PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	COVID-19 in pregnancy; The fetal perspective- a systematic review
AUTHORS	Dube, Rajani Kar, Subhranshu Sekhar

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Aarti Kinikar Institution and Country: BJ Government Medical College and Sasoon General Hospitals, Pediatrics, India Competing interests: None
REVIEW RETURNED	27-Sep-2020

GENERAL COMMENTS	The authors have undertaken a Systematic Review of the available published literature to determine the effects of confirmed cases of COVID-19 in pregnant women from the fetal perspective by estimation of vertical transmission, perinatal outcome and possible teratogenicity. Studies published between November 1, 2019 up to August 10, 2020 have been included in the Systematic Review. It is an important issue they have handled. A total of 35 case reports and 34 cohort/case series studies describing 1213 tested neonates were included for evidence of vertical transmission. Similarly, 26 case reports and 31 case series/cohort studies describing 1255 fetuses were included for evaluation of perinatal outcome and congenital anomalies. However , their search of published articles have not been complete. The following Case report – first case of vertical transmission from India can be added: ** Rajesh Kulkarni, Uday Rajput, et al. Early-onset symptomatic neonatal COVID-19 infection with high probability of vertical transmission. Infection https://doi.org/10.1007/s15010-020-01493-6. Published online on 2nd August 2020. They have concluded that chances of vertical transmission of the virus is low. The perinatal outcome for the fetus is favourable. There is very low rate of stillbirth and neonatal deaths. There were no reported congenital anomalies in babies born to SARS CoV-2 positive mothers. Similar observations have been made by authors of previously two published Systematic Review Articles : 1. J.Juan, Gil M M , Rong Z et al Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol 2020; 56: 15–27

	Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.22088. 2. Ashraf MA, Keshavarz P, Hosseinpour P, Erfani Ah, Roshanshad Ah, Pourdast A, et al. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Pregnancy and the Possibility of Vertical Transmission. J Reprod Infertil. 2020;21(3):157-168. How is the present study in comparison to the two above mentioned Systematic Reviews involving covid positive pregnancy outcomes' Need to be discussed, otherwise it is a repetition. "The phrase in Abstract "Neonates with shortness of breath" to could be changed to – breathing difficulty / respiratory distress as is commonly noted in newborns. Supplemental Table 6 : Neonatal Outcomes should include ICU admissions for Neonatal sepsis – an important cause of neonatal mortality . The tables are readable and easy to understand.

REVIEWER	Reviewer name: Dr. Michael Ceulemans Institution and Country: Katholieke Universiteit Leuven, Pharmaceutical and Pharmacological Sciences, Belgium Competing interests: None
REVIEW RETURNED	09-Sep-2020

GENERAL COMMENTS	Dear, Thank you very much for giving me the opportunity to review this manuscript, focusing on neonatal outcomes, vertical transmission and congenital anomalies in the context of maternal SARS-CoV-2 infection. Overall, I really appreciate the hard work and the great efforts of the authors to summarize the existing evidence (> 100 references!). The references are very up-to-date. However, I do have some substantial remarks which need to be considered to enhance the scientific quality and correctness of the manuscript's conclusion. Major comments - A classification system of in utero transmission of SARS-CoV-2 has been published by Shah and colleagues (Acta Obstet Gynecol Scand, May 2020). Please have a look at this paper and modify your manuscript and the interpretation of your findings with regard to vertical transmission accordingly (e.g. probable, …). It's not correct to state that 4% vertical transmission is observed, as a positive neonatal nasopharyngeal swab does not necessarily correspond to in utero transmission of the virus. - Some authors prefer to use the words 'in utero', 'intrapartum' and 'postpartum transmission', instead of vertical transmission. A reference to a reliable definition of vertical transmission is at least required if you prefer to continue this wording (see results, line 17). - It is unclear how many published studies used 'congenital anomalies' as a study objective. This is very relevant information

