12-Jun-2020
BMJ-2020-058888 entitled "Coronavirus disease (COVID-19) in pregnancy: A living systematic review on clinical manifestations, maternal and perinatal outcomes"

Dear Dr. Allotey,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Sincerely,

Dr Elizabeth Loder

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**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Present: Wim Weber (chair); Rafael Perera (statistician); David Ludwig; Tim Feeney; John Fletcher; Helen Macdonald; Elizabeth Loder

Decision: Request additional information before final decision. Revision to be seen by our statistician.
* We were interested in this topic and of course the matter of covid in pregnancy is of great clinical importance. With regard to the request for a living systematic review, we will make a decision when we see the revised paper and decide whether to proceed. Our procedures for living systematic reviews allow for no more than 3 updates per year, separate open access fees to cover the costs of the update. Updates are published under the original doi so they are not considered separate publications in Pubmed.

* Several editors remarked that they did not find the estimates of clinical symptom prevalence (Figure 2) and maternal and perinatal outcome prevalence (Figure 3) to be very informative because a) they are just prevalence estimates; b) they are not relative to patients without COVID; and c) there is a large amount of heterogeneity.
* In contrast, while we found the relative risk estimates (Table) very interesting, these are based (primarily) on 1-2 studies and have very wide confidence intervals, with lots of uncertainty. It’s possible that in 6 months the studies used to population the Table will increase in number and the results will be more reliable, but at this time we were not sure what we learn (except that, from Figure 3, risk is appears low).

* We think you should consider excluding case reports and case series. Even now, most of the included studies are small retrospective cohorts of fewer than 100 patients, many of which are from China (where there have been concerns about patients being included in multiple case series).

* We wonder whether the low rates seen here simply reflect the lower risk of women in their younger reproductive years, and that women with major predisposing conditions tend not to get pregnant as often as healthy women? We don’t have a meaningful and generalizable comparison group.

* Despite the low quality of the evidence available at present, we think this paper has potential because you could put together a framework for adding studies to a review in a situation where it is likely that new evidence will be coming along at a fast enough pace to see change in a matter of months or a few years.

* One of our clinical editors commented that the information patients and doctors want centers around the questions listed below, and wondered whether it might make sense to construct the review so it can answer these questions as evidence becomes available:
  - Am I more likely as a pregnant woman to contract covid?
  - How will I spot it? ie Does my presentation differ from those who are not pregnant?
  - How likely am I to need hospital admission?
  - If I am admitted or have severe disease how likely am I/my child to have bad outcomes?
  - Will I pass it to my child? (And if so does that really matter?)
  - Finally I’d like to see results by trimester.
  - Should pregnant women be advised to be more physically distant than other people? Do they need special monitoring if they are suspected of infection? Does their baby?

* Other things to include are data (supplementary material) on the actual included studies (forest plots or tables). Right now we only have summary measures for most of the signs and symptoms and outcomes and not information at the study base level which we need to verify the level of heterogeneity.

* Please clarify how you pooled the proportion data. Typical approaches use some form of transformation to account for being close to the extremes of the parameter space (see: https://doi.org/10.1186/2049-3258-72-39) for reference.

* Our statistician felt this was comprehensive at the moment, but that some of the methods might require adjusting as further evidence is collected (he agreed that case reports might be excluded).
Our patient editors would like you to include information about why patients or members of the public were not included. This should go in the methods section. For example, were they unavailable due to COVID restrictions, was there no funding available, was the data or software not open access? How might you involve them in future?

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
I commend the authors for being able to pull together such an important “living review” and for the strong collaboration.

The methods are robust and the authors are clearly aware of the critical limitations of previous work. This research is an important contribution to the literature and especially timely given the need for synthesis as huge amounts of research, of varying quality, are produced daily.

