

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study
AUTHORS	Du, Min; Yang, Jie; Han, Na; Liu, Min; Liu, Jue

VERSION 1 – REVIEW

REVIEWER	Julia Townson Cardiff University, South Wales, UK
REVIEW RETURNED	12-Oct-2020

GENERAL COMMENTS	<p>Minor comments:</p> <ol style="list-style-type: none"> 1) Some sections (particularly the Introduction) could be improved with better use of the English language. The opening line 'Coronavirus disease 2019 (COVID-19) is a global pandemic respiratory disease which has led to the largest and deadliest pandemic' should be clarified and placed in context. Clarity is needed on the phrase 'taking antenatal care', this may be a misuse of English but a definition would also be useful. Is this clinical care? The spelling of 'caeserean' is inconsistent. The manuscript requires careful editing to correct some typographical errors. 2) A CONSORT type diagram, would be helpful. Please demonstrate the total number of pregnant women who delivered during the two time periods and if there were any women excluded from the analyses. 3) Table 3 is difficult to interpret, this may be a formatting issue but I am unable to read the confidence intervals and p-values for the three models. The legend states *P<0.05 but I cannot see a '*' in the table. 4) Full references for SAS 9.4 and R 3.4.2 should be provided within the text. <p>Major comments:</p> <ol style="list-style-type: none"> 1) The introduction focuses mainly on the adverse outcomes of pregnant women infected with COVID-19, which I believe is slightly misleading. I would like to see the introduction re-written to consider how a pandemic may affect the delivery of services and how women engage with services during a pandemic. How the introduction of policies at the beginning of the pandemic may influence pregnancy outcomes overall. 2) The method of calculating gestational weight gain needs further clarification, as presumably not all women would have the same number of days between their last routine pregnancy check-up and the first. In addition, presumably women would have been at different stages of their pregnancy. Can the authors provide further clarification on how this calculation was made and adjusted for in the analyses?
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	<p>3) Could the authors provide more insight on the reported demographic differences in the two cohorts? I do not understand why there would be a greater proportion of women aged > or = to 35 years in the COVID 19 cohort and why would this cohort contains more women with a family history of chronic diseases?</p> <p>4) Can the authors present the number of women included in the study who were infected with COVID 19? The discussion should include how this may have affected the results.</p> <p>5) Can the authors expand the discussion to consider the influence of any changes to management of services or policy implementation, which may have occurred during the initial stages of the pandemic. Were there any changes to the delivery of services which may have led to an increase in c-sections?</p>
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REVIEWER	Anita Banerjee Guys and St Thomas' Hospital
REVIEW RETURNED	16-Oct-2020

GENERAL COMMENTS	This study does not provide new information. A post COVID analysis of outcome is required. The lack of information around physical exercise, diet, and psychological status limits the findings and outcomes.
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REVIEWER	Ghulam Nabi Hebei Normal University
REVIEW RETURNED	17-Nov-2020

GENERAL COMMENTS	<p>The manuscript is drafted very clearly and have very important findings. However, i found one weakness about the mental health of pregnant women. Amidst COVID-19 pandemic, pregnant women suffered a lot and most probably some maternal or neonatal outcomes are linked with psychological stress due to COVID-19, isolation, financial crisis, ..etc. I have therefore, provided three papers for reference to include some information about the maternal-neonatal health and COVID 19. Also, there are some information about other neonatal and maternal cases that can help to improve the manuscript further.</p> <p>1.Wang L, Nabi G, Li D (2020) Potential neurochemical and neuroendocrine effects of social distancing amidst the COVID-19 pandemic. <i>Frontiers in Endocrinology</i>.</p> <p>2.COVID-19 induced psychosocial stressors during gestation: possible maternal and neonatal consequences. <i>Current Medical Research and Opinion</i>. https://doi.org/10.1080/03007995.2020.1815003.</p> <p>3.Coronaviruses disease 2019 (COVID-19): Causative agent, mental health concerns, and potential management options. <i>J Infect Public Health</i>. 25:S1876-0341(20)30576-1.</p> <p>4.Association of COVID-19 infection with pregnancy outcomes in healthcare workers and general women. <i>Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases</i>, S1198-743X(20)30180-4.</p> <p>5.Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth. <i>Infect Control Hosp Epidemiol</i>. 2020 Mar 19:1-3.</p> <p>6.Selected Micronutrients: An Option to Boost Immunity against COVID-19 and Prevent Adverse Pregnancy Outcomes in Pregnant Women: A Narrative Review. <i>Iranian Journal of Public Health</i>, 49(11):2032-2043.</p>
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VERSION 1 – AUTHOR RESPONSE

