
	Representative of the exposed cohort	Selection of external control	Ascertainment of exposure	Outcome of interest not present at the start	Control	Assessment of outcomes	Sufficient follow-up time	Adequacy of follow-up		
(AABAKKE *et al.*, 2021)	☆	☆	☆		☆☆	☆	☆	☆	8	Good
(ABEDZADEH-KALAHROUDI *et al.*, 2021)		☆	☆	☆	☆☆	☆	☆	☆	8	Good
(ADHIKARI *et al.*, 2020)		☆	☆	☆	☆☆	☆	☆	☆	8	Good
(AKBAR *et al.*, 2022)		☆	☆	☆	☆☆	☆	☆	☆	8	Good
(ALIPOUR *et al.*, 2021)		☆	☆		☆☆	☆	☆	☆	7	Fair
(BADR *et al.*, 2021)		☆	☆		☆☆	☆	☆	☆	7	Fair
(BARACY *et al.*, 2021)		☆	☆		☆☆	☆	☆	☆	7	Fair
(CROVETTO *et al.*, 2021)		☆	☆	☆	☆☆	☆	☆	☆	8	Good
(CRUZ-LEMINI *et al.*, 2021)		☆	☆	☆	☆☆	☆	☆	☆	8	Good

(CRUZ MELGUIZO *et al.*, 2021)		☆	☆	☆	☆☆	☆	☆	☆	8	Fair
(GUPTA; KUMAR; SHARMA, 2021)		☆	☆		☆☆	☆	☆	☆	7	Fair
(HCINI *et al.*, 2021)		☆	☆	☆	☆☆	☆	☆	☆	8	Good
(KATZ *et al.*, 2021)		☆	☆	☆	☆☆	☆	☆	☆	8	Good
(NAYAK *et al.*, 2020)		☆	☆		☆☆	☆	☆	☆	7	Fair
(PRABHU *et al.*, 2020)		☆	☆	☆	☆☆	☆	☆	☆	8	Good
(TIMIRCAN *et al.*, 2021)		☆	☆	☆	☆☆	☆	☆	☆	8	Good
(VIELMA *et al.*, 2020)		☆	☆		☆☆	☆	☆	☆	7	Fair
(VILLAR *et al.*, 2021)	☆	☆	☆	☆	☆☆	☆	☆	☆	9	Good
(YANG *et al.*, 2020)		☆	☆			☆	☆	☆	7	Fair
CASE-CONTROL										
	Selection				**Comparability**		**Exposure**			
Study	**Adequate case definition**	**Representativeness of the cases**	**Selection of Controls**	**Definition of controls**	**The study controls for the most important factor.**	**Ascertainment of exposure**	**The same method of ascertainment for cases and controls**	**Non-response rate**	**Total score**	**Study quality**
(BRANDT *et al.*, 2021)	☆	☆	☆		☆☆	☆	☆	☆	8	Good

