Response to reviewer and editor comments

Editorial Board comments

* 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 have removed the multivariable adjustment as suggested and have presented simple proportions, with 95% confidence intervals where appropriate.

* 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 have rewritten the paper as suggested, removing all reference to the comparison group as we understand the concerns raised. We did want to attempt to set the findings about black and minority ethnicity, obesity and maternal age in some sort of context, so have added a new table estimating incidence rates and rate ratios amongst different population groups using national population denominator data. Given the large disparity in maternal mortality by ethnic group in the UK (prior to the SARS-CoV-2 pandemic, black women were known to have a 5 times higher maternal mortality rate than white women), as highlighted in the recent BMJ ‘Racism in medicine’ special issue, this observation will attract considerable interest and we wanted to include a quantification of the disparity. We would be grateful for your thoughts as to whether this presents the findings in a more appropriate and understandable way.

* 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.

We have updated the outcomes (based on data received up to 12th May 2020), which reflects a further 19 women who have now given birth. Thank you for the excellent suggestion and are delighted to commit to update the article with a rapid response with a final update on outcomes. 99% of women in the cohort are due to give birth by September, so we anticipate it would be on or after that date.

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)

As the comparison with a historical cohort has now been removed at the suggestion of the editors and other reviewers, we have removed reference to associated factors (and ORs) but have added the figures for the proportions of women in these different groups as noted above.

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.

Given the uncertainty in these estimates of the proportions of women in the different subgroups, and associated rate ratios, we have not over-emphasised them in the text, but would be happy to draw them out further if the editors felt this was warranted.

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

Correction made.

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".

Change made as suggested.

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.

We have clarified in the methods, as suggested, that body mass index (BMI) was defined on the basis of the first recorded weight in pregnancy.

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?

These women’s deaths are currently undergoing full investigation through the UK Confidential Enquiry into Maternal Deaths, thus causes of death are only provisional at this stage. Adding full details may also risk deductive disclosure. We have therefore simply clarified that three women died directly from complications of COVID-19, rather than adding potentially identifiable clinical detail.

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?

We do not have information on whether these infants were isolated from the mother immediately following delivery, nor whether skin-to-skin contact was permitted, but the UK policy at the time was, and remains, that women should not be isolated from their infants. We have added this to the limitations section and enhanced discussion of classification of neonatal infection status based on different tests. No viral analyses were performed on umbilical cord blood, placenta or vaginal secretions, and we have added this to the results.

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?

Unfortunately, we do not have this information.

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?

We were using the term vertical transmission to refer to all these different possible means of transmission. To avoid confusion, we have removed the term and replaced with ‘mother-to-infant
viral transmission’, and indicated the multiple possible modes of transmission as suggested. We have also expanded our discussion of the classification of neonatal infection status as noted above.

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

We have made the corrections as suggested.

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.

Thank you. Following the suggestion by the editors and other reviewers we have removed the comparison with the historical cohort and thus all odds ratios have been removed and any remaining figures are only given to one decimal place.

Reviewer: 4

Comments:
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.

Thank you. No response required.

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).

As requested by the editors, we have removed the formal comparison with the historical cohort, and have limited the paper to the description of the pregnant women hospitalised with SARS-CoV-2.

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.

The reviewer is correct. We have added this reflection to the discussion.

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).

We have removed the formal comparison discussing this, and, therefore, given the reviewer’s comments about concerns over the robustness of this association, we have not added a comment.

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.

In light of this concern, and that of the editors, we have removed the comparison group.

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 comorbidity 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.

Given the rarity of some outcomes, as emphasised by the editorial board, we are concerned that analysing in multiple small subgroups, as suggested by the reviewer, would be uninformative because of very low statistical power. We have, however, calculated rates amongst different population subgroups (new table 2) as an alternative, to allow comparison. Unfortunately, national
denominator data are only available on women’s ages, BMI and ethnic groups (not smoking or the presence of co-morbidities) and therefore we have had to limit our analysis to these characteristics.

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

We have removed this calculation as suggested by the editorial board.

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).

We have removed all reference to the comparison group, as noted above.

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.

We believe this conclusion is substantiated. The majority of women hospitalised with SARS-CoV-2 in pregnancy were in their third trimester. Hospitalisation is a measure of disease severity, thus women in their third trimester appear either at greater risk of infection, or at greater risk of severe disease once infected. In the absence of a vaccine or an effective treatment, the only way to mitigate this risk is to avoid infection, and the most effective way to avoid infection is through social distancing. The conclusion is hence directly linked to the findings. We have not therefore changed this statement.

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

We have updated the literature review (on 12th May) as suggested. We have not identified any population-based cohorts in this update, but have referenced the two largest new case series (n~100).
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?

We have revised the paper to describe solely the cohort of infected women. For the purposes of this study, confirmed infection was defined as either detection of viral RNA on PCR testing of blood or a nasopharyngeal swab, and/or respiratory compromise in the presence of characteristic x-ray changes of COVID-19. We have added this to the methods.

