11-May-2020
BMJ-2020-057946 entitled "Characteristics and outcomes of pregnant women hospitalised with confirmed SARS-CoV-2 infection in the UK: a national cohort study using the UK Obstetric Surveillance System (UKOSS)"

Dear Dr. Knight,

Thank you for sending us your paper. We sent it for external peer review on a fast track basis, and discussed it among senior editors.

We are interested in proceeding with the paper. We hope very much that you will be willing and able to revise your paper as explained below so that we can reach a final 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.

Thank you for sending this to us!

Sincerely,

Dr Elizabeth Loder
Head of Research
eloder@bmj.com

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

These comments are an attempt to summarise the discussions of the BMJ research editors. They are not an exact transcript.

Members of the committee were: Wim Weber; Elizabeth Loder; Tiago Villanueva; David Ludwig; Joseph Ross

Decision: Request revisions before final decision

* We noted the small numbers for many of the outcomes (1% stillbirth, 1% pregnancy loss, 1% neonatal loss) and think these are so low that they don’t allow for robust, multivariable adjustment.
* We were not convinced that the comparison group added much value here and think this would be better presented as simple descriptive paper providing baseline characteristics and outcomes - in other words, a case series without a comparison group, providing reassurance that rates of bad outcomes are very low. We would like you to update this to provide any additional outcomes that have occurred since you submitted the paper; we also would like you to commit to providing a final update on outcomes by sending us a rapid response (letter to the editor) for the paper once you have those outcomes. This will travel alongside the paper and allow readers in the future to know the outcomes of all the pregnancies in the series.

First, please revise your paper to respond to all of the comments by the editors and also those of the reviewers. The reviewer reports are available at the end of this letter, below.

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. Please upload the clean version of the paper as the main paper and also include a “track changes” version in the supplemental files.

Comments from Reviewers

Reviewer: 1

Comments:
This manuscript describes the largest series of COVID-19 in pregnancy using the well established UK Obstetric Surveillance System and a protocol developed specifically for pandemics. The inclusion of data from all 194 maternity units in the UK provides a Nationwide picture of the impact of the virus on pregnant women, their offspring and maternity services. The authors used a historical control cohort from a previous study of influenza A/H1N1 thereby allowing them to determine risk factors for admission to hospital with COVID -19 using odds ratios. Further, a sensitivity analysis excluding urban areas with the highest prevalence of the virus demonstrated that the increased risks in BAME, obese and older women remained excluding confounding by geography as an explanation for the significant associations.

The study is unique in its size, its scientific robustness and its National relevance. The manuscript is well written, with one clear table summarising the results.

I have 2 major comments and one minor:

Major comments:
1. I would suggest that the risk factors of increased maternal age, obesity BAME, comorbidities are referred to specifically in the section on 'what this study adds' as now but perhaps with the addition of some figures / OR (particularly the 4.49 for BAME)
2. The authors found that the OR for black ethnicity was > 10. This is not mentioned in the text and I think is worthy of comment, particularly as the significance remained after sensitivity analysis.

Minor comments:
Page 5, line 39, delete 'that'

Additional Questions:
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I consent to the publication of this review

Please enter your name: Professor Catherine Nelson-Piercy

Job Title: Consultant Obstetric Physician

Institution: Guy’s & St Thomas’ Foundation Trust

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: Yes

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Speakers fees sanofi, falk, UCB, JENSSEN

Reviewer: 2

Comments:
This communication describes the result of a national observational study from data derived from the UK Obstetric Surveillance System (UKOSS) describing epidemiological features and pregnancy outcomes of
hospitalized women with COVID-19 in the United Kingdom. In particular, this well-written and well-organized communication describes clinical characterizes and risk factors from 427 hospitalized pregnant women infected with SARS-CoV-2 and compares them with a cohort of 697 pregnant women who did not have COVID-19. The experimental design of this investigation is valid, statistical analyses are appropriate, the results are summarized in 4 easily interpreted data tables and 1 figure, and the discussion highlights the data and overall goals of the investigation. The references are as complete as can be made given the continuous publication of new studies on a daily basis. This is a highly important investigation reporting the largest cohort of pregnant women with COVID-19 and their clinical obstetrical and neonatal outcomes, and will significantly add to our knowledge of the effects of SARS-CoV-2 during pregnancy.