Minor comments:

1) Some sections (particularly the Introduction) could be improved with better use of the English language. The opening line 'Coronavirus disease 2019 (COVID-19) is a global pandemic respiratory disease which has led to the largest and deadliest pandemic' should be clarified and placed in context. Clarity is needed on the phrase 'taking antenatal care', this may be a misuse of English but a definition would also be useful. Is this clinical care? The spelling of 'caeserean' is inconsistent. The manuscript requires careful editing to correct some typographical errors.

Response: Thanks. We had rewritten some sections including introduction, methods and discussion in revision. Furthermore, the manuscript had been corrected by a native English writer. This manuscript was copy edited for proper English language at LetPub. We had corrected 'taking antenatal care' as 'prenatal visit', 'caeserean' as 'cesarean section' in revision.

2) A CONSORT type diagram, would be helpful. Please demonstrate the total number of pregnant women who delivered during the two time periods and if there were any women excluded from the analyses.

Response: Thanks. We had corrected this part in methods and added diagram of included and excluded participants (as shown in supplemental Figure 1) (page 4-5; supplemental Figure 1, page 29).

3) Table 3 is difficult to interpret, this may be a formatting issue but I am unable to read the confidence intervals and p-values for the three models. The legend states *P<0.05 but I cannot see a '*' in the table.

Response: Thanks. We had adjusted the format of table 3 (page 19) and deleted the legend of *P<0.05.

4) Full references for SAS 9.4 and R 3.4.2 should be provided within the text.

Response: Thanks. we added new description of data analysis for SAS 9.4 and R 3.4.2 in revision (page 6, lines 35-37 and page 7, lines 5-6).

Major comments:

1) The introduction focuses mainly on the adverse outcomes of pregnant women infected with COVID-19, which I believe is slightly misleading. I would like to see the introduction re-written to consider how a pandemic may affect the delivery of services and how women engage with services during a pandemic. How the introduction of policies at the beginning of the pandemic may influence pregnancy outcomes overall.

Response: Thanks. Thanks. We had searched related studies by using the combined terms [((COVID-19 pandemic[Title/Abstract]) AND (Effect[Title/Abstract])) AND ((maternal[Title/Abstract]) or (new born[Title/Abstract]) or (pregnancy[Title/Abstract]) or (pregnant[Title/Abstract]))] until November 29, 2020 in PubMed. There were 36 articles, after we have read them fully, 4 articles compared the effect of COVID-19 pandemic on mental health, 4 studies reported that the effect of COVID-19 pandemic on obstetric care, and 5 studies reported the change of obstetric outcomes because of COVID-19 pandemic. We had rewritten the introduction and discussion of the revision (page 3-4 and page 8-9).

2) The method of calculating gestational weight gain needs further clarification, as presumably not all women would have the same number of days between their last routine pregnancy check-up and the first. In addition, presumably women would have been at different stages of their pregnancy. Can the authors provide further clarification on how this calculation was made and adjusted for in the

analyses?

Response: Thanks. There was an error that gestational weight gain was the difference between weight of the last routine pregnancy check-up and the pre-pregnancy weight, we had corrected this sentence in revision. Furthermore, in order to adjust the different number of days between these two events, we added the rate of gestational weight gain in this revision (as shown in table 1 page 16, lines 58-59 and supplemental table 1 page 28, lines 4) which shown that there was no difference between pre-COVID-19 cohort and COVID-19 cohort. Besides, we also added additional full model C by replacing categorical variables into continuous variables including maternal age, gravidity, parity, history of miscarriage, history of induced abortion, pre-pregnancy BMI, the rate of gestational weight gain and the number of prenatal visit. The results of additional full model C showed the results were stable (as shown in supplemental table 2, page 29-30).