My comments are mostly minor.
1) In the abstract and the methods, the authors state that they searched the various databases from inception to May 12th, 2020. Given that the first known cases of COVID-19 were reported in December 2019, it seems that the search period could be narrowed considerably (from December to May 12th, 2020).
2) I agree with the authors’ careful interpretation of the higher rates of preterm birth observed in the review. The following statement, however, needs some elaboration/explanation. “It is essential to compare disease severity to that of age-matched non-pregnant women with COVID-19. The relatively high rates of preterm birth and caesarean section in pregnant women with COVID-19 is likely iatrogenic with urgent delivery required due to deteriorating maternal condition, often resulting in fetal distress, than a direct effect of SARS-CoV-2 infection.” The first part of the statement about the need for age-matched comparisons is important. Chronic conditions and advancing age are both risk factors for COVID-19, preterm birth, and C-section. I think the discussion could be improved by adding more about the need for improved consideration of confounders in these studies, including chronic conditions and their risk factors: obesity, diabetes, hypertension. The second part of the sentence regarding iatrogenic causes of maternal deterioration requires some justification. I am uncertain how the data presented in this article support iatrogenic causes for the higher rates of preterm birth or C-section. Some additional explanation for this conclusion is needed.
3) While there is an appendix with information about the studies included in the review, more of these details need to be in the main manuscript (both results and discussion). Specifically, it needs to be clearer to the reader that most of the studies had tiny sample sizes (<100). While the authors report in the results where the various studies came from, they omit information about which ones are most influential to the results. From my reading, only about 7 studies have 100 or more COVID-19 confirmed or suspected individuals in the sample. Thus, while 94 studies were included, a very small number are driving most of the estimates. This is an important limitation of the existing literature base.

Major comment: More information and discussion is needed about the comparison samples used to obtain the odds ratios for the COVID-19 infected women versus the non-infected women. It seems like only 3 or 4 studies had comparison samples of women without COVID-19. There are limited details about these comparison samples. I am concerned about selection bias in the comparison sample and think that any results presented on these comparisons need to be very, very cautious (including in the abstract). For example, approximately 60% of COVID-19 suspected or diagnosed women had a
c-section, based on 2 studies only (where are these? Are these tertiary hospitals, high risk women, etc.). The authors, however, state “there were no differences in rates of c-section between the groups.” First, the confidence interval is enormous and it is hard to draw any conclusion here. Second, the c-section rate in the comparison group is just over 30%. The difference may not be statistically significant, but it is huge (60 versus 30%). More information about the few studies used to calculate these ORs is needed so the reader can better assess potential threats to internal validity (e.g. should we believe these ORs or not?).

For the comparisons between the COVID-19 women and those without the virus, I would prefer more care in the presentation of these results for fear of readers not necessarily recognizing the preliminary “living” nature of the results. If a reader scans the abstract only, he/she may think that there is a higher pre-term birth rate based on systematic review of the literature and not realize the review consisted of only two studies. The abstract, results, and discussion need to be more explicit about how limited the literature base is for these types of comparisons.

Additional Questions:

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Please enter your name: Catherine Pirkle

Job Title: Associate Professor

Institution: University of Hawaii at Manoa

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No
In conclusion, it's an interesting paper, however, not enough for BMJ. Considering its issues, as described below, I do not recommend to publish in this journal. It may be suitable in another BMJ affiliated journal with a lower impact factor after a revision.

Please consider the following suggestions:

- **Methods**: Ambiguous exclusion criteria: is it only duplicated patients? Very few studies on high-risk pregnant patients. Follow-up time is also unclear.
- **Results** - answer the research question? Credible? Well presented?: the paper needs some rewording (ie babies to neonates or infant, depending on child-age). Presentation of results could be improved.
- **Interpretation and conclusions**: based on the analysis, concerning pregnancy-related maternal outcomes the rates of preterm birth increased 3-fold (15%) and preterm premature rupture of membranes (PPROM) was 5%, which are significant results to focus on clinical decision making and policies. Should pregnant women be considered a high-risk group? especially in the 3rd trimester. Please clarify.

There's also no data on first trimester abortions related to COVID-19 causes. If asymptomatic or slightly symptomatic, many women are not being tested. Is there an impact? Any results? As for perinatal outcomes, 43% (95% CI 8 – 87%, I2=100%) of newborns were admitted to the neonatal unit. Of those admitted to the NICU, only 19% were breast fed, this is a big impact for the mother-child contact and attachment. If they were not contaminated, any speculations are of why there where not breast fed?