The authors may wish to consider the following comments and suggestions for revising their manuscript:

Pg 4 Lns 56-57. The authors state that "only a few instances of reported transmission of SARS-CoV-2 infection to the neonate.20-23". This wording may be confusing and indicate that there have been instances of intrauterine viral transmission. Could you please consider rewording this to say (as an example) "only a few instances of neonates who had positive tests for SARS-CoV-2 following delivery".

Pg 5 Ln 26. Methods. As obesity and overweight were significant risk factors for hospitalization of pregnant women with COVID-19, please explain the criteria used for determining overweight and obesity in this study population. Did you use pre-pregnancy BMI? Did you take into account variations in gestational weight gain? Gestational weight gain does demonstrate potential variation between various ethnic groups.

Pg 8 Ln 31. There were a total of 5 maternal deaths. Is there information available whether these deaths were due as a direct result of complications of COVID-19? If yes, was COVID-19 the major underlying cause of death? If yes, is there specific information available on whether these women had an immediate cause of maternal death from respiratory insufficiency, cardiac disease, thrombosis, multiple organ dysfunction syndrome (MODS) or other causes?

Pg 9 Lns 35-45. Six neonates tested positive for SARS-CoV-2 within 12 hours of birth. Please specify (if known) whether these infants were isolated from the mother immediately following delivery and if skin-to-skin contact was permitted. Also, if known, please state if viral analyses were performed on umbilical cord blood, placenta, vaginal secretions, neonatal anal swab and/or neonatal blood?

Pg 9 Ln 35. The authors may not have this information, but did any of the neonates who had positive tests for Sars-CoV-2 have a prior test that was negative?

Pg 12 Ln 39. The authors use the term vertical transmission - this term indicates mother-to-infant viral transmission, and is not specific for a time period. Vertical transmission can occur in utero, during delivery via an infected birth canal, or postpartum via respiratory droplets, skin-to-skin contact or breast feeding. In this statement, did you mean to indicate that intrauterine maternal-fetal transmission may be occurring?

Pg 18. References #6, 7 and 8 require the left margins to be revised.

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Please enter your name: David A. Schwartz

Job Title: Clinical Professor

Institution: Medical College of Georgia

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A fee for organising education?: No

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Funds for a member of staff?: No

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Reviewer: 3

Comments:

This is an important paper. I recommend acceptance and publication as rapidly as possible. SARS-CoV-2 is a serious infection in pregnancy, carrying, as these authors report, a one percent mortality for the mother. Current information about it, is based on hospital-based series and case reports, which are biased in two ways. Firstly there is selection bias as to what cases get reported. There is also a serious risk of duplicate publication.
The present series is original since there have been no case series or case reports in the scientific literature from the UK. It is likely that UKOSS is notified of all cases and therefore this is the first paper to give a reasonable estimate of the rate of this infection in pregnancy. Cases are reported to UKOSS anonymously, so these cases will inevitably overlap with future case series from the UK. This is unavoidable. The authors make this clear.

Since the pandemic is ongoing the UKOSS database is of course constantly being added to. The authors acknowledge this. It is not a reason to delay publication.

The paper is beautifully written. I could not find any typos. My only minor quibble is that the odds ratios and confidence intervals are given to two decimal places. For some this leads to excessive precision I would suggest that all such numbers were given to two significant figures. This should not be a reason to delay publication.

Jim Thornton. Nottingham. 5 May 2020

Additional Questions:
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Please enter your name: Jim Thornton

Job Title: Professor of obstetrics & gynaecology

Institution: University of Nottingham

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No
The authors carried out a prospective study of all pregnant women with Covid-19 disease admitted to 194 obstetric centres in the United Kingdom between March 1, 2020 and April 14, 2020. A total of 427 pregnant cases were included in the study and their characteristics were compared with a cohort of 694 women recruited in a previous study of seasonal influenza in 2017-2018. The rate of hospitalization with confirmed Covid-19 disease in pregnancy was 4.9 per 1000 maternities. Compared with the historical cohort, pregnant women with Covid-19 disease were more likely to be older, of Black or other minority ethnicity, overweight and obese or to have pre-existing comorbidity. 9% of the women with Covid-19 disease required respiratory support, and 5 women died. Preterm birth rates and cesarean delivery rates were relatively high among the women who delivered during the study period.