3) Could the authors provide more insight on the reported demographic differences in the two cohorts? I do not understand why there would be a greater proportion of women aged > or = to 35 years in the COVID 19 cohort and why would this cohort contains more women with a family history of chronic diseases?

Response: Thanks. In our study, we found that there be was a greater proportion of women aged > or = to 35 years in the COVID 19 cohort and this cohort contain more women with a family history of chronic diseases which may be related to two-child policy implemented in January 2016 in China. Zhao et al. found that the percentage of elderly pregnant women increased significantly in 2017 and 2018 compared with those in 2014, 2015, and 2016. We had explained it in discussion of revision ().

4) Can the authors present the number of women included in the study who were infected with COVID 19? The discussion should include how this may have affected the results.

Response: Thanks. There were no pregnant women infected with COVID-19. We had added this statement in revision (page 9, lines 51-59).

5) Can the authors expand the discussion to consider the influence of any changes to management of services or policy implementation, which may have occurred during the initial stages of the pandemic. Were there any changes to the delivery of services which may have led to an increase in c-sections?

Response: Thanks. After we searched related references and website, there was limited specific management or policy about prenatal care in Beijing, China. The National Health Commission of China launched a new notice on Feb 8, 2020,15, which proposed strengthening health counselling, screening, and follow-ups for pregnant women (<http://www.nhc.gov.cn/xcs/zhengcwj/202002/4f80657b346e4d6ba76e2cfc3888c630>) and the Tong Zhou hospital had tried their best to ensure the normal progress of prenatal care (eg, online appointment service, online consultation work, outpatient service and so on). The influence of management or policy on pregnancy outcomes in our study may be limited. But we still discussed the effect of management or policy on pregnancy outcomes based other similar studies (page 8, lines 56-59 and page 9, lines 4-35).

Additional points:

- The quality of the English needs improving throughout your manuscript. We recommend asking a native English-speaking colleague to assist you or to enlist the help of a professional copyediting service.

Response: Thanks. All the manuscript had been corrected by a native English writer. This manuscript was copy edited for proper English language at LetPub.

- The first two bullet points of the strengths and limitations section after the abstract need revising. This section should contain up to five short bullet points, no longer than one sentence each, that

relate specifically to the methods of the study reported (see: <http://bmjopen.bmj.com/site/about/guidelines.xhtml#articletypes>). It should not be a general summary of the study and its findings.

Response: Thanks. We had rewritten five bullet points in revision (page 4, lines 5-25).

- The relevant page number(s) from the manuscript should be added next to all reporting items in the STROBE checklist or you should state 'n/a' next to items that are not applicable to your study. There are currently some missing items.

Response: Thanks. We had stated these missing items after revising.

- We note that this study is reporting relative risks. Is it possible to translate estimates of relative risk into absolute risk and produce absolute numbers in the results sections? This is suggested in item 16c of the STROBE checklist.

Response: Thanks. We had added absolute numbers in the results sections (page 7, lines 47-52).

Reviewer: 2

Comments to the Author

This study does not provide new information. A post COVID analysis of outcome is required. The lack of information around physical exercise, diet, and psychological status limits the findings and outcomes.

Response: Thanks. We had searched related studies by using the combined terms [((COVID-19 pandemic[Title/Abstract]) AND (Effect[Title/Abstract])) AND ((maternal[Title/Abstract]) or (new born[Title/Abstract]) or (pregnancy[Title/Abstract]) or (pregnant[Title/Abstract]))] until November 29, 2020 in pubmed. There were 36 articles, after we have read them fully, 4 articles compared mental health between before COVID-19 pandemic and during COVID-19 pandemic, 4 studies reported that the effect of COVID-19 pandemic on obstetric care, and 5 studies reported the change of obstetric outcomes between before COVID-19 pandemic and during COVID-19 pandemic. Though there were 5 studies related with pregnancy outcomes. There still had some limitations and differences compared with our study. Firstly, the Setting of 4 studies were tertiary level centre, only one study (Ashish et al.) were multicenter studies in Nepal. Secondly, all of them just compared the rate of adverse outcomes without controlling some confounding factors (eg. occupation, education, gestational weight gain and so on). Finally, our study considered more special adverse outcomes including cesarean section, fetal distress, low birth weight and macrosomia. So we thought our study may be an important supplement for this area.

