Vertical transmission of COVID-19 through breastfeeding: A living systematic review protocol

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ABSTRACT

Objective

This living systematic review aims to evaluate the vertical transmission of SARS-CoV-2 through breast milk and breastfeeding in patients with COVID-19 providing a timely, rigorous and continuously updated summary of the evidence available on .

Data sources

We will conduct searches in the L-OVE (Living Overview of Evidence) platform for COVID-19, a system that maps PICO questions to a repository maintained through regular searches in electronic databases, preprint servers, trial registries and other resources relevant to COVID-19. No date or language restrictions will be applied. In response to the COVID-19 emergency, L-OVE was adapted to expand the range of evidence it covers and customised to group all COVID-19 evidence in one place. The search will cover the period until the day before submission to a journal.

Eligibility criteria for selecting studies and methods

We adapted an already published common protocol for multiple parallel systematic reviews to the specificities of this question.

We will include primary studies evaluating the role of breast milk and breastfeeding transmission. Randomised trials evaluating breast milk and breastfeeding in infections caused by other coronaviruses, such as MERS-CoV and SARS-CoV, and non-randomised studies in COVID-19 will be searched in case we find no direct evidence from randomised trials, or if the direct evidence provides low- or very low-certainty for critical outcomes.

Two reviewers will independently screen each study for eligibility, extract data, and assess the risk of bias. We will pool the results using meta-analysis and will apply the GRADE system to assess the certainty of the evidence for each outcome.

A living, web-based version of this review will be openly available during the COVID-19 pandemic. We will resubmit it every time the conclusions change or whenever there are substantial updates.

Ethics and dissemination

No ethics approval is considered necessary. The results of this review will be widely disseminated via peer-reviewed publications, social networks and traditional media.

PROSPERO Registration

Submitted to PROSPERO CRD42020199542

Keywords

COVID-19, severe acute respiratory syndrome coronavirus 2, Coronavirus Infections, Systematic review, Breastfeeding, Breast milk, vertical transmission.

INTRODUCTION

COVID-19 is an infection caused by the SARS-CoV-2 coronavirus(1). It was first identified in Wuhan, China, on December 31, 2019 (2); three months later, almost half a million cases of contagion had been identified across 197 countries(3). On March 11, 2020, WHO characterised the COVID-19 outbreak as a pandemic (1). The transmission of this illness is by droplets, that's why it is extremely contagious and actually there are eighteen millions of people around the world who has been infected.(4-6)

While the majority of cases result in mild symptoms, some might progress to pneumonia, acute respiratory distress syndrome and death(7-9). The case fatality rate reported across countries, settings and age groups is highly variable, but it ranges from about 0.5% to 10%(10). In hospitalised patients it has been reported to be higher than 10% in some centres (11).

According with the Chinese preliminary report, the overall case-fatality was 2,3%, however in the group of 9 years or least, there are no cases of death, but between 70 to 79 years old, the mortality was 8.0% and at 80 years and older 14,8%. Apparently 49% of patients with chronic disease present critical cases (12). Children and pregnant women were not more affected than others groups of risk, because it is not been reported an important numbers of several or critical cases and the mortality wasn't elevated.(13)

Breastmilk is the best source of nutrition for newborns and protects them against illness. Disruption of breastfeeding can lead to a drop in milk supply, refusal by the infant to take the breast, and a decrease in protective immune factors contained in breastmilk (14). Existing recommendations on whether mothers with COVID-19 should continue breastfeeding are still conflicting (15). The evidence is not conclusive, some systematic reviews dismiss the possibility of vertical transmission, however the evidence is still limited and it is not possible to discard contagion (15,16)

Antenatal vertical transmission can not be excluded. There are reports based in the antibodies levels (IgM-IgG) that suggest contagion, although this does not confirm the presence of SARS-CoV 2 in the newborn (17). That's why the chinese healthcare decided to keep isolation between postpartum women and their newborns (18). In the other hand, the Centers for disease Control and Prevention (CDC) states that if the mother and the medical team decide to breastfeed the newborn, it is necessary to use face covering and rigorous hand wash, because SARS-CoV 2 transmission by breast milk is not discarded(19).

Using innovative and agile processes, taking advantage of technological tools, and resorting to the collective effort of several research groups, this living systematic review aims to provide a timely, rigorous and continuously updated summary of the evidence available on the in patients with COVID-19.

