

SARS-COV-2 INFECTION DURING PREGNANCY AND RISK OF PREECLAMPSIA: A SYSTEMATIC REVIEW

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ABSTRACT

Background: The concurrence of pregnancy-related diseases (gestational hypertension, preeclampsia and eclampsia) with the COVID-19 virus is a clinical novelty, classified as a serious maternal risk. 1 2 A living systematic review with meta-analysis in pregnant and recently pregnant women reported severe COVID-19 infection in 9%; the intensive care unit admission required in 4%; invasive ventilation used in 2%; and extracorporeal membrane oxygenation administered in 0.2%.

The aim: This study aims to show about SARS-CoV-2 infection during pregnancy and risk of preeclampsia.

Methods: By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Result: In the PubMed database, the results of our search brought up 99 articles, whereas the results of our search on SagePub brought up 66 articles. The results of the search conducted for the last year of 2013 yielded a total 98 articles for PubMed and 36 articles for SagePub. The result from title screening, a total 2 articles for PubMed and 16 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.

Conclusion: The characteristics of SARS-CoV-2-infected pregnant women and preeclamptic women seem to be more or less similar with regard to proteinuria, elevated liver enzymes, thrombocytopenia, and increased pro-inflammatory markers. Hence, diagnosis of preeclampsia could be quite difficult.

Keyword: SARS-CoV-2, Pregnancy, Preeclampsia.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent behind Coronavirus disease 19 (COVID-19) in late 2019. Since then it has already caused over 649,147,421 infections and over 6,730,382 deaths worldwide. In 11 March 2020 WHO declared a state of pandemic. SARS-CoV-2 is an RNA virus related to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Pregnant women with COVID-19 are at higher risk of severe course and negative pregnancy outcomes (caesarean delivery, pre-term birth (PTB), low birth weight, preeclampsia (PE), ICU admission and need for mechanical ventilation). As well as are at higher risk of developing pregnancy specific disorders (PE, PTB and premature preterm rupture of membranes). We focus on the subcellular changes that occur in pregnant women with COVID-19 to try to elucidate how those disorders may be triggered by the infection with SARS-CoV-2.^{1,2}

During pregnancy, the risk of adverse obstetric and neonatal outcomes is heightened by various respiratory viral infections. The physiological and immunological changes inherent to a normal pregnancy can result in systemic effects that make pregnant individuals more susceptible to complications from respiratory infections. Alterations in maternal cardiovascular and respiratory systems, including increased heart rate and oxygen consumption, higher stroke incidence, reduced lung capacity, and immune adaptations to accommodate the tolerance of the fetus to different antigenic characteristics, collectively contribute to an increased likelihood of pregnant women experiencing severe respiratory illnesses.^{3,4}

PE is a condition that complicates pregnancy, poses a substantial risk to the health of both the mother and the fetus, resulting in adverse perinatal outcomes and induced premature birth. PE occurs in approximately 2–4% of pregnancies, and its precise etiology remains incompletely understood. However, it is believed to involve maternal vascular malperfusion and cardiovascular maladaptation due to an imbalance in angiogenic factors, endothelial dysfunction, coagulopathy, and insufficient complement regulation. Acknowledging the syndrome-based nature of PE, the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy made a significant change in 2013 with updates and recommendations made in 2019 and 2020. They eliminated the requirement of proteinuria for diagnosis and instead focused on new-onset hypertension accompanied by indicators of organ dysfunction. These indicators include thrombocytopenia, hypertransaminasemia, elevated serum creatinine in the absence of other kidney disease, pulmonary edema, or the onset of cerebral or visual disturbances.^{3,5}

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we showed about SARS-CoV-2 infection during pregnancy and risk of preeclampsia. It is possible to accomplish this by researching or investigating the SARS-CoV-2 infection during pregnancy and risk of preeclampsia. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about SARS-CoV-2 infection during pregnancy and risk of preeclampsia. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "SARS-CoV-2 infection during pregnancy"; "SARS-CoV-2 infection risk of preeclampsia" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: (*"SARS-Cov-2"[MeSH Subheading] OR "SARS-CoV-2 during pregnancy"[All Fields] OR "SARS-CoV-2 risk of preeclampsia"[All Fields]*) AND (*"SARS-CoV-2 and preeclampsia"[All Fields] OR "SARS-CoV-2 infection"[All Fields]*) AND (*"preeclampsia"[MeSH Terms] OR ("infection covid during pregnancy"[All Fields]) OR ("the impact SARS-CoV-2 during pregnancy [All Fields])*) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to