What about the impact of obesity? Was BMI a factor considered?

- **Abstract/summary/key messages/What this paper adds**: there are many limitations in the study. A long delay between symptoms initiation and randomization (which could have an influence on the time to recovery, a parameter that was not analyzed statistically). Is there a difference in the category distribution? with more severe patients in the placebo group, was there a substantial difference?

A primary conclusion that is disputable (including the speculation that pre-term birth is due to iatrogenic causes may be not justified). The absence of evidence is not the evidence of absence, therefore cautions are needed and required until we know more.

What’s the effect on mortality?

What was the main COVID treatment, do we need to give an expansive drug to shorten the time to recovery?

We need to know more:

- statistical analysis in the treatment and therapy used
- what are the distribution between the trimesters. Does the outcome change if only 2nd and 3rd trimester considered?
- what are the proportion of worsening categories in each group?
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Please confirm that you understand and consent to the above terms and conditions. I consent to the publication of this review.

Please enter your name: Isabel Cardona
Job Title: OBGYN Research fellow
Institution: Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland.
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No
Funds for research?: No
Funds for a member of staff?: No
Fees for consulting?: No

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Reviewer: 3
Comments:

Dear professor
Thanks for sending me this manuscript for reviewing, I've been studied it very carefully. It was very interesting and very well designed. I think it is appropriate to publish it after some minor revisions as below:

1. Please mention the critical appraisal tool and add a subheading as quality assessment.

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Please enter your name: Somaye Pouy

Job Title: Nursing

Institution: Guilan University of Medical Sciences

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No
Reviewer: 4

Comments:
In their manuscript, Dr. Allotey et al. report their initial findings from a living systematic review on COVID-19 in pregnancy. In this report, the authors identified 94 cohort studies and case series that met their inclusion criteria. The outcomes of interest were grouped into maternal outcomes related to COVID, pregnancy outcomes, and neonatal outcomes. The number of studies and patients with data for each outcome varied dramatically. The authors included all women who tested positive for COVID, regardless of their indication for testing. Their conclusions are that pregnant women may be less likely to exhibit symptoms than the non-pregnant population and that few are admitted to the ICU.

The number of case reports on COVID-19 in pregnancy is increasing rapidly as more people around the world are affected with the disease. This work attempts to collate and present data from multiple reports of COVID-19 in pregnancy through a living systematic review, which they describe would be updated monthly. This type of resource would be helpful to patients, clinicians, and policymakers.

The authors included of all women with COVID-19, regardless of the indications for being tested. There likely is a significant publication bias introduced from early studies when testing was very limited, where only the sickest women or those with typical symptoms were tested. Until testing becomes more wide spread and more studies with universal screening are published, the true associations between COVID-19 and pregnancy outcomes will not be fully understood. The authors do perform sensitivity analyses by individual symptom status, but these results are not discussed in the manuscript. The authors may consider discussing the following notes and highlighting the results from their sensitivity analyses in the main text:
- Why were studies where the indications for testing were unknown grouped with the symptomatic group? Was this appropriate?
- Did the authors examine what percent of women reported any symptoms (not just stratified by individual symptoms)?
- Was testing indication considered/weighted in the pooled estimates?

Once more studies are published, the authors should consider further delineating studies by testing indications for more meaningful interpretations of the outcome data.