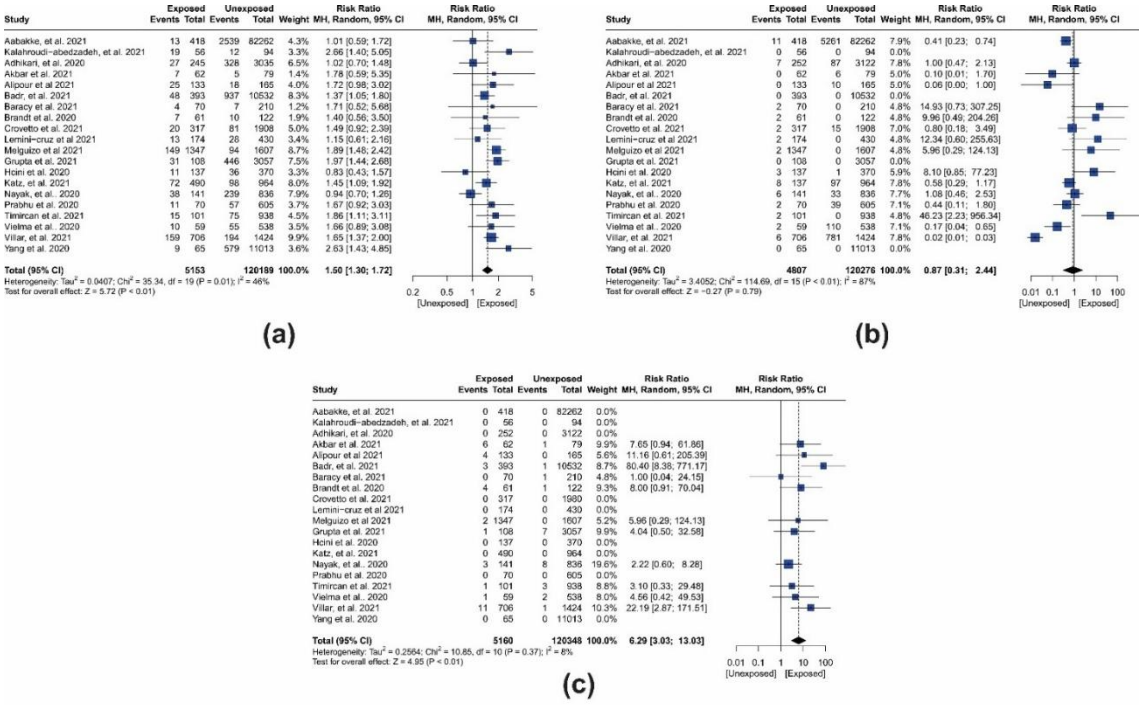

Figure 2. Metanalysis of the comparison between exposed pregnant women and non-exposed pregnant women to the primary outcomes of **(a)** preterm delivery, **(b)** termination of pregnancy, and **(c)** maternal death. The data was expressed using relative risks and confidence intervals (95% CI) (Random effects meta-analysis; heterogeneity was measured via I^2).

Eighteen studies have demonstrated that exposure to COVID-19 increases the RR of pregnant women experiencing preterm birth, and ten studies for maternal death. As for neonates, the statistical analysis showed that exposure to COVID-19 does not increase the relative risk of NICU admission and death (Figures 3a and 3b).

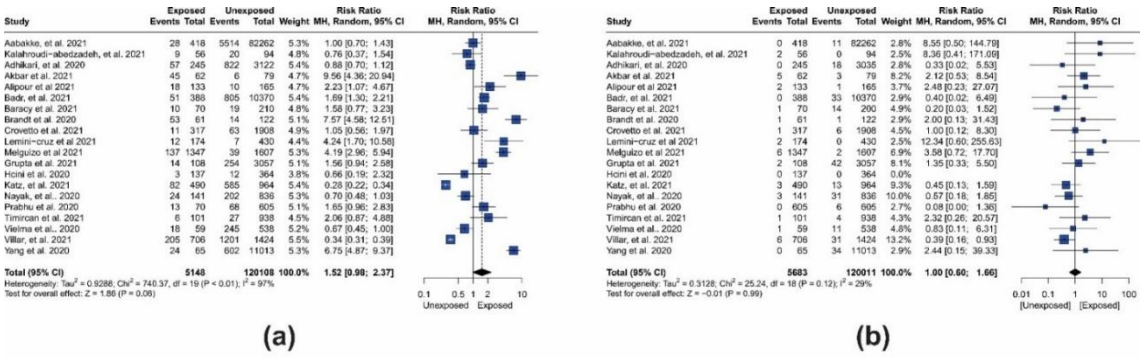

Figure 3. Metanalysis of the comparison between exposed pregnant women and non-exposed pregnant women to the primary outcomes among neonates: **(a)** NICU admission and **(b)** death. The data was expressed using relative risks and confidence intervals (95% CI) (Random effects meta-analysis; heterogeneity was measured via I^2).

Regarding the secondary outcomes, the data showed that for elective cesarean delivery, preeclampsia/eclampsia and emergency cesarean there was an increase in relative risk in pregnant women exposed to covid-19 (figure 4a, 4b, and 4c, respectively).