METHODS

This manuscript complies with the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA-P) guidelines for reporting systematic reviews and meta-analyses (20). A protocol stating the shared objectives and methodology of multiple evidence syntheses (systematic reviews and overviews of systematic reviews) to be conducted in parallel for different questions relevant to COVID-19 was published elsewhere(21). This protocol was adapted to the specificities of the question assessed in this review and submitted to PROSPERO.

Search strategies

Electronic searches

Our literature search was devised by the team maintaining the L-OVE platform (<https://app.iloveevidence.com>), using the following approach:

1. Identification of terms relevant to the different components of the answer using Word2vec technology (22) to the corpus of documents available in Epistemonikos Database.
2. Discussion of terms with content and methods experts to identify relevant, irrelevant and missing terms.
3. Creation of a sensitive boolean strategy encompassing all the relevant terms
4. Iterative analysis of articles missed by the boolean strategy, and refinement of the strategy accordingly.

Our main search source will be Epistemonikos database (<https://www.epistemonikos.org>), a comprehensive database of systematic reviews and other types of evidence(23) that we supplemented with articles from [multiple sources relevant to COVID-19](#) (24).

In sum, Epistemonikos Database acts as a central repository. Only articles fulfilling Epistemonikos criteria are visible by users. The remaining articles are only accessible for members of COVID-19 L-OVE Working Group.

The searches will cover from the inception date of each database until the day before submission. No study design, publication status or language restriction will be applied to the searches in Epistemonikos or the additional searches.

The following strategy will be used to search in Epistemonikos Database. We will adapt it to the syntax of other databases.

(coronavir* OR coronavirus* OR "corona virus" OR "virus corona" OR "corona virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-nCoV" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR "sars-cov2" OR (wuhan* AND (virus OR viruses OR viral)) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome" OR "covid-19-related" OR "SARS-CoV-2-related" OR "SARS-CoV2-related" OR "2019-nCoV-related" OR "cv-19-related" OR "n-cov-related") AND ((pregnant* OR gestation* OR primigravid* OR "mid-pregnancy"))

Other sources:

In order to identify articles that might have been missed in the electronic searches, we will do the following:

1. Screen the reference lists of other systematic reviews and evaluate in full text all the articles they include.
2. Scan the reference lists of selected guidelines, narrative reviews and other documents.
3. Conduct cross-citation search in Google Scholar and Microsoft Academic, using each included study as the index reference.
4. Email the contact authors of the included studies in case of lack of data or if it is not possible to access the full text.
5. Review the reference list of each included study.

Eligibility criteria

Types of studies

We will include primary studies, that report vertical transmission by breast milk and breastfeeding in patients with COVID-19

We will exclude studies evaluating the effects on animal models or in vitro conditions.

Types of participants

We will include trials assessing postpartum women with COVID-19 diagnosed by PCR or clinical criteria and their newborns.

Type of exposed

The exposure of interest are healthy infants fed by breast milk directly or by expressed breast milk from a woman with confirmed COVID-19 infection.

The comparison of interest will be newborns fed by formula or by human milk banking.

Type of outcomes

We will not use the outcomes as an inclusion criteria during the selection process. Any article meeting all the criteria except for the outcome criterion will be preliminarily included and assessed in full text.

We used the core outcome set COS-COVID (25), the existing guidelines and reviews and the judgement of the authors of this review as an input for selecting the primary and secondary outcomes, as well as to decide upon inclusion. The review team will revise this list of outcomes, in order to incorporate ongoing efforts to define Core Outcomes Sets (e.g. COVID-19 Core Outcomes(26).

Primary outcome

- Positive RT-PCR for SARS-CoV-2 in breastmilk of patients with COVID-19
- SARS-CoV-2 RT-PCR positivity in newborns *(>48hrs).

Secondary outcomes

- Neonatal mortality.
- Neonatal Care Intensive Unit (NCIU) admission.
- Neonatal acute respiratory distress syndrome .

Primary and secondary outcomes will be presented in the GRADE 'Summary of Findings' tables, and a table with all the outcomes will be presented as an appendix (27) .