the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

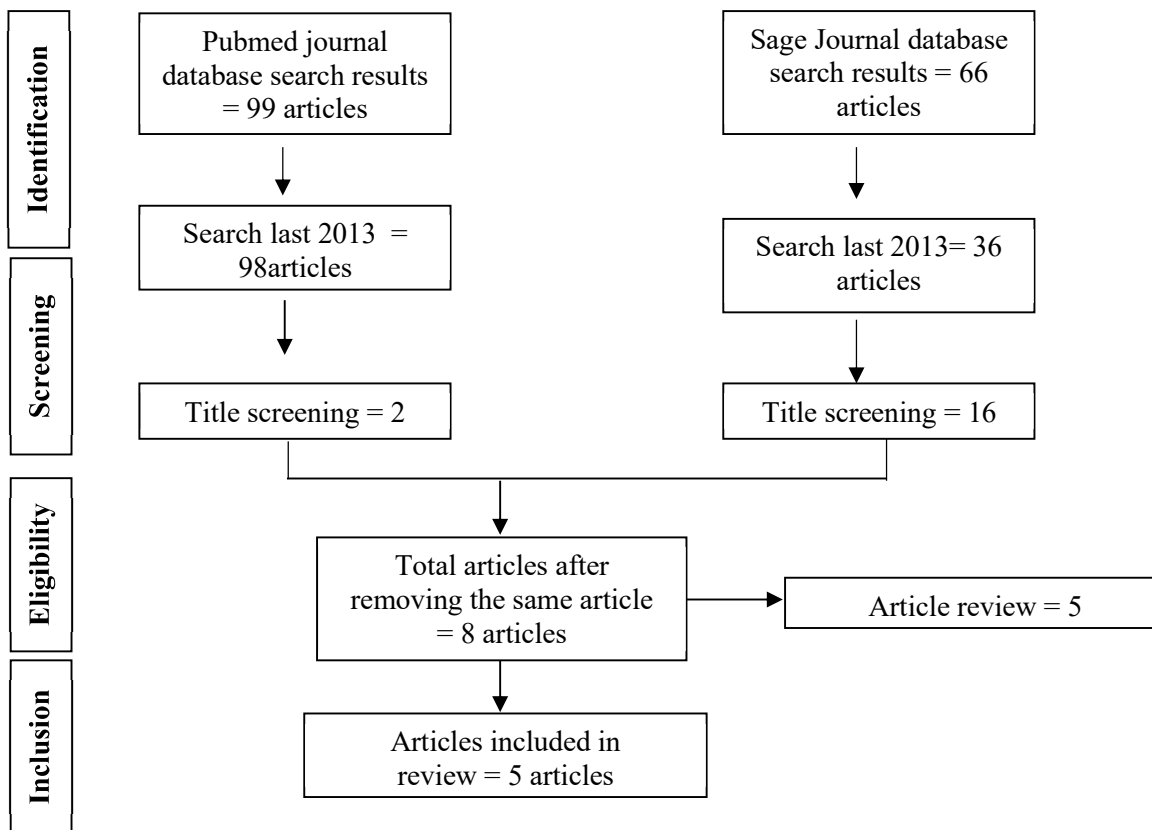


Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 99 articles, whereas the results of our search on SagePub brought up 66 articles. The results of the search conducted for the last year of 2013 yielded a total 98 articles for PubMed and 36 articles for SagePub. The result from title screening, a total 2 articles for PubMed and 16 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.

Ortqvist, AK *et al* (2022)⁶ showed with nationwide registry data from Sweden and Norway, we did not find any evidence of an association between SARS-CoV-2 infection during pregnancy and subsequent development of hypertension during pregnancy or pre-eclampsia. They accounted for timing of infection and onset of hypertension during pregnancy. Because infection with the SARS-CoV-2 virus in pregnancy is related to other adverse outcomes of pregnancy, vaccination of pregnant individuals is recommended.

Papageorgiou, AT *et al* (2021)⁷ showed COVID-19 during pregnancy is strongly associated with preeclampsia, especially among nulliparous women. This association is independent of any risk factors and preexisting conditions. COVID-19 severity does not seem to be a factor in this association. Both conditions are associated independently of and in an additive fashion with preterm birth, severe perinatal morbidity and mortality, and adverse maternal outcomes.

Women with preeclampsia should be considered a particularly vulnerable group with regard to the risks posed by COVID-19.