In addition, we were regretful that we could not get more information including physical exercise, diet, and psychological status. We have added it in limitation in this revision (page 10, lines 21-37).

Reviewer: 3

The manuscript is drafted very clearly and have very important findings. However, i found one weakness about the mental health of pregnant women. Amidst COVID-19 pandemic, pregnant women suffered a lot and most probably some maternal or neonatal outcomes are linked with psychological stress due to COVID-19, isolation, financial crisis, ..etc. I have therefore, provided three papers for reference to include some information about the maternal-neonatal health and COVID 19. Also, there are some information about other neonatal and maternal cases that can help to improve the manuscript further.

1.Wang L, Nabi G, Li D (2020) Potential neurochemical and neuroendocrine effects of social distancing amidst the COVID-19 pandemic. *Frontiers in Endocrinology*.

2.COVID-19 induced psychosocial stressors during gestation: possible maternal and neonatal

consequences. Current Medical Research and Opinion.

<https://doi.org/10.1080/03007995.2020.1815003>.

3. Coronaviruses disease 2019 (COVID-19): Causative agent, mental health concerns, and potential management options. J Infect Public Health. 25:S1876-0341(20)30576-1.

4. Association of COVID-19 infection with pregnancy outcomes in healthcare workers and general women. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases, S1198-743X(20)30180-4.

5. Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth. Infect Control Hosp Epidemiol. 2020 Mar 19:1-3.

6. Selected Micronutrients: An Option to Boost Immunity against COVID-19 and Prevent Adverse Pregnancy Outcomes in Pregnant Women: A Narrative Review. Iranian Journal of Public Health, 49(11):2032-2043.

Response: Thanks. These information was crucial to improving our study, after we read them fully. We had added some of them in revision (page 13, lines 51 and page 14, lines 27).

VERSION 2 – REVIEW

REVIEWER	Julia Townson Cardiff University, UK
REVIEW RETURNED	18-Dec-2020

GENERAL COMMENTS	Thank you for responding to my previous comments and substantially re-writing the manuscript, which I think now reads well. I still question why the women who delivered during the pandemic (COVID cohort) were significantly older and more likely to have family history of chronic disease. Can the authors provide any further explanation. I question whether the 2 child policy introduced in 2016, is likely to have had more influence in 2020 than 2019. The authors mention that pregnancy rates in women over 35 increased in the years following the introduction of the policy, do they have figures to show that the rate is still increasing? Is there an explanation of why women who delivered in the COVID cohort were more likely to have a family member with a history of chronic disease?
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REVIEWER	Anita Banerjee Guys and S Thomas' Hospitals NHS Foundation Trust England, UK
REVIEW RETURNED	21-Jan-2021

GENERAL COMMENTS	This edited manuscript reads well and would be of interest to our readers. Please correct the word 'creatine' ;p8 line 46-46 to 'creatinine'
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Julia Townson, Cardiff University

Comments to the Author:

Thank you for responding to my previous comments and substantially re-writing the manuscript, which I think now reads well.

Response : Thank you so much for the valuable suggestions on our manuscript.

I still question why the women who delivered during the pandemic (COVID cohort) were significantly older and more likely to have family history of chronic disease. Can the authors provide any further explanation. I question whether the 2 child policy introduced in 2016, is likely to have had more influence in 2020 than 2019. The authors mention that pregnancy rates in women over 35 increased in the years following the introduction of the policy, do they have figures to show that the rate is still increasing? Is there an explanation of why women who delivered in the COVID cohort were more likely to have a family member with a history of chronic disease?