Selection of studies

The results of the literature search in Epistemonikos database will be automatically incorporated into the [L-OVE platform](#) (automated retrieval), where they will be de-duplicated by an algorithm comparing unique identifiers (database ID, DOI, trial registry ID), and citation details (i.e. author names, journal, year of publication, volume, number, pages, article title and article abstract).

In L-OVE platform, two researchers will independently screen the titles and abstracts yielded by the search against the inclusion criteria. We will obtain the full reports for all titles that appear to meet the inclusion criteria or require further analysis to decide about their inclusion.

We will record the reasons for excluding trials in any stage of the search and outline the study selection process in a PRISMA flow diagram adapted for the purpose of this project.

Extraction and management of data

Using standardised forms, two reviewers will independently extract data from each included study. We will collect the following information: study design, setting, participant characteristics and study eligibility criteria; details about, the outcomes assessed and the time they were measured; the source of funding of the study and the conflicts of interest disclosed by the investigators; the risk of bias assessment for each individual study.

We will resolve disagreements by discussion, and one arbiter will adjudicate unresolved disagreements.

Risk of bias assessment

The assessment of the included studies' risk of bias, will be using the Joanna Briggs Institute Critical Appraisal Tools by two independent reviewers; disagreements will be resolved by discussion (30)

Strategy for data synthesis

If we include more than one trial we will conduct a formal quantitative synthesis (meta-analysis) for studies clinically homogeneous using RevMan 5 (31), using the inverse variance method with the random-effects model. For any outcomes where data were insufficient to calculate an effect estimate, a narrative synthesis will be presented, describing the direction and size of the effects, along with any reported measure of precision.

Subgroup and sensitivity analysis

We will perform subgroup analysis according to the definition of severe COVID-19 infection (i.e. respiratory failure vs respiratory distress syndrome vs ICU requirement). In case we identify significant differences between subgroups (test for interaction <0.05) we will report the results of individual subgroups separately.

Assessment of certainty of evidence

The certainty of the evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE Working Group) (32), across the domains of risk of bias, consistency, directness, precision, reporting bias, large effect, dose-response gradient, effect of potential residual confounders. Certainty will be adjudicated as high, moderate, low or very low. For the main comparisons and outcomes, we will prepare Summary of Findings (SoF) tables (27,32) and also interactive Summary of Findings tables (<http://isof.epistemonikos.org/>). A SoF table with all the comparisons and outcomes will be presented as an appendix. This assessment will be realized in the second actualization of this living systematic review.

Living evidence synthesis

An artificial intelligence algorithm deployed in the [Coronavirus/COVID-19 topic of the L·OVE platform](#) will provide instant notification of articles with a high likelihood to be eligible. The authors will review them, will decide upon inclusion, and will update the [living web version](#) of the review accordingly. We will consider resubmission to a journal if there is a change in the direction of the effect on the critical outcomes or a substantial modification to the certainty of the evidence.

This review is part of a larger project set up to produce multiple parallel systematic reviews relevant to COVID-19.

NOTES

Acknowledgements

The members of the [COVID-19 L·OVE Working Group](#) and [Epistemonikos Foundation](#) have made possible to build the systems and compile the information needed by this project. Epistemonikos is a collaborative effort, based on the ongoing volunteer work of over a thousand contributors since 2012.

Roles and contributions

GR conceived the common protocol for all the reviews being conducted by the COVID-19 L·OVE Working Group. GR drafted the manuscript, and all other authors contributed to it. The corresponding author is the guarantor and declares that all authors meet authorship criteria and that no other authors meeting the criteria have been omitted.

The COVID-19 L·OVE Working Group was created by Epistemonikos and a number of expert teams in order to provide decision makers with the best evidence related to COVID-19. Up-to-date information about the group and its member organisations is available here: epistemonikos.cl/working-group

Competing interests

All authors declare no financial relationships with any organisation that might have a real or perceived interest in this work. There are no other relationships or activities that might have influenced the submitted work.

Funding

This project was not commissioned by any organisation and did not receive external funding.

Epistemonikos Foundation is providing training, support and tools at no cost for all the members of the COVID-19 L·OVE Working Group.

PROSPERO registration

This protocol has been submitted, ID allocation CRD42020199542.

Ethics

As researchers will not access information that could lead to the identification of an individual participant, obtaining ethical approval was waived.

Data sharing

All data related to the project will be available. Epistemonikos Foundation will grant access to data.

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