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.

We apologise that this was not clear. The historical cohort has now been removed.

Outpatient cases were excluded, which is a major limitation that should be acknowledged in Discussion.

We sought, from the inception of this study, to collect national, population-based information on severe SARS-CoV-2 infection, defined as hospitalisation, in order to capture the incidence and outcomes of severe disease in pregnancy. The UK strategy at the time of this study was only to test those admitted to hospital, thus any community or outpatient cohort would necessarily be biased and/or diluted by ‘presumed’ cases, thus severely limiting the accuracy of the findings. We do not therefore believe this to be a major limitation, but have added further discussion to the limitations section, noting that this study cannot be used to estimate overall incidence rates.

The authors might gain knowledge by comparing the characteristics and outcomes between inpatients and outpatients to identify risk factors for admission.

This is indeed possible, if testing is universal and all the outpatient cohort is identified and correctly classified (i.e. tested). However, in the absence of universal testing (as is the case in the UK), the outpatient cohort is likely to be biased (it will only include women who have attended hospital, and not those who have self-isolated at home), and therefore we believe such a comparison would be of limited value.

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.

We sought to collect national, population-based information on severe SARS-CoV-2 infection, defined as hospitalisation, in order to capture the incidence and outcomes of severe disease in pregnancy and we do not therefore believe this to be a limitation of our study. All women with severe disease will be admitted to hospital in the UK, and, since our reporting system covers all hospitals with obstetric units, they will be identified and included in this study. However, what this study cannot provide data on is overall infection rates, and we have noted this in the limitations section.
Authors should comment on measures to be undertaken in order to minimise duplicate reporting in future publications (perhaps by individual hospitals or other registries).

As researchers, we cannot prevent other clinicians or researchers from reporting their own centre-based data. However, UKOSS is the only national research platform in the UK for conducting such population-based studies, and thus all other reports of women hospitalised with SARS-CoV-2 in pregnancy in the UK will be subsets of UKOSS data. We have added this to the discussion as a potential limitation.

Results
Where applicable please provide counts with percentages throughout.

We have reviewed and provided counts and percentages where applicable 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).

We have removed all ORs with removal of the comparison group.

Please give s 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?

We had provided the figure for pregnancy losses in table 3, but have now added this additionally to the text, clarifying that this refers to women who have miscarried.

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?

We have updated the figures for this paper with data received up to 12th May. At this time, 41 women had required critical care, of whom 33 had been delivered. 27 of the 33 had been delivered due to worsening respiratory condition. We have added this to the paper.

"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.

We have clarified that this referred to women admitted to critical care.

"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.

We had used this phrasing to avoid referring to women as ‘cases’; we have modified to remove reference to the positive test, and have expanded detail on the case definition in the methods.

For the nine women who were treated with an antiviral, what were the indications? Can the authors comment on their response to treatment?
Unfortunately we have no information on the indications for antiviral use, although none were given in the context of a randomised controlled trial. All nine women have been discharged home and we have indicated this in the manuscript.

**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.**

Not all women given corticosteroids for fetal lung maturation were preterm, since in the UK guidelines suggest that steroids can be given to other groups, e.g. diabetic women, at later gestations. We have therefore retained the denominator as the total population.

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

Thank you for highlighting this, we have added information about preterm birth rates from the published literature to the introduction.

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

We have updated this figure with the new outcome data.

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

Given the risks of deductive disclosure we have not included clinical details about individual deaths in the paper. We have therefore elaborated that these deaths were due to obstetric conditions unrelated to COVID-19 and/or pre-existing fetal conditions.

**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.**

UK guidance is that neonates should only be tested if symptomatic or if admitted to neonatal units, and we have expanded on this in the results and discussion in response to reviewer 2.

**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.

We have removed the comparison group as noted above.

**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?**

We have removed this with the revisions to the paper.
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.

We have expanded the discussion of the testing of neonates to highlight uncertainties around testing. Nevertheless the statement as made is correct; we have emphasised that this does not exclude the possibility of asymptomatic infection in untested infants.

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 added the exclusion of outpatients, and hence the fact that this study does not estimate overall infection rates, to the limitations in the discussion. We do not feel significant under-reporting based on our case definition is likely, since the case definition did not specify that women had to have symptoms, however, we have also noted in the limitations section that this study does not provide any information about the possibility of asymptomatic infection.

“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.

We have expanded this discussion. Guidance in the UK does not recommend such testing, and, at the period of this study, no validated tests were available.

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.

We have expanded this discussion as noted above to emphasise the potential modes of transmission of infection.

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

We have retained our original groupings, since the use of the lower limit of 22 weeks is the recognised current limit of viability, and this division thus clearly separates viable pregnancies from non-viable pregnancy losses.
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.

We have revised as noted to focus solely on the cohort of pregnant women admitted with SARS-CoV-2 infection.