Impact of SARS-CoV-2 (COVID-19) on pregnancy: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has been growing at an accelerating rate, and has become a public health emergency. Pregnant women and their fetuses are susceptible to viral infection, and outcomes in this population need to be investigated.

Methods and analysis PubMed, Web of Science, Embase, CINAHL, Latin American and Caribbean Health Sciences Literature, clinicaltrials.gov, SCOPUS, Google Scholar and Cochrane Central Controlled Trials Registry will be searched for observational studies (cohort and control cases) published from December 2019 to present. This systematic review and meta-analysis will include studies of pregnant women at any gestational stage diagnosed with COVID-19. The primary outcomes will be maternal and foetal morbidity and mortality. Three independent reviewers will select the studies and extract data from the original publications. The risk of bias will be assessed using the Newcastle-Ottawa Scale for observational studies. To evaluate the strength of evidence from the included data, we will use Grading of Recommendation Assessment, Development, and Evaluation method. Data synthesis will be performed using Review Manager software V.5.2.3. To assess heterogeneity, we will compute the I² statistics. Additionally, a quantitative synthesis will be performed if the included studies are sufficiently homogenous.

Ethics and dissemination This study will be a review of the published data, and thus it is not necessary to obtain ethical approval. The findings of this systematic review will be published in a peer-reviewed journal.

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INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has been growing at an accelerating rate, and has become a public health emergency. Studies of previous human coronavirus outbreaks, namely the SARS-CoV and the Middle East respiratory syndrome coronavirus, indicate that pregnant women and their fetuses are susceptible to viral infection.1 2

Physiological changes, such as immune-suppressed conditions, which occur during pregnancy, make the mother more vulnerable to severe infections.3 4 The elevation of the diaphragm, along with increased oxygen consumption and oedema of the respiratory tract mucosa, decrease residual lung functional capacity during pregnancy.5 Some studies have reported that pregnant women with pneumonia have a higher risk of caesarean section and premature delivery, and decreased Apgar Score and low birth weight of the newborn. Even patients with COVID-19, who only have mild respiratory symptoms, can still be at a high risk of severe pneumonia and adverse pregnancy outcomes, especially in those with pre-eclampsia or other complications.6

Vertical transmission after maternal infection usually occurs during intrauterine life through the transplacental pathway, by ingestion or aspiration of cervicovaginal secretions, or postpartum via breast feeding. Although breast feeding is discouraged by many authors, since viral transmission occurs through contact with infected body fluids, it is possible for the mother to produce enough neutralising antibodies during infection, which can have a protective effect on the newborn.6 7

Strengths and limitations of this study

► The results obtained in this systematic review will indicate through evidence-based medicine if there is a greater risk of unfavourable outcomes for pregnant women and newborns infected with COVID-19.
► Three independent reviewers will select the studies included in this review, extract data without different variables and assess the risk of bias.
► There may be a limitation of outcome due to the type and quality of studies used in the systematic review.
► Potential limitations include a small sample size and a limited number of studies, which may influence the validity and reliability of the findings.
Currently, there is limited knowledge regarding the clinical impact of COVID-19 on maternal, foetal and placental aspects of pregnancy due to limited scientific data outcomes from a handful of case reports and series. The sample sizes in these publications were small, and the findings were diverse. Thus, it is vital that scientific information concerning the disease is shared concisely and practically.1,2

Additional information is critically needed to inform key decisions, such as whether pregnant healthcare workers should receive special consideration, whether to separate infected mothers and their newborns and whether it is safe for infected women to breast feed. There are other unanswered questions specific to pregnant women, such as whether pregnant women are more severely affected and whether intrauterine transmission occurs.1,3

More studies are needed to clarify COVID-19’s relationship to other outcomes inherent to pregnancy,6 such as foetal–maternal morbidity and mortality,1,3 intrauterine growth restriction, arterial hypertension, renal failure, HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Lowered Platelets), miscarriage and placenta previa.4

OBJECTIVES
This systematic review and meta-analysis protocol aims to clarify the clinical features of COVID-19 and analyse maternal and foetal morbidity and mortality, as well as the obstetric and neonatal outcomes, of pregnant patients with COVID-19.

MATERIALS AND METHODS
The proposed systematic review and meta-analysis conforms to the Meta-analysis of Observational Studies in Epidemiology8 and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.7,9 This protocol is registered with the International Prospective Register of Systematic Reviews.

Inclusion criteria
This systematic review will include the following studies: those with observational designs (control case and cohort); studies that describe women affected by SARS-Cov-2/COVID-19 in pregnancy; and studies published since December 2019 (because the first case of COVID-19 was registered in Wuhan, China, in December 201910). There will be no language restrictions when selecting studies.

The PECOT strategy
► Population/participants: pregnant women at any gestational age.
► Exposure: pregnant women diagnosed with COVID-19.
► Comparator/control: pregnant women without COVID-19.
► Outcome: maternal and foetal morbidity and mortality according to WHO.11,12
► Types of studies: observational studies (cohort and control cases).

Types of patients
Participants will be pregnant women diagnosed with COVID-19 at any stage of pregnancy. There will be no age restrictions.