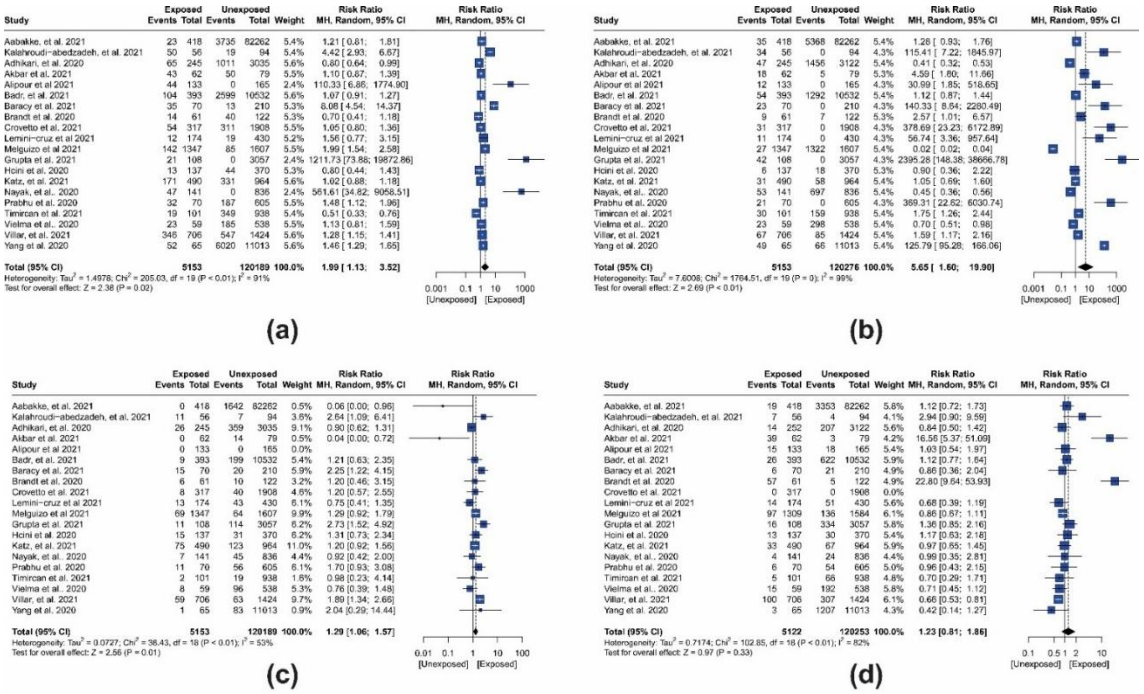

Figure 4. Metanalysis of the comparison between exposed pregnant women and non-exposed pregnant women to the secondary outcomes of **(a)** elective cesarian delivery, **(b)** emergency cesarian delivery, **(c)** preeclampsia/eclampsia, and **(d)** gestational diabetes mellitus. The data was expressed using relative risks and confidence intervals (95% CI) (Random effects meta-analysis; heterogeneity was measured via I^2).

The quality of the evidence varied depending on the outcome (see Table 3). In general, whenever the quality of evidence was either moderate or low, it would be due to either problems with precision or consistency of the studies, or even both in the case of low-quality studies. In most analyses, a high heterogeneity between studies is also observed as demonstrated above.

The "baujat" plot was used in RStudio to visually inspect the statistical heterogeneity. For most outcomes, namely preterm delivery, maternal death, preeclampsia / eclampsia, gestational diabetes mellitus and neonatal death, a group of usually three to four studies were found to justify up to 90-100% of the heterogeneity, and in all cases removing such studies from the analysis did not change significant or non-significant relative risk increases. For the outcomes of elective and emergency cesarean delivery and NICU admission, we weren't able to single out a small group of studies that justified most of the heterogeneity; however, removing the studies that contributed the most to the heterogeneity also did not change significant or non-significant results.

Table 3. Analysis of the certainty of the evidence found.

COVID-19-infected pregnant women compared to not-infected pregnant women

Patient or population: Pregnant women
Setting: Hospitals / obstetric centers
Exposition: COVID-19
Comparison: NON-COVID-19

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NON-COVID-19	Risk with COVID-19				
Maternal Death (MD)	0.2 per 1.000	**1.3 per 1.000** (0.6 to 2.6)	**RR 6.29** (3.03 to 13.03)	125508 (20 non-randomized studies)	⊕⊕⊕⊕ High	COVID-19 results in a significant increase in maternal Death.
Preterm delivery	49 per 1.000	**73 per 1.000** (63 to 84)	**RR 1.50** (1.30 to 1.72)	125342 (20 non-randomized studies)	⊕⊕⊕⊕ High	COVID-19 increases preterm delivery slightly.
Termination of pregnancy	54 per 1.000	**47 per 1.000** (17 to 131)	**RR 0.87** (0.31 to 2.44)	124883 (20 non-randomized studies)	⊕⊕◯◯ Low[a,b]	The evidence suggests that COVID-19 results in little to no difference in termination of pregnancy.
NICU admission	88 per 1.000	**133 per 1.000** (86 to 207)	**RR 1.52** (0.98 to 2.37)	125256 (20 non-randomized studies)	⊕⊕◯◯ Low [c]	The evidence suggests that COVID-19 does not increase NICU admissions.
Neonatal death	2 per 1.000	**2 per 1.000** (1 to 4)	**RR 1.00** (0.60 to 1.66)	125694 (20 non-randomized studies)	⊕⊕⊕◯ Moderate[d]	COVID-19 likely results in little to no difference in neonatal death.
Elective cesarean delivery	0 per 1.000	**0 per 1.000** (0 to 0)	not estimable	(20 non-randomized studies)	⊕⊕⊕⊕ High	