Comments
1. The authors deserve praise for having previously created the infrastructure for the surveillance of maternal and perinatal health during a pandemic and for having carried out this population-based study quickly.
2. The characteristics of the affected women and their outcomes will be of interest to the scientific community, especially since study includes a census of Covid-19 cases in pregnancy (during a short period). The information provided by the historical comparison cohort of pregnant women is a useful addition, although the contrast may be inappropriate in some respects (see below).
3. Factors identified as being associated with Covid-19 disease in pregnancy included older maternal age, Black or other minority ethnicity, overweight and obese and pre-existing comorbidity. This could reflect a higher risk for infection or a higher risk of disease given infection among vulnerable subgroups, or both.
4. The lower risk of Covid-19 disease among current smokers deserves comment as this negative association has also been reported among non-pregnant adults (even if the robustness of the association and its implications remain uncertain).
5. Although the inclusion of the historical cohort strengthens the study in some ways, it is unclear if this cohort represents an appropriate comparison group. The Covid-19 women were hospitalized on account of symptoms, whereas most women in the historical cohort were admitted for delivery. The substantial fraction of undelivered women in the Covid-19 cohort attests to this lack of comparability.
6. There may be utility in estimating the likelihood of delivery among pregnant women with Covid-19 by maternal characteristics. For example, comparing the proportion of women who delivered within 1 week following onset of Covid-19 disease by maternal age may reveal if the disease is more likely to cause spontaneous labour initiation (or a pregnancy complication such as maternal or fetal compromise) in older women. Similarly, analyses by race, BMI and pre-existing co-morbidity would also be informative. Such analyses may be more indicative of Covid-19 effects (given age, race, etc) than the contrast involving the historical cohort (which could be indicative of exposure to infection). Estimating the probability of delivery in the week following symptom onset (for example, among women at say 28
weeks' gestation; among women with mild vs severe disease) may be informative and helpful from a clinical perspective.

Minor comments
The calculation of odds ratios for pregnancy loss and stillbirth was unclear (a footnote to identify the reference group may be helpful).

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Job Title: Professor

Institution: University of British Columbia

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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: 5

Comments:
Thank you for asking me to review this manuscript.

I have the following comments in order to improve the manuscript for publication in the BMJ:

Abstract
Main outcome measures: it should be "odds ratio for admission being infected versus comparison women". Please put OR in parenthesis. Comparison women should be clearly defined in the Abstract. In the Abstract, it is not clear that you have chosen a historical influenza cohort as comparison group. All the adjusted OR must be clearly defined as compared to comparison women (influenza cohort). The Conclusion should be more factual about the outcomes of the cases. The first sentence "The majority of pregnant women hospitalised with SARS-CoV-2 were in the late second or third trimester, supporting guidance for continued social distancing measures in later pregnancy" is confusing - just because the majority of pregnant women hospitalised with SARS-CoV-2 were in the late second and third trimester, why does it support guidance for continued social distancing measures in later pregnancy? Have the authors demonstrated data suggesting that pregnant women are more susceptible to acquiring the virus during the late second or third trimester? Have the authors demonstrated data suggesting that social distancing measures in later pregnancy in preventative of SARS-CoV-2 infection? I am fully supportive of social distancing but I do not think the conclusion has been substantiated with evidence from the study.

Introduction
Two weeks have passed since 16 April, as the situation is evolving rapidly I would recommend an update on the published literature.

Methods
The study design appears to be a hybrid of cohort study and case-control study. This should be fully justified. The Methods is lacking a proper description of the study population. How was a case defined? Was it confirmed by laboratory testing? I understand the desire of working out the risk factors for SARS-CoV-2 infection in pregnant women and this can only be done with the inclusion of a comparison cohort. Were the controls healthy pregnant women from a historical influenza cohort? Please clarify this. The main challenge of any case-control study is good selection of controls and I have doubts that the right controls were selected. Outpatient cases were excluded, which is a major limitation that should be acknowledged in Discussion. The authors might gain knowledge by comparing the characteristics and outcomes between inpatients and outpatients to identify risk factors for admission. Women were only tested if symptomatic for SARS-CoV-2 infection. This should be acknowledged as a limitation as we know the rate of COVID-19 in asymptomatic pregnant women could be substantial in regions with widespread community transmission. Authors should comment on measures to be undertaken in order to minimise duplicate reporting in future publications (perhaps by individual hospitals or other registries).