Types of exposures
The review will include studies that describe pregnant women diagnosed with COVID-19 at any stage of pregnancy. Pregnant women should be diagnosed using the principal method: nasopharyngeal swabs for real-time reverse-transcriptase polymerase chain reaction (RT-PCR).13–15

Types of outcome measures

Pregnancy outcomes
► Caesarean delivery5,16–21 (due to maternal hypoxaemia).
► Pre-existing and pregnancy-related maternal comorbidities (diabetes).14
► CT of the chest revealing bilateral or unilateral pneumonia,14 multiple regions of patchy consolidation and ground glass opacities,15–17,21,22 or inflammation in both lungs and a small amount of pleural effusion,15,20,21
► Intraoperative blood loss.17,23
► Lymphopaenia (<1·0×10^9 cells/L).16,17,19–21
► Elevated concentrations of C reactive protein (>10 mg/L).16,17,19–22
► Decreased albumin.19,22
► Intensive care unit admissions.14–16
► Foetal distress,14,15,18 premature rupture of the membrane and stillbirth12 (here categorised as a pregnancy outcome).11,14,15
► Preterm labour.5,16
► Maternal death.
► Clinical management and treatment.
  – Hospital admission.4,15,18–20,22–24
  – Carbetocin or carboprost tromethamine for uterine contraction fatigue.23
  – Induction of labour with oxytocin.10
  – Oxygen therapy.15,16
  – Human serum albumin.24
  – Antiviral medication15,16,19,20,22,24 (oseltamivir,19,20 ganciclovir, lopinavir,22,24 ritonavir,22,24 arbidol24).
  – Use of interferon inhalation.24
  – Use of empirical antibiotic treatment15,16,20 (cefeoperazone sodium and sulbactam sodium,22,24 azithromycin,19,20 cefotiam hydrochloride and ornidazole,20 or ceftazidime20).
  – Methylprednisolone for pneumonia.20,22
  – Dexamethasone for lung maturation and magnesium sulphate as prophylaxis for foetal neuroprotection.24

Neonatal outcomes
► The neonatal birth weight14,21,24 and Apgar Scores were normal, and no complications were observed in the newborns.14,16,17,19,21,22
► Foetal brachycardia, with regard to the possibility of foetal distress.16 23
► Neonatal tranpharyngeal smear,16 17 20 21 23 amniotic fluid, umbilical cord blood, placental and breast milk.16 21 samples negative for nucleic acid amplification tests.5 7 23 24
► Stillbirth with no clinical or serologic evidence suggestive of vertical transmission of SARS-CoV-2.5

For these reasons, the neonatal outcomes assessed will be: birth weight, sex, Apgar Score, asphyxia markers, NICU (Neonatal Intensive Care Unit) admission, neonatal death and signs of vertical transmission (RT-PCR, serology, breast milk and placenta).

Patient and public involvement
The systematic review protocol, therefore, individual patient data will not be presented. An extensive literature search will be carried out from defined databases. For this reason, no patient will be involved in the study planning, application process during neither the analysis nor dissemination of results.

Search strategy
PubMed, Web of Science, Embase, CINAHAL, Latin American and Caribbean Health Sciences Literature, clinicaltrials.gov, SCOPUS, Google Scholar and Cochrane Central Controlled Trials Registry will be used to search for articles dating from December 2019 to the present (due to the fact that the first case of COVID-19 was registered in Wuhan, China, in December 201910).

The Medical Subject Headings (MeSH) terms will be: (gravidity OR gestation OR pregnancy OR pregnant women OR labour OR preterm labour OR obstetric OR maternal-foetal exchange) OR (foetal OR neonate OR newborn) AND (coronavirus disease 2019 OR severe acute respiratory syndrome coronavirus 2 OR SARS-CoV-2 infection OR 2019-nCoV disease OR Covid-19 virus disease OR COVID-19 virus infection) AND (Observational Study OR Cohort Studies OR Case-control Studies) (table 1).

Data collection and analysis
Selection of studies
Three authors, KSM, ESM and ACAS, will independently screen the search results using titles and abstracts. The articles will be included in Excel in Google (Google Drive). Duplicates and reviews will be removed from the database. The same authors will review the full text to determine whether the studies meet the inclusion criteria. A fourth reviewer, APFC, will resolve any discrepancies. The selection of studies will be summarised in a PRISMA flow diagram (figure 1).

| Table 1 | Search strategy for Medline |
| Search items | |
| 1 | Gravidity |
| 2 | Gestation |
| 3 | Pregnancy |
| 4 | Pregnant Women |
| 5 | Labour, Obstetric |
| 6 | Preterm labour |
| 7 | Maternal-Foetal Exchange |
| 8 | Foetal |
| 9 | Neonate |
| 10 | Newborn |
| 11 | Or/1–10 |
| 12 | COVID-19 |
| 13 | coronavirus disease 2019 |
| 14 | severe acute respiratory syndrome coronavirus 2 |
| 15 | SARS-CoV-2 infection |
| 16 | 2019-nCoV disease |
| 17 | Covid-19 virus disease |
| 18 | COVID-19 virus infection |
| 19 | Or/12–18 |
| 20 | Observational Study |
| 21 | Cohort Studies |
| 22 | Case-control Studies |
| 23 | Or/20–22 |
| 24 | 11 AND 19 AND 23 |

Data extraction and management
The following data will be extracted from the selected articles: the surname of the first author, year of publication, study location (country), study design, primary objective, level of evidence, pregnancy (population), average gestational age of a pregnancy (weeks), diagnostic methods, pregnancy results and treatment. These data will be extracted in standardised forms designed exclusively for this review, and the results will be inserted in a database. A double check will be performed on this database.

