PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of COVID-19 on female fertility: a systematic review and meta-analysis protocol
AUTHORS	Li, Fangyuan; Lu, Hua; Zhang, Qi; Li, Xinyun; wang, Tong; Liu, Qianchen; Yang, Qian; Qiang, Lingxia

VERSION 1 – REVIEW

REVIEWER	Fei Chen Department of Physiology, Jining Medical University, Jining, China
REVIEW RETURNED	18-Oct-2020

GENERAL COMMENTS	In this protocol, the authors plan to perform a systematic review and meta-analysis to increase the understanding of the relationship between COVID-19 and female fertility. Given the COVID-19 pandemic , we think it is necessary. However, the entire text needs to be reviewed closely to ensure good English usage and consistent formatting. In attach files, I marked some areas for improvement. Most of it is clear but there are some areas where improvement would be welcome.

REVIEWER	Jennifer Gordon University of Regina, Canada
REVIEW RETURNED	26-Nov-2020

GENERAL COMMENTS	The proposed systematic review and meta-analysis address an important and interesting question and is well thought out. It will make an important contribution to the current literature. I offer just a few remarks/suggestions: -There is mention of inclusion of randomized controlled trials where they exist but it's unclear to me what RCT could exist since animal studies are excluded. Obviously, there would be no RCT exposing some individuals to COVID and others not. Please clarify what is meant by RCT in this case. -Perhaps the authors might consider adding study quality/risk of bias to the variables considered in the subgroup analyses?

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REVIEW RETURNED	26-Nov-2020

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	animal studies are excluded. Obviously, there would be no RCT exposing some individuals to COVID and others not. Please clarify what is meant by RCT in this case. -Perhaps the authors might consider adding study quality/risk of bias to the variables considered in the subgroup analyses?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1:
Q: Comments to the Author (see attached file), In this protocol, the authors plan to perform a systematic review and meta-analysis to increase the understanding of the relationship between COVID-19 and female fertility. Given the COVID-19 pandemic , we think it is necessary. However, the entire text needs to be reviewed closely to ensure good English usage and consistent formatting. In attach files, I marked some areas for improvement. Most of it is clear but there are some areas where improvement would be welcome.
A: Thank you for your comments. We are sorry for the poor English of the manuscript. We have reviewed closely to ensure good English usage and consistent formatting. We have made the appropriate changes in the areas marked for improvement.
Title page
A: Line 2 : “Tongwang” (Page 3, line 6/7) was revised as “ Tong Wang” .
A: Line 5 and 12: The English name of the hospital (成都中医药大学附属医院) to which the author belongs was corrected: “Chengdu University of Traditional Chinese Medicine Affiliated Hospital” (Page 3, line 14/27) was revised as “Hospital of Chengdu University of Traditional Chinese Medicine”.
ABSTRACT
A: Introduction, Line 31/33: “It is essential to investigate whether COVID-19 hurts female fertility and to early prevention and intervention of its secondary effects.” (Page 5, line 17/18) was corrected as “Tus, it is essential to investigate if the novel COVID-19 hampers female fertility, given that there is no systematic and comprehensive evidence on the association of COVID-19 with female fertility ”.
A: Methods and analysis, Line 37: “WangFang” (Page 5, line 28/29) was revised as “WanFang”.
INTRODUCTION
A: Line 63: “2019 Novel Coronavirus (2019-nCoV)” (Page 6, line 20/21) was revised as “coronavirus disease 2019 (COVID-19)”.
A: Line 64/66: “Globally, as of 2 September 2020, 25,602,665 confirmed cases of COVID-19, including 852,758 deaths, were reported to WHO” (Page 6, line 24/27) was revised as “Globally, as of the 2nd of September 2020, there have been 25,602,665 confirmed cases of COVID-19, including 852,758 deaths, reported by the WHO ”.
A: Line 70: “Sperm” ((Page 6, line 34/35) was revised as “sperm”.
A: Line 54/55: “virus” (Page 6, line 54/55) was deleted.
A: Line 71 : “Sars-cov-2” (Page 7, line 25/26) was revised as “SARS-CoV-2”.
A: Line 99/100: “immune-modulators” (Page 7, line 33) was revised as “immune modulators”.
METHODS AND ANALYSIS
A: Line 124: “Participants” (Page 8, line 27/28) was revised as “females”.
A: Line 151: “WangFang” (Page 9, line 25/26) was revised as “WanFang”.
A: Line 157/158: “Taking the search model developed for PubMed as an example to demonstrate the detailed search strategy, as shown in Table S1 of supplementary appendix 1.” (Page 9, line37/41) was revised as “A detailed search strategy is described in Table S1 of Supplementary Appendix 1, using PubMed as an example.”
A: Line 180: “outcome is ” (Page 10, line32/33) was revised as “outcomes are”.
A: Line 220: “.”(Page 12, line16/17) was added after the word “heterogeneity.”

SUMMARY

A: Line 233/234: “Given the overwhelming magnitude of the COVID-19 and its worldwide prevalence, it has been a significant public health issue.” (Page 12, line48/52) was revised as “COVID-19 has been a significant public health issue, given its overwhelming magnitude and worldwide prevalence”.

A: Line 243 : “Sars-cov-2” (Page 13, line 6/7) was revised as “SARS-CoV-2”.

A: “)” (Page 13, line 46/47) was deleted.

REFERENCES

A: The 22nd reference: “https://www.genecards.org/cgi-bin/carddisp.pl?gene=ACE2#protein_expression.” (Page 16, line 7/8) was revised as“https://www.genecards.org/cgi-bin/carddisp.pl?gene=ACE2&keywords=ACE2#protein_expression”.