	to correctly interpret your conclusion on absence of congenital anomalies, and really needs to be included in the manuscript. - I doubt whether in the last month no other reviews on neonatal outcomes have been published. Please reconsider the phrasing of your key message. - I would suggest to put more emphasis on your three study outcomes in the description of the methods' section. Definitions of the study outcomes should also be mentioned in the methods' section, not in the results' section. - I am a bit confused about the remarks on RCTs (for example in line 40 and line 56). How can you do RCTs in this field?? - ORs are not specified, so it remains unclear what they represent - The results' section (e.g. the two first paragraphs) consists of many general phrases that should be placed in the introduction section but not in the results' section where I expect to read the main findings. Results: Page 10: start with your results, not with repeating the conclusions of previous reviews. Discuss the findings of other reviews in the discussion section + include references of these reviews. - Try to not put too much weight on a single case-report, for example page 13 lines 30-33. I might have understood it wrongly, but I thought you only included/discussed studies with at least 5 cases? Minor comments Abstract: - The sentence on cord blood is unclear (2x cord blood mentioned) - No % is mentioned after shortness of breath Introduction: - Line 7: '… was reported': a reference is missing - Line 13: I would suggest to only refer to the original study from the colleagues of the CDC (Ellington) Methods: - It would be interesting to provide insight in how the search terms were combined in the search strategy. This would allow other researchers to replicate the search. - Inclusion criteria: 1 2 4 -> where's number 3? It is further unclear whether the included studies met both criterium 1 AND 2 AND 4? - More information on how the ORs were calculated is required. Results: - Line 40: needs a reference - Pag 8 line 24: 'mother to child transmission': can it be excluded that transmission occurred through health care staff during or after delivery? - Page 9 line 5: '…single and 2 cases': this is unclear - Page 10 line 18: '..IgM': references are missing here - Page 10 line 10: 'breastmilk': references are missing here - Page 11 line 7: PROM n=29 and other variables with reported numbers: what does these numbers mean? How should the reader interpret these numbers? This might be relevant to discuss at some point.

	- Page 12 line 30-46: sometimes this section is hard to follow due to the variation in words such as LBW, IUGR and SGA. It seems like they are interchangeable, which isn't. - Page 13 line 7-8: '… found to be causes unrelated to…' : this is not clear Discussion: - Start your discussion with repeating your aims - It might be appropriate to more extensively discuss your findings, for example with regard to the biological plausibility of in utero transmission (see paper Pique-Regi which is mentioned in the reference list but of which the findings are not really discussed), congenital malformations, … - Ref 80 is a systematic review; I would not describe this as a 'study' in the text, but as a systematic review - Line 19: maternal outcomes were not studied: this should be part of the limitations of your work - Line 22-23: does this conclusion not deserve more attention / could be discussed earlier in the discussion section? - Do you think there has been an overlap in cases reported by different studies/authors, for example in the Chinese publications? This might be relevant to discuss in the paragraph on your methodological considerations? - Start your methodological considerations with your strengths. - Line 41: do you mean lack of classification system for in utero transmission? See my previous comment on this. Tables: - Table 1: It is unclear what the **, ***, *** exactly represent? Please use footnotes to clarify this. - Table 1: "evidence of vertical transmission": see my major comment on this definition. - Table 1: "perinatal outcome": what does the √ mean (details available or favorable outcome?) - Table 1: "outcome": lab parameters is mentioned here, but did you include this as a study outcome? - Table 2: there is no table with the results of the other types of biologic samples? - Table 5: ORs should be explained.

REVIEWER	Reviewer name: Dr. Caique Jordan Nunes Ribeiro Institution and Country: Instituto Federal de Educação Ciência e Tecnologia de Sergipe, Coordenadoria de Saúde Escolar, Brazil Competing interests: None
REVIEW RETURNED	09-Sep-2020

GENERAL COMMENTS	The manuscript shows an important topic, but there are other similar published studies. The structure of this systematic review is akward and confusing to readers. The PRISMA Flowchart should be adapted to clarify the sections/categories of analysis. Sectional and case-control studies were not included. Only English papers were considered. Furthermore, it is necessary a thorough grammar editing. Therefore, I suggest that the article be rejected.

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, United States Competing interests: None
REVIEW RETURNED	12-Sep-2020

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. These were well done and I recommend publication. Peter Flom

VERSION 1 – AUTHOR RESPONSE

Dear Sir,
Greetings of the day!
Please note that we have extensively revised the manuscript basing on the reviewers comments and suggestions. So, the latest files were only uploaded deleting the previous ones. The point to point rebuttal file, marked copy-main document-revised manuscript with track changes-1, revised supplemental material-tables 1 to 6 and revised PRISMA figures-1 and 2 are attached herewith for your perusal.
Should there be any other documents required, please let us know.
Thanks and regards,
Subhranshu Sekhar Kar