Emergency cesarean delivery	90 per 1.000	**505 per 1.000** (144 to 1.000)	**RR 5.6** (1.6 to 19.9)	125229 (20 non-randomized studies)	⊕⊕⊕⊕ High	COVID-19 results in a significant increase in emergency cesarean delivery.
Preeclampsia and eclampsia	25 per 1.000	**32 per 1.000** (27 to 40)	**RR 1.29** (1.06 to 1.57)	125342 (20 non-randomized studies)	⊕⊕⊕⊕ High	COVID-19 increases preeclampsia and eclampsia slightly.
Gestational diabetes mellitus	56 per 1.000	**69 per 1.000** (45 to 104)	**RR 1.23** (0.81 to 1.86)	125375 (20 non-randomized studies)	⊕⊕⊕◯ Moderate [e]	COVID-19 likely results in little to no difference in gestational diabetes mellitus.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

[a.] Studies in our first plot confidence intervals do not coincide in many instances of our meta-analysis.

[b.] Wide interval of confidence (0.31 to 2.44).

[c.] Studies in our first plot confidence intervals do not coincide in many instances of our meta-analysis. Significant heterogeneity was left unexplained as well.

[d.] a relatively wide interval of confidence given the relevance of the outcome (0.60 to 1.66)

[e.] Somewhat wide interval of confidence (0.81 to 1.86)

GRADE Working Group grades of evidence

High certainty: we are confident that the actual effect is close to the effect estimates.

Moderate certainty: we are moderately confident in the effect estimate: the actual effect is likely to be close to the estimate of the impact, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the actual effect may differ substantially from the impact estimate.

Very low certainty: we have very little confidence in the effect estimate: the actual effect is likely to be substantially different from the estimate of effect.

4. DISCUSSION

We were able to ascertain that COVID-19 in pregnancy is associated with preterm delivery and that it is strongly associated with maternal death. We also found that there isn't any significant link between COVID-19 in the mothers of neonates and their outcomes. Finally, our study also found that COVID-19 was strongly associated with both elective, emergency cesarean deliveries and preeclampsia or eclampsia among patients.

A unique aspect of our study is the fact that it has reviewed the literature after the end of the Public Health Emergency of International Concern declared by the WHO (Burki, 2023), meaning it is up to date regarding what took place during the pandemic and was able to screen for the highest quality observation studies at the time; during 2020, most systematic reviews were based on case reports or case series. At times, some reports reported no clinical differences among both groups of patients Matar and Colleagues (2020) or that pregnant women would be protected from symptoms compared to non-pregnant women with COVID-19. Prior systematic reviews had similar results to ours, albeit with some differences. Prior reviews included the one by Di Toro and Colleagues (2021), which included 17 case series among their reviewed studies out of 24 and exposed a higher cesarean rate but didn't review the data for many of our outcomes. Islam and colleagues (2020) very early effort was able to include 13 retrospective studies reviewing the data on COVID-19 pregnant women, concluding that there were no clinical differences between these and the general population infected. Wei and colleagues (2021) included more studies than our review, opting not to include case series, with 42 studies among prospective cohorts, retrospective cohorts, and case-control studies. It also came to similar conclusions compared to our findings regarding COVID-19's association with preeclampsia, preterm births, and cesarean deliveries. However, our review included more data per outcome; for instance, Wei included 18 studies for the preterm outcome compared to our 20 studies, and all the other outcomes associated in a statically significant fashion had fewer studies for each. They also found a substantial association with NICU admission, which we did not find statistically significant. In sharp contrast to Wei's or our findings, Allotey and colleagues (2020) living systematic review, which included studies with comparison groups of women who were not pregnant and studies without comparison groups, actually concluded that pregnant women were at a lesser risk of symptomatic disease and adverse outcomes compared to the general population. Finally, Marchand and colleagues, (2020) systematic review, having included case studies and

even short communications in the literature, came to a similar conclusion to ours except in terms of maternal death, in which they did not find an association, possibly influenced by the pattern of the lower quality studies of the early phase of the pandemic which, as previously established, tended to minimize the outcomes due to COVID-19 exposure in pregnant women.