We will conduct a meta-analysis if we find a pool of included articles with similar characteristics based on the information in the data extraction table.

Addressing missing data
If any selected article has insufficient information, we will contact the corresponding author by email or phone to receive the missing data. If not possible, the data will be deleted and will be commented on in the Discussion section.

Risk of bias assessment
Three review authors, KSM, ESM and ACAS, will independently assess the risk of bias in the included studies. The quality of cohort and case-control studies will be
assessed using the Newcastle-Ottawa Scale for observational studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Bias will be assessed as a judgement (high, low or unclear) for individual elements from eight domains. A high score indicates a low risk of bias. Raters will resolve disagreements by consensus. A fourth rater will arbitrate cases for which consensus is unreachable.

Assessment of heterogeneity
We will use the $\chi^2$ test to evaluate the study outcomes (significance level of $p<0.1$). The evaluation of the heterogeneity will be realised according to the Cochrane Handbook criteria through the $I^2$ statistic. We consider that a value of 0% demonstrates a lack of heterogeneity in studies; $\geq$50% values indicate considerable heterogeneity. It is essential to mention that this evaluation will be executed if the meta-analysis’s achievement was appropriate.

If the $I^2$ value is less than 50%, the heterogeneity is low, and a fixed-effect model will be used in the analysis. Otherwise, the heterogeneity will be considered high if the $I^2$ value is 50% or more, and a random-effects model will be used. Forest plots will be constructed to show the study-specific RR/OR estimates and pooled RR/OR estimates. Along with the forest plots, we will use Eggers’s test and Duval and Tweedie’s trim-and-fill method.

Analysis
We will use the Review Manager software V.5.2.3 to enter the data. In the presence of dichotomous results, we will extract or calculate the OR and the 95% CI for each study. When there is heterogeneity ($I^2 \geq 50\%$), a random-effect model will combine the studies to calculate the OR and 95% CI.

If a study is eligible for inclusion in the systematic review but does not provide adequate data for inclusion in the meta-analysis, other study characteristics and results will be summarised narratively to synthesise and tabulate the results.

If the meta-analysis cannot be performed for all or some of the included studies, then sensitivity analyses will be important to explore the robustness of the findings regarding the study quality and sample size; however, this...
is only possible to consider if a meta-analysis is undertaken. This will be shown in a summary table.

**Grading quality of evidence**

We will use the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach to evaluate the strength of evidence of the systematic review results. GRADE tool classifies the studies as low, moderate and high quality. Two authors will independently realise this evaluation, and any disagreements will be decided through discussion (third author).

**DISCUSSION**

Many studies have examined COVID-19. However, there are limited case series reporting on its impact on women during pregnancy. Zaigham et al. showed that pregnant women are more susceptible to viral infection due to immune and anatomic alterations. In addition, COVID-19 associated with respiratory insufficiency in late pregnancies creates a complex clinical scenario because the case fatality rate appears to be higher in infected pregnant women compared with non-pregnant women.

Another worrying factor is that no COVID-19-specific treatments have been approved by the US Food and Drug Administration. COVID-19 might increase the risk for pregnancy complications, due to the fact that severe maternal morbidity resulting from COVID-19 and perinatal deaths have been reported. Therefore, vertical transmission cannot be ruled out. Although vertical transmission of COVID-19 has been excluded thus far and the outcome for mothers and fetuses has been generally good, the high rate of preterm caesarean delivery is a reason for concern. However, in another study, Muhidin et al. found no evidence of intrauterine or transplacental transmission of COVID-19 to the fetus in the third trimester of pregnancy.

Moreover, Muhidin et al. show that, in the third trimester of pregnancy, the risks of foetal distress, preterm delivery and prelabour rupture of membranes rise with the onset of COVID-19.

**Ethics and dissemination**

Ethical approval is not required because this review will draw on publicly available scientific literature. The findings of this systematic review will be published in a peer-reviewed journal and updates will be conducted if there is new evidence that may cause any changes in the conclusions of the review. Any amendments made to the protocol during the review will be reported in the manuscript.

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**Contributors**

KSM, ESM, ACAS and APFC contributed to the design of this review. KSM and ACAS drafted the protocol manuscript, and APFC and AKG revised it. KSM, AKG and APFC conducted the search strategies, and KSM, ESM and ACAS will implement them. KSM, ESM, ACAS and APFC will track potential studies, extract data and assess quality. In cases of disagreement between the data extractors, AKG will advise on the methodology and will work as a referee. JEJ will complete the data synthesis. All authors will approve the final version for publication.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not required.

**Provenance and peer review**

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**Open access**

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