In their attempts to be comprehensive and increase their sample size, the authors included studies published from many countries. The review, as submitted, is predominantly weighted by studies from China. I think this approach is appropriate for understanding disease characteristics and severity among pregnant women. However, it is major source of heterogeneity when considering pregnancy and neonatal outcomes. The baseline characteristics of pregnant women, how/where they receive care, and their pregnancy outcomes vary dramatically by country (and even within some countries). Thus, most of the pregnancy and perinatal outcomes, including cesarean delivery, preterm birth, stillbirth, NICU admission, are impossible to interpret without having a comparison to a non-COVID-19 pregnant population from the same institution/country (much of the pregnancy and neonatal outcome data presented in Figure 3). Table 1, while not stratified by country, does present the available cohort data, including odds ratios, which are more meaningful. However, at this time, there are only 1 or 2 studies, making the results not generalizable (and not enough to warrant a systematic review). The authors do acknowledge these issues as a limitations, though I am not certain having more pooled cohort studies from very different populations will provide meaningful insights into the effects of COVID-19 on pregnancy outcomes. This may be best studied on a local or national level.
Additional Questions:
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Please enter your name: Mark Clapp, MD MPH

Job Title: Physician Investigator, Maternal-Fetal Medicine

Institution: Massachusetts General Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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If you have any competing interests please declare them here: (please see BMJ policy)
Reviewer: 5

Comments:
The authors present a living systematic review on clinical manifestations, maternal and perinatal outcomes of COVID19 in pregnancy. The research questions are scientifically sound, and the analyses were well conducted. In addition, literature selection criteria and information management strategies as well as sensitivity analyses contribute to gain more evidence robustness in comparison to other publications. Regarding interpretation of their findings, I would suggest the authors to discuss about the following:
1) Since typical symptoms were less frequent in pregnant women than in the general population and admission rate to ICU was lower than in other studies, should we imply that pregnant women have a milder clinical presentation than non-pregnant?
2) Would selection bias be a possible explanation to those findings? For instance, are pregnant women more likely to be tested than non-pregnant and therefore mild cases are overrepresented? Is the likelihood of being tested related to the increased awareness of pregnant women to health harms, including COVID19?
3) As compared to other populations, the proportion of severe cases among pregnant women was lower (5% vs 5%-17%). However, as compared to individuals aged 22-44, it was higher (5% vs 2%-4.2%) So, should we still consider pregnant women as a high-risk group in clinical practice settings?
4) What would be the quantitative impact (on results) of excluding suspected cases from the analyses? How do authors plan to address these exclusions in the future updates of this living systematic review?

Minor

Abstract: I would mention that prediction intervals were also estimated.

Page 13: Line 43. Not sure why 84% pneumonia. From Fig. 3, it seems like it was 40%.

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Please enter your name: Eduardo Ortiz-Panozo

Job Title: Professor-Researcher

Institution: National Institute of Public Health
Reviewer: 6

Comments:
Are the questions the paper addresses relevant and important to patients and/or carers?
● The reviewer’s understanding of this paper is that the key questions being addressed are whether pregnant women are a high risk group within a population affected by COVID-19; the likelihood of the baby having COVID-19 transferred to them and what needs to be learnt in order to manage the care of mother and baby. These are clearly questions important to patients and/or carers.

Are there topics or issues that are missing, or need to be highlighted more?
● Should the issue of ethnicity of the mother be included or highlighted more in light of this being an issue emerging more generally in data being collected on susceptibility to and outcomes from contracting COVID-19.

Is the treatment or intervention suggested or guidance given something which patients/carers can readily take up? or does it present challenges?
● Not applicable.

Are the outcomes described/measured in the study important to patients/carers? Are there others that should have been considered?
● It would be useful to have it explained clearly whether the outcomes being considered in this LSR can be reassessed, changed and/or expanded in the future to potentially include parameters of importance to patients and/or carers following consultation with patients and/or carers.

Do you have any suggestions that might help the author(s) strengthen their paper and make it more useful for doctors to share and discuss with patients/ carers?
- Expand the details on how the LSR will change (or not change) as time moves on and more and different data are available from studies on COVID-19 and pregnancy and childbirth.

Do you think the level of patient/carer involvement in the study could have been improved? If there was none do you have ideas on how they might have done so?

- This study could report on the ease or difficulty of including patient/carer involvement data because of the nature of current studies and whether studies, in the future, on this topic should more proactively involve patients/carers.

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Please enter your name: Bette Baldwin

Job Title: Retired

Institution: Retired

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Funds for research?: No

Funds for a member of staff?: No
Fees for consulting?: No

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