Table 1. The literature include in this study

Author	Origin	Method	Sample Size	Result
Ortqvist, AK et al., 2022⁶	Sweden	Prospective, population based cohort study	312 456 patients	Of 312 456 individuals available for analysis, 8% (n=24 566) had SARS-CoV-2 infection any time during pregnancy, 6% (n=18 051) had a diagnosis of hypertension during pregnancy, and 3% (9899) had pre-eclampsia. SARS-CoV-2 infection during pregnancy was not associated with an increased risk of hypertension during pregnancy (adjusted hazard ratio 0.99, 95% confidence interval 0.93 to 1.04) or pre-eclampsia (0.98, 0.87 to 1.10). The results were similar for SARS-CoV-2 infection in all gestational trimesters and in different time periods that corresponded to dominance of different variants of the SARS-CoV-2 virus. Conclusions This population based study did not find any evidence of an association between SARS-CoV-2 infection during pregnancy and an increased risk of hypertension during pregnancy or pre-eclampsia.
Papageorghiu, AT et al., 2021⁷	United Kingdom	A large, longitudinal, prospective, unmatched diagnosed and not-diagnosed observational study	2184 pregnant women	We enrolled 2184 pregnant women; of these, 725 (33.2%) were enrolled in the COVID-19 diagnosed and 1459 (66.8%) in the COVID-19 not-diagnosed groups. Of these women, 123 had preeclampsia of which 59 of 725 (8.1%) were in the COVID-19 diagnosed group and 64 of 1459 (4.4%) were in the not-diagnosed group (risk ratio, 1.86; 95% confidence interval, 1.32–2.61). After adjustment for sociodemographic factors and conditions associated with both COVID-19 and preeclampsia, the risk ratio for preeclampsia remained significant among all women (risk ratio, 1.77; 95% confidence interval, 1.25–2.52) and nulliparous women specifically (risk ratio, 1.89; 95% confidence interval, 1.17–3.05). There was a trend but no statistical significance among parous women (risk ratio, 1.64; 95% confidence interval, 0.99–

				<p>2.73). The risk ratio for preterm birth for all women diagnosed with COVID-19 and preeclampsia was 4.05 (95% confidence interval, 2.99–5.49) and 6.26 (95% confidence interval, 4.35–9.00) for nulliparous women. Compared with women with neither condition diagnosed, the composite adverse perinatal outcome showed a stepwise increase in the risk ratio for COVID-19 without preeclampsia, preeclampsia without COVID-19, and COVID-19 with preeclampsia (risk ratio, 2.16; 95% confidence interval, 1.63–2.86; risk ratio, 2.53; 95% confidence interval, 1.44–4.45; and risk ratio, 2.84; 95% confidence interval, 1.67–4.82, respectively). Similar findings were found for the composite adverse maternal outcome with risk ratios of 1.76 (95% confidence interval, 1.32–2.35), 2.07 (95% confidence interval, 1.20–3.57), and 2.77 (95% confidence interval, 1.66–4.63). The association between COVID-19 and gestational hypertension and the direction of the effects on preterm birth and adverse perinatal and maternal outcomes, were similar to preeclampsia, but confined to nulliparous women with lower risk ratios.</p>
Sessa, R <i>et al.</i>, 2023⁸	Italy	A prospective observational study	204 pregnant women	<p>The cases showed a significant association with the development of some obstetric complications, such as intrauterine growth restriction and pregnancy-associated hypothyroidism and diabetes, as compared to controls; their newborns were more likely to have a low birth weight and an arterial umbilical pH less than 7. The viral genome was detected in maternal and cord blood and placental samples in six cases.</p>
Tran, M <i>et al.</i>, 2022⁹	France	Retrospective exposed/unexposed cohort study	279 participants	<p>The frequency of preeclampsia was 3.2% (3/93) in the exposed group, versus 2.2% (4/186) in the unexposed group (P = 0.58). Among the nulliparous patients, the frequency of preeclampsia was 4.9% (2/41) in the exposed group versus</p>

				0.9% (1/106) in the unexposed group (P = 0.13). The association between COVID-19 and preeclampsia was not significant after multivariate analysis (OR 3.12, 95% CI 0.39-24.6).
Lai, J <i>et al.</i> , 2021 ¹⁰	United Kingdom	A retrospective observational study	1223 patients	The prior risk of preeclampsia in a cohort of patients with comparable risk factors as those of the study population was approximately 1% (Figure , A). The observed rate of preeclampsia, after excluding the cases diagnosed before SARS-CoV-2 infection, was higher than expected: 1.9% in asymptomatic patients, 2.2% in patients with mild COVID-19, 5.7% with moderate disease, and 11.1% among patients with severe disease (Figure, A). This monotonic relationship between the severity of COVID-19 and the risk of developing preeclampsia was statistically significant (chi-square test for trend; P=.0017). We then compared the risk of preeclampsia between asymptomatic patients (reference group) and patients with COVID-19 symptoms while adjusting for differences in the prior risk of preeclampsia, as determined by the competing risk model. Severe COVID-19 disease was associated with a higher risk of preeclampsia (adjusted risk ratio [RR], 4.9; 1.56–15.38). There was a higher risk for patients with moderate or severe COVID-19 diagnosis as compared to those with asymptomatic or mild disease (adjusted RR, 3.3; 1.48–7.38).