Reviewer: 1

Serial No.	Comment	Status	Highlight
1	A classification system of in utero transmission of SARS-CoV-2 has been published by Shah and colleagues (Acta Obstet Gynecol Scand, May 2020). Please have a look at this paper and modify your manuscript and the interpretation of your findings with regard to vertical transmission accordingly (e.g. probable, …). It's not correct to state that 4% vertical transmission is observed, as a positive neonatal nasopharyngeal swab does not necessarily correspond to in utero transmission of the virus.	Changes done	Highlighted in the text in the methods section also
2	Some authors prefer to use the words 'in utero', 'intrapartum' and 'postpartum transmission', instead of vertical transmission. A reference to a reliable definition of vertical transmission is at least required if you prefer to continue this wording (see results, line 17).		
3	It is unclear how many published studies used 'congenital anomalies' as a study objective. This is very relevant information to correctly interpret your conclusion on absence of congenital anomalies, and really needs to be included in the manuscript.	No studies were identified having primary objective of congenital anomaly	
4	I doubt whether in the last month no other reviews on neonatal outcomes have been published. Please reconsider the phrasing of your key message.	Changes done	Highlighted in the text
5	I would suggest to put more emphasis on your three study outcomes in the description of the methods' section. Definitions of the study outcomes should	Changes done	Highlighted in the text in the methods section

	also be mentioned in the methods' section, not in the results' section.		
6	I am a bit confused about the remarks on RCTs (for example in line 40 and line 56). How can you do RCTs in this field??	In these scenarios RCTs can be conducted involving the effect of different treatment modalities on transmission rate and severity of neonatal infection etc. However, as indicated by you, RCTs are currently not available.	
7	ORs are not specified, so it remains unclear what they represent	Changes done	Highlighted in the text
8	The results' section (e.g. the two first paragraphs) consists of many general phrases that should be placed in the introduction section but not in the results' section where I expect to read the main findings.	Changes done	
9	Results: Page 10: start with your results, not with repeating the conclusions of previous reviews. Discuss the findings of other reviews in the discussion section + include references of these reviews.	Changes done	Highlighted in the text in discussion
9	Try to not put too much weight on a single case-report, for example page 13 lines 30-33. I might have understood it wrongly, but I thought you only included/discussed studies with at least 5 cases?	We have included studies with 5 or more cases but the studies with 4 or less cases were also separately analyzed as they contained more detailed account of fetal and neonatal outcomes like symptoms, exclusion of other infections etc.	
10	Abstract: - The sentence on cord blood is unclear (2x cord blood mentioned) - No % is mentioned after shortness of breath	Changes done	Highlighted in the text
11	Introduction: - Line 7: '… was reported': a reference is missing - Line 13: I would suggest to only refer to the original study from the colleagues of the CDC (Ellington)	Changes done	Highlighted in the text

12	Methods: - It would be interesting to provide insight in how the search terms were combined in the search strategy. This would allow other researchers to replicate the search. - Inclusion criteria: 1 2 4 -> where's number 3? It is further unclear whether the included studies met both criterium 1 AND 2 AND 4? - More information on how the ORs were calculated is required.	Changes done	Highlighted in the text
13	Results: - Line 40: needs a reference - Page 8 line 24: 'mother to child transmission': can it be excluded that transmission occurred through health care staff during or after delivery? - Page 9 line 5: '…single and 2 cases': this is unclear - Page 10 line 18: '..IgM': references are missing here - Page 10 line 10: 'breastmilk': references are missing here - Page 11 line 7: PROM n=29 and other variables with reported numbers: what does these numbers mean? How should the reader interpret these numbers? This might be relevant to discuss at some point. - Page 12 line 30-46: sometimes this section is hard to follow due to the variation in words such as LBW, IUGR and SGA. It seems like they are interchangeable, which isn't. - Page 13 line 7-8: '… found to be causes unrelated to…' : this is not clear	Changes done, mentioned in the methods section, results section and discussion section.	
14	Discussion: - Start your discussion with repeating your aims - It might be appropriate to more extensively discuss your findings, for example with regard to the biological plausibility of in utero transmission (see paper Pique-Regi which is mentioned in the reference list but of which the findings are not really discussed), congenital malformations, … - Ref 80 is a systematic review; I would not describe this as a 'study' in the text, but as a systematic review - Line 19: maternal outcomes were not studied: this should be part of the limitations of your work - Line 22-23: does this conclusion not deserve more attention / could be discussed earlier in the discussion section? Done in discussion section - Do you think there has been an overlap in cases reported by different studies/authors, for example in the Chinese publications? This might be relevant to	Changes done Findings of the paper discussed	Highlighted in the text