Response : Thank you for the comment. The possible reason for the women who delivered during the pandemic (COVID cohort) were significantly older is that with the implementation of the two-child policy in China in 2016, an increased number of advanced maternal aged women give birth in recent years (Zhao F et al. Eur J Obstet Gynecol Reprod Biol; Liu Jue et al. BMJ Global Health; Liu Jue et al. BMJ Sex Reprod Health). The proportion of pregnant women over 35 years old in the hospital was steadily increased since 2016, that the proportion of pregnant women over 35 years old were 5.6% (533/9524) in 2014, 4.8% (690/14343) in 2015, 7.5% (1143/15210) in 2016, 7.5% (938/12504) in 2017, 10.7% (1332/12396) in 2018, 11.4% (1508/13241) in 2019, 12.1% (1529/12608) in 2020, respectively. We agree with your opinions that the second-child policy introduced in 2016 may have a greater impact on 2020 than in 2019, due to policies of isolation in home and travel restrictions in the pandemic. As the proportion of older pregnant women increased, correspondingly, their family members were more likely to have a history of chronic diseases. We have added the discussion in the revised draft (page 10, lines 6-19).

Reviewer: 2

Dr. Anita Banerjee, Guy's and Saint Thomas' Hospitals NHS

Comments to the Author:

This edited manuscript reads well and would be of interest to our readers.

Please correct the word 'creatine' ;p8 line 46-46 to 'creatinine'

Response : Thank you for suggestions. We have corrected it in this manuscript (page 9, line 11).

VERSION 3 – REVIEW

REVIEWER	Julia Townson Cardiff University, UK
REVIEW RETURNED	10-Feb-2021

GENERAL COMMENTS	<p>Thank you for providing additional information on the increasing age of pregnant women, following the 2nd child policy. I am happy with this explanation. There are some minor language and typo issues in the Discussion (Page 10), paragraph heading "Implications for clinicians and policy makers (Sentence 3 onwards) :-</p> <p>To ensure the access to prenatal care, hospital should take comprehensive and case-by-case measures, assess and monitor in follow-up visits as often as possible³³. Additionally, except for healthcare services, pregnant women should be educated about the importance of regular visits, healthy lifestyle and reasonable precautions but not at the cost of compromising health (wearing masks, personal hygiene, etc.). The indirect impact of COVID-19 pandemic on the vulnerable pregnant women is needed to paid more attention to. Additionally, long-term impact and the mechanism of COVID-19 pandemic on pregnant women and their babies should be explored in the future to ensure the maternal and new-borns health by lager multi-centre cohort study.</p>
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VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Dr. Julia Townson, Cardiff University

Comments to the Author:

Thank you for providing additional information on the increasing age of pregnant women, following the 2nd child policy. I am happy with this explanation.

Response : Thank you so much for the valuable suggestions on improving our manuscript.

There are some minor language and typo issues in the Discussion (Page 10), paragraph heading "Implications for clinicians and policy makers (Sentence 3 onwards) :-

To ensure the access to prenatal care, hospital should take comprehensive and case-by-case measures, assess and monitor in follow-up visits as often as possible³³. Additionally, except for healthcare services, pregnant women should be educated about the importance of regular visits, healthy lifestyle and reasonable precautions but not at the cost of compromising health (wearing masks, personal hygiene, etc.). The indirect impact of COVID-19 pandemic on the vulnerable pregnant women is needed to paid more attention to. Additionally, long-term impact and the mechanism of COVID-19 pandemic on pregnant women and their babies should be explored in the future to ensure the maternal and new-borns health by lager multi-centre cohort study.

Response : We are really sorry for the minor language and typo issues in the Discussion (Page 10), paragraph heading "Implications for clinicians and policy makers (Sentence 3 onwards). The manuscript has been revised by a native English speaker, especially for the paragraph heading "Implications for clinicians and policy makers in the Discussion section. This paragraph has been revised as "To ensure the access to prenatal care, hospitals should take comprehensive and case-by-case measures, assess and monitor the risk of adverse pregnancy outcomes in follow-up visits as often as possible. Additionally, apart from healthcare services, pregnant women should be educated about the importance of regular prenatal visits, healthy lifestyle and measures to prevent infection (wearing masks, hand hygiene, etc.) during the COVID-19 pandemic. More attention should be paid to reduce the indirect impact of COVID-19 pandemic on vulnerable pregnant women. Additionally, large multi-centre cohort studies should be conducted in future to further explore the long-term impact and the mechanism of COVID-19 pandemic on pregnant women and their babies to ensure maternal and child health."