Sessa, R *et al* (2023)⁸ showed pregnant women positive for SARS-CoV-2 infection are more likely to develop severe obstetric outcomes; their newborns could have a low birth weight and arterial pH. Vertical transmission seems a rare event, and further investigation is strongly needed.

Tran, M *et al* (2022)⁹ showed Symptomatic COVID-19 infection during pregnancy does not appear to increase the risk of preeclampsia strongly, although the size of our sample prevents us from reaching a conclusion about a low or moderate risk. It therefore does not appear necessary to reinforce preeclampsia screening in patients with symptomatic COVID-19 infection during pregnancy.

Lai, J *et al* (2021)¹⁰ showed that the more severe the infection with SARS-CoV-2, the greater the risk of preeclampsia and preterm birth. SARS-CoV-2 infection can lead to endothelial dysfunction, intravascular inflammation, proteinuria, activation of thrombin, and hypertension, which are all features of preeclampsia. Therefore, a causal relationship must be considered.

DISCUSSION

Pregnant women are at high risk of viral pneumonia compared to the general population, especially in the absence of antiviral therapy. The unfavorable impact of SARS-CoV-2 infection during pregnancy might be due to the RAAS dysregulation. The most common COVID-19 related adverse outcomes in the pregnant women include maternal sepsis, preeclampsia, premature rupture of membrane and post-partum hemorrhage. Also, hypertension is known as a strong risk factor for complicated COVID-19. Preeclampsia is presented with hypertension, proteinuria, edema, and a coagulation cascade activation. The RAAS dysregulation is involved in the pathogenesis of preeclampsia. Angiotensin is produced through the action of ACE2 on angiotensin I and the imbalance between angiotensin (Ang) II and Ang-(1-7) might be involved in the etiology of the preeclampsia.¹¹

Hypertensive disorders of pregnancy are common complications that put mothers and their fetuses at heightened risk for perinatal morbidity and mortality in addition to life-long sequelae and long-term risk of cardiovascular disease. Preeclampsia is the most frequent hypertensive complication of pregnancy, occurring in approximately five to seven percent of pregnancies globally, with a higher incidence in some indigenous women and those from low- and middle-income countries, such as those in sub-Saharan Africa. In addition to its being an obstetrical management challenge, preeclampsia is also a major global maternal health and public health problem as it is responsible every year for over 70,000 maternal deaths and 500,000 fetal deaths worldwide.¹²

Pregnant women with SARS-CoV-2 infection may experience more severe symptoms compared with nonpregnant women. Existing limited data have reported on rapid deterioration in women who had no symptoms on arrival and were subsequently diagnosed as having severe COVID-19. In some, but not all, patients, maternal comorbidities were present (hypertension, diabetes, cholestasis of pregnancy). Case reports have also described cases of quickly worsening maternal status with the ultimate diagnosis of cardiomyopathy. Unfortunately, these rapidly progressive maternal complications have led to a high rate of cesarean deliveries (CDs) for either worsening maternal status or nonreassuring fetal status secondary to the worsening maternal clinical state.^{13,14}

Preeclampsia is an example of a common pregnancy-related complication that may be exacerbated by, or may exacerbate, COVID-19, as previously discussed. The picture becomes further complicated because the two processes share common laboratory abnormalities. Thus, it may be difficult to discern whether certain abnormal laboratory findings are due to SARS-CoV-2 infection or preeclampsia, and this interplay may have treatment implications. For example, thrombocytopenia and liver function abnormalities, both of which are diagnostic criteria for preeclampsia with severe features, are also associated with worsening COVID-19.^{13,15}

CONCLUSION

The characteristics of SARS-CoV-2-infected pregnant women and preeclamptic women seem to be more or less similar with regard to proteinuria, elevated liver enzymes, thrombocytopenia, and increased pro-inflammatory markers. Hence, diagnosis of preeclampsia could be quite difficult. In view of the above scenario, verification of VEGF, PIGF, sFlt-1, and sFlt-1/PIGF, along with other biochemical markers, plays a crucial role in the differential diagnosis of preeclampsia, and would help to avoid unnecessary interventions and induced preterm labor among SARS-CoV-2-positive pregnant women.

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