Results
Where applicable please provide counts with percentages throughout. All adjusted OR should be clearly defined "as compared to a historical cohort of healthy women admitted for delivery" (if this is the case following confirmation by the authors).
Please give a separate figure for women who had a pregnancy loss. I believe the number should be four. Please state clearly what pregnancy loss meant. Do you have more details on these cases? 31 of 40 critically ill patients had been delivered due to COVID-19. Can more details be provided (i.e. worsening respiratory condition etc)? Was decision for delivery driven by gestational age at presentation?

"three had died" - Did you mean three postnatal women had died or three women who required level 3 critical care had died? Please make this clearer.

"were admitted and had a positive test for SARS-CoV-2 died" - "a positive test for SARS-CoV-2" should be provided in Methods so there is no need to write this in Results. With this phrase it makes me wonder if all cases were laboratory confirmed COVID-19.

For the nine women who were treated with an antiviral, what were the indications? Can the authors comment on their response to treatment?

There were 61 women given corticosteroids for fetal lung maturation, I think the denominator should be the number of cases presented preterm and not 427. It would also be important to learn more if corticosteroids had any impact on the course of disease.

The rate of iatrogenic preterm birth is comparable to that of the published literature.

Twenty-eight women had general anaesthesia - the percentage should be 19%.

"Three deaths were definitely unrelated to SARS-CoV-2 infection." Please elaborate on why three deaths were definitely unrelated to SARS-CoV-2 infection.

Can the authors state how many neonates born to the 243 pregnant women were tested for SARS-CoV-2? Were the neonates tested only because of symptoms? How were they tested? What biological samples were collected? We need more details regarding the neonatal infection.

Discussion
In your first paragraph, you further confirmed that indeed you were looking for risk factors associated with admission with SARS-CoV-2 infection. The control group should be those with SARS-CoV-2 infection managed as outpatients. The choice of control group in this study was incorrect. If you do not have enough outpatients, then you should delay publishing your results on risk factors associated with admission with SARS-CoV-2 infection.

You have commented that advanced maternal age, black and minority ethnicity, overweight and obesity and pre-existing co-morbidities were risk factors for admission with SARS-CoV-2 infection, the writing style for smoking was changed. Smoking was associated with adjusted OR of 0.3 suggestive of a protective effect?

One in twenty of the babies of mothers admitted to hospital subsequently had a positive test for SARS-CoV-2. This rate is questionable - we need to know if all neonates were tested. If not all neonates born to infected mothers were tested then this number does not stand.

Only inpatients with SARS-CoV-2 were included - please acknowledge exclusion of outpatients. Please also acknowledge that pregnant women were presumably only tested when symptomatic so number of cases are likely to be under-reported.

"We have no evidence as to whether IgM was raised in these infants..." Does it mean antibodies testing was not undertaken? Please make this clearer.

As testing of the neonates was not performed immediately after birth, the reported early SARS-CoV-2 neonatal infection cases could be postnatal infection as mother and baby were kept together.

Tables
Gestation at symptom onset and end of pregnancy should be divided according to the following groups:

- <24
- 24-27
- 28-31
- 32-36
- 37 or more

It would also be good to see the data in the following groups:

- <24
- 24-33
- 34-36
- >37
To me, this paper is diluted and too much focused on risk factors, which are similar to those observed in nonpregnant populations. This paper lacks good description of findings that matter to physicians and pregnant patients: maternal deaths, adverse outcomes, treatments and complications. If this is a cohort study, I think it should remain to be a cohort study and provide important findings as such, and not be mixed with a case-control design.

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Please enter your name: Liona C. Poon

Job Title: Clinical Professor in Obstetrics and Gynaecology

Institution: The Chinese University of Hong Kong

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: Yes

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