Abbreviations

A: We have supplemented the full name of ACE2: “ACE2 = angiotensin-converting enzyme 2”.

A: “-CoV” (Page 15, line 52/53) was deleted.

Response to Reviewer 2:

Q: The ms will benefit by linguistic improvement. The authors may elaborate about the role of covid-19 on female fertility by using several updated references.

A: We have sought the help of a professional English editing service, and linguistic improvement will be reflected in the Overview section. We have reviewed the recently updated studies and found that a small amount of updated literature on the impact of COVID-19 on female fertility /span>offers additional insights. To collect more comprehensive meta-analysis data, we will continue to track the relevant literature closely. We have added some contents in the “Introduction” section, specifically as follows:

A: Introduction, Line 75-77: It has been reported that COVID-19 is usually accompanied by high levels of IL-6, IL-8, TNF-α, and other cytokines, which trigger a procoagulant state that is unfavorable to the development of blastocyst or fetus in a normal human uterus (Sills ES, Wood SH, 2020).

A: Introduction, Line 95-98: Basigin (BSG) is also one of the most crucial receptors for COVID-19 that mediates its entry to host cells (Mahdian S, Shahhoseini M, Moini A,2020). BSG is expressed not only in the uterus but also in the stroma and granulosa cells of the ovary (Mahdian S, Shahhoseini M, Moini A,2020; Chen L, Bi J, Nakai M, Bunick D, et al, 2010). BSG may play a role during follicle development, corpus luteum formation, and embryo implantation (Chang H, Ni H, Ma XH, et al, 2004).

Reference :

1. Sills ES, Wood SH. An Experimental Model for Peri-conceptual COVID-19 Pregnancy Loss and Proposed Interventions to Optimize Outcomes. Int J Mol Cell Med. 2020 Summer;9(3):180-187. doi: 10.22088/IJMCM.BUMS.9.3.180. Epub 2020 Nov 10. PMID: 33274180; PMCID: PMC7703664.
2. Mahdian S, Shahhoseini M, Moini A. COVID-19 Mediated by Basigin Can Affect Male and Female Fertility. Int J Fertil Steril. 2020 Oct;14(3):262-263. doi: 10.22074/ijfs.2020.134702. Epub 2020 Oct 12. PMID: 33098397; PMCID: PMC7604703.
3. Chen L, Bi J, Nakai M, Bunick D, Couse JF, Korach KS, Nowak RA. Expression of basigin in reproductive tissues of estrogen receptor-{alpha} or -{beta} null mice. Reproduction. 2010 Jun;139(6):1057-66. doi: 10.1530/REP-10-0069. Epub 2010 Apr 13. PMID: 20388736; PMCID: PMC4778977.
4. Chang H, Ni H, Ma XH, Xu LB, Kadomatsu K, Muramatsu T, Yang ZM. Basigin expression and regulation in mouse ovary during the sexual maturation and development of corpus luteum. Mol Reprod Dev. 2004 Jun;68(2):135-41. doi: 10.1002/mrd.20060. PMID: 15095333.

Response to Reviewer 3:

Q: There is mention of inclusion of randomized controlled trials where they exist but it’s unclear to me what RCT could exist since animal studies are excluded. Obviously, there would be no RCT exposing some individuals to COVID and others not. Please clarify what is meant by RCT in this case.

A: Thank you for your comments and reminders. We apologize for the lack of consideration given to the inclusion of the literature. Although a small number of randomized controlled trials have been registered for COVID-19 (ChiCTR2000039369, et al), the homogeneity of the subjects in the randomized controlled trials was ignored when we wrote the manuscript. There is no RCT exposing some individuals to COVID and others not. So we have deleted “randomized controlled trials (if available)” in the absract section (page 5, Line 25) and “randomized controlled trials if available” in the methods and analysis section (page 8, Line 15/16). At the same time, we have deleted the quality assessment of RCT in the quality and bias assessment section. “If any randomised controlled trials are included in this review, we will assess study quality using the Cochrane Collaboration's tool for risk of bias (ROB) assessment. This tool includes 7 items grouped into 5 domains: reporting bias, selection bias, detection bias, performance bias, and attrition bias. The risk of bias will be classified as low, high or unclear risk according to the following items, such as random sequence generation, blinding of participants andresearchers, allocation concealment, blinding of outcome assessment, completeness of outcome data , selective outcome reporting, and other bias” (page 11, Line 11-21) was deleted.

Q: Perhaps the authors might consider adding study quality/risk of bias to the variables considered in the subgroup analyses?

A: We will consider the risk of bias, assess heterogeneity, and explore potential influencing factors via subgroup analyses and sensitivity analyses. As we considered the age (13–35 years and 35–49 years old), COVID-19 stage, and other factors as likely being the critical confounders, we will perform subgroup analyses and meta-regressions to determine the influence of different potential moderator variables if a sufficient number of studies were available. To inform our subgroup analyses based on the risk of bias, we will perform subgroup analyses on a component-by-component basis if we detect variability within the individual risk of bias components. Study quality may also be important variables associated with heterogeneity across studies. Because the scales designed for the observational studies are different, subgroup analyses by study quality scores or risk of bias will be conducted separately for the studies. At present, Considering the limited relevant studies of overall analysis and subgroup analysis, larger sample size and higher-quality studies wil be needed to be collected to make further verification.

VERSION 2 – REVIEW

REVIEWER	Fei Chen Jining Medical University, China.
REVIEW RETURNED	12-Jan-2021

GENERAL COMMENTS	In this protocol, the authors plan to perform a systematic review and meta-analysis to increase the understanding of the relationship between COVID-19 and female fertility. Given the COVID-19 pandemic , we think it is necessary.