	discuss in the paragraph on your methodological considerations? Mentioned in methods section - Start your methodological considerations with your strengths. - Line 41: do you mean lack of classification system for in utero transmission? See my previous comment on this.		
15	Tables: - Table 1: It is unclear what the **, ***, *** exactly represent? Please use footnotes to clarify this. - Table 1: "evidence of vertical transmission": see my major comment on this definition. - Table 1: "perinatal outcome": what does the √ mean (details available or favorable outcome?) - Table 1: "outcome": lab parameters is mentioned here, but did you include this as a study outcome? - Table 2: there is no table with the results of the other types of biologic samples? **Incorporated in Table 2,3a,3b** - Table 5: ORs should be explained. **- explained**	Changes done Lab parameters were available in the studies but not included in the outcome	Highlighted in the supplementary file

Dear,

Thank you very much for giving me the opportunity to review this manuscript, focusing on neonatal outcomes, vertical transmission and congenital anomalies in the context of maternal SARS-CoV-2 infection. Overall, I really appreciate the hard work and the great efforts of the authors to summarize the existing evidence (> 100 references!). The references are very up-to-date. However, I do have some substantial remarks which need to be considered to enhance the scientific quality and correctness of the manuscript's conclusion.

Reviewer: 4

Serial No.	Comment	Status	Highlight
1.	The following Case report – first case of vertical transmission from India can be added: ** Rajesh Kulkarni, Uday Rajput, et al. Early-onset symptomatic neonatal COVID-19 infection with high probability of vertical transmission. Infection https://doi.org/10.1007/s15010-020-01493-6. Published online on 2nd August 2020.	This was initially excluded from our study as the NP-RT PCR in the mother was negative. Maternal serology was negative on delivery but was	Highlighted

		positive on D10 of delivery. However, it is included now.	
2.	Similar observations have been made by authors of previously two published Systematic Review Articles : 1. J.Juan, Gil M M , Rong Z et al Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol 2020; 56: 15–27 Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.22088. 2. Ashraf MA, Keshavarz P, Hosseinpour P, Erfani Ah, Roshanshad Ah, Pourdast A, et al. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Pregnancy and the Possibility of Vertical Transmission. J Reprod Infertil. 2020;21(3):157-168. How is the present study in comparison to the two above mentioned Systematic Reviews involving covid positive pregnancy outcomes' Need to be discussed, otherwise it is a repetition.	The differences are discussed in the discussion section and our review outcomes were found to be different. The number of studies included in our review was also significantly higher	Highlighted in discussion section
3.	"The phrase in Abstract "Neonates with shortness of breath" to could be changed to – breathing difficulty / respiratory distress as is commonly noted in newborns.	Changes done	Highlighted in the abstract
4.	Supplemental Table 6 : Neonatal Outcomes should include ICU admissions for Neonatal sepsis – an important cause of neonatal mortality .	Changes done	Highlighted

Comments to the Author
The authors have undertaken a Systematic Review of the available published literature to determine the effects of confirmed cases of COVID-19 in pregnant women from the fetal perspective by estimation of vertical transmission, perinatal outcome and possible teratogenicity. Studies published between November 1, 2019 up to August 10, 2020 have been included in the Systematic Review. It is an important issue they have handled.

A total of 35 case reports and 34 cohort/case series studies describing 1213 tested neonates were included for evidence of vertical transmission. Similarly, 26 case reports and 31 case series/cohort studies describing 1255 fetuses were included for evaluation of perinatal outcome and congenital anomalies.

However , their search of published articles have not been complete.

They have concluded that chances of vertical transmission of the virus is low. The perinatal outcome for the fetus is favourable. There is very low rate of stillbirth and neonatal deaths. There were no reported congenital anomalies in babies born to SARS CoV-2 positive mothers.
The tables are readable and easy to understand.

Editor in Chief

Serial No.	Comment	Status	
1	State how many non-English papers you identified This is a major limitation and needs to be stated as such	There were 37 Chinese studies, 6 Italian, 3 Portugese, 3 French, 2 Swedish,1 German and 2 Korean studies. However, not all non English studies were excluded. Only studies where English translations were not available were excluded.	Already mentioned in the methodology
2	Shorten your Public and Patient Involvement statement: to a single sentence	Done	
3	Tables. Better to list by country, i.e all papers from China together, etc	Changes done	