The increased rates of maternal death among the exposed, as shown by the majority of the studies in our review and elsewhere, are strongly associated with the presence of comorbidities such as obesity and chronic respiratory disease. Age is also a relevant risk factor that is related to an increase in death among patients. Given the current state of the virus outbreak, it may not be feasible nor even necessary to screen every pregnant patient presenting with respiratory symptoms for COVID-19; however, those older and with comorbidities should be considered for screening and, if positive, be under careful clinical observation and management, to avoid unfavorable outcomes. Hospitalar admission in severe cases could be considered whenever a more severe case presents in the obstetrical emergency room; even if admission is not opted, a closer arterial blood pressure monitoring or more frequent pre-natal consults should be considered as well.

It is not fully understood the mechanism behind why COVID-19 infection among pregnant women is associated with increased preterm birth rates. Mak, Cicero an Hui (2023), reasoning as well why some of the literature differs, proposes that this may be due to the significant stress that pregnant women, in general, were put during the pandemic, including but not limited to work-related limitations, lockdowns, social distancing, etc. We would also argue that another factor that may be considered is that pre-natal care was severely hindered during the pandemic, particularly in undeveloped countries (Santos *et al*., 2022). The lack of access may have led to preventable causes of preterm birth that could've been diagnosed and managed early on during pre-natal care to be left unchecked. Services then should organize themselves to enable continuous access to pre-natal care for their patients, even if they may become infected with COVID-19, via digital means of care such as telemedicine. In any case, even today, if a patient presents with COVID-19, the data indicates that she should be closely monitored for the possibility of labor during a hospital stay. Should such patients require respiratory support, they should also receive corticosteroids, which may aid with respiratory distress and, in the context of possible preterm birth, may be worthwhile for pulmonary maturation (Vidaeff; Aagaard; Belfort, 2021).

The mechanism of development of preeclampsia in COVID-19-infected patients is still up for debate. Still, a proposed one includes the virus binding to the Angiotensin-Conversing Enzyme 2 receptor, which is linked with arterial blood pressure regulation and angiogenesis in the placenta (Torres-Torres *et al*., 2022). It was also shown that SARS-CoV-2 upregulates antiangiogenic factors that may also contribute to this specific pathogenesis (Beys-da-Silva *et al*., 2021).

The association between COVID-19 infection and preeclampsia and eclampsia suggests that clinicians should closely monitor blood arterial pressure and laboratory markers to diagnose and manage such complications readily. Preeclampsia and eclampsia are not only outcomes strongly linked to maternal morbidity and mortality but are also associated with fetal mortality due to fetal distress and growth restriction.

In general, COVID-19 infection in the population of pregnant women should elicit closer clinical monitoring, especially if the patient already has other clinical comorbidities, such as older age, obesity, respiratory and cardiovascular diseases. Often times such clinical and maternal comorbidities are indications of scheduling delivery prior to 40 weeks; given how COVID-19 infection may more often than not worsen such conditions, it may be worthwhile to individualize each case and consider the most appropriate time for delivery given the patient context.

5. LIMITATIONS

Our study avoided including case reports and case series for our systematic. Therefore, we decisively avoided the bias associated with these types of observation studies, which often are of poor quality, in particular, the ones written in the early stages of the pandemic; it also means we end up not including a vast portion of the available data regarding COVID-19 pregnant women in 2020 and 2021.

It is important to consider as well that given the pandemic state and the worldwide stress that it offered to healthcare systems, the outcomes described may suffer from publication bias. The high heterogeneity observed in many of the outcomes may be attributed to that. For instance, both emergency and elective cesareans may have had overly inflated rates due to the significant stress that obstetric centers suffered due to the pandemic, leading to sometimes iatrogenic indications of cesarean delivery.

6. CONCLUSION

The meta-analysis showed a significant association between COVID-19 and preterm delivery and maternal death. It was also associated with cesarean delivery, preeclampsia/eclampsia, and emergency cesarean. Our study, in general, these findings are consistent with clinical practice and, through a set of observational studies of moderate to high quality, firmly confirm the adverse outcomes associated with COVID-19 infection in pregnant patients. Even as the virus circulation has significantly decreased as of 2024, patients who present with the diagnosis warrant careful clinical and obstetrical vigilance due to their higher risk of adverse outcomes and measures to reduce the risk for patients and fetuses.

DECLARATION OF COMPETING INTEREST

None.

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AUTHORSHIP CONTRIBUTION

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Gustavo Roberto Villas Boas: General guidance for the development of the manuscript; Conceptualization; Investigation; Methodology; Project administration; Software (Making figures); Supervision; Validation; Visualization; Roles/Writing—original draft; Writing—review and editing.