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The impact of COVID-19 on female fertility: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction

The increased social and economic burdens for COVID-19 outbreaks and epidemics make the prevention of such secondary injuries a major public health goal. The novel coronavirus invades the target cell by binding to ACE2 which is widely expressed in the ovaries, uterus, vagina, and placenta. SARS-CoV-2 might disturb the female fertility through regulating ACE2. However, there is no systematic and comprehensive evidence on the association of COVID-19 with female fertility. It is essential to investigate whether COVID-19 hurts female fertility and to early prevention and intervention of its secondary effects.

Methods and analysis

We will systematically search cohort studies, cross-sectional studies, case-control studies, self-controlled case series designs, and randomized controlled trials (if available) in the following databases: Web of Science, PubMed, EMBASE, Cochrane Library, Ovid, EBSCO, WHO COVID-19 database, CBM, CNKI, VIP, and WangFang database. Medical subject headings and free text terms for "COVID-19" AND "female" AND "fertility" will be performed. Eligibility criteria are as follows: population—female patients, aged 13-49 years; exposure—infection with SARS-CoV-2; comparison—population without SARS-CoV-2 infections or latent SARS-CoV-2 infections; and outcome—female fertility, such as ovarian reserve function, uterine receptivity, oviducts status, and menstruation status. Article screening and data extraction will be undertaken independently by two reviewers, and discrepancies will be resolved through discussion. We will use the I^2 statistics to assess the heterogeneity and perform a meta-analysis when sufficiently homogeneous studies are provided. Otherwise, a narrative synthesis will be performed. We will explore the potential sources of heterogeneity using subgroup analyses and meta-regression.

Ethics and dissemination

Formal ethical approval is not required, and findings will be published in a peer-reviewed journal.

PROSPERO registration number

CRD42020189856

Keywords: novel coronavirus, COVID-19, female fertility, systematic review

Strengths and limitations of this study

This systematic review will first synthesize the available evidence on the association between COVID-19 and female fertility and will fill in the literature gaps.

The current network meta-analysis results provide more substantial evidence for fertility protection decisions in the female with COVID-19.

A potential limitation may be that relevant papers may have been omitted despite extensive searches.

INTRODUCTION

The national and global spread of 2019 Novel Coronavirus (2019-nCoV), which is caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), has made it one of the most severe public health threat. Globally, as of 2 September 2020, 25,602,665 confirmed cases of COVID-19, including 852,758 deaths, were reported to WHO[1]. SARS-CoV-2 infection disrupts normal immune responses[2], leading to tissue damage locally and systemically[3]. Local tissue damage mainly affects the lower respiratory tract and presents as pneumonia, including fever, cough, expectoration, haemoptysis, etc[4]. The extrapulmonary damage of COVID-19 includes acute kidney injury, hepatocellular injury, neurologic illnesses, myocardial dysfunction and arrhythmia, and gastrointestinal symptoms[5]. Besides, Sperm are also susceptible to viral attack[6] and SARS-CoV-2 infection may most likely to cause male infertility[7]. Some studies have shown that SARS-CoV-2 might affect female fertility and disturb female reproductive functions[8,9]. However, the association between COVID-19 and female fertility has not been systematically evaluated.

COVID-19 appears to have shown negative effects on the reproductive system. The scale of the COVID-19 pandemic, there appears to be a potential decline in fertility[10]. A study showed that many young people have a wide range of problems affecting their sexual and reproductive health due to COVID-19 pandemic and related containment measures[11]. An epidemiological study demonstrated that coronaviruses could have adverse effects on fetuses and infants, including preterm delivery, intrauterine growth restriction, spontaneous abortion, and death[12]. Moreover, studies have documented the presence of SARS-COV-2 virus across the placenta even in pregnant patients with mild COVID-19 disease, potentially leading to fetal growth restriction and other pregnancy complications[13]. Accumulating evidence now suggests that 2019-nCoV/ACE2 may interfere with the female reproductive functions, leading to menstrual disorder,

infertility, and fetal distress[8].

Angiotensin-converting enzyme (ACE) 2 is a receptor for severe acute respiratory syndrome (SARS)-CoV[14]. SARS-CoV-2, as a subgenus Sarbecovirus of the genus Betacoronavirus, shares 76% amino acid sequence homology with SARS-CoV[15]. The protein expression profile of ACE2 is also considered to be the host receptor of SARS-COV-2[16]. Thus SARS-CoV-2 can invade target host cells by using the ACE2 as the primary receptor binding site[17-19]and regulate the expression of ACE2 in host cells [8]. ACE2 expression has been assessed in various human organs, such as respiratory tracts, heart, kidney, ovary, uterus, testis, vagina and placenta, and gastrointestinal system[8,20]. Notably, ACE2 is highly expressed in the ovaries[21]. The available evidence suggests that ACE2 is expressed in stromal cells, granulosa cells, and oocytes in immature rat ovaries[22]. ACE2 regulates follicular development and ovulation, regulates luteal angiogenesis and degeneration, and affects the regular changes of endometrial tissue and embryo development[8]. ACE2 plays a regulatory role in reproduction[7]. Taking these factors into account, Sars-cov-2 may disturb female fertility by attacking ovarian tissue and granulosa cells or by damaging endometrial epithelial cells[9]. In addition, COVID-19, as an impaired immune system and uncontrolled inflammatory responses severe disease, may alter the function of the hypothalamic-pituitary-gonadal axis[2,23]. Sex steroids are potent immune-modulators, different concentrations of progesterone (P) 4 and androgen are likely to influence the immune response and inflammatory outcomes of COVID-19[23]. However, the magnitude of the association between COVID-19 and female fertility remains less clear.

With the overwhelming magnitude of COVID-19 and its worldwide prevalence, the associated health burden, as well as social and economic costs, might be a massive loss around the world. To our knowledge, there is no systematic review of the potential role of COVID-19 in female fertility. One of the most critical questions that remain to be answered is whether or how the COVID-19 will affect female fertility. Therefore, we will perform a systematic review and meta-analysis to increase our understanding of the relationship between COVID-19 and female fertility and to facilitate the development of prevention strategies at the individual and population levels.

METHODS AND ANALYSIS

This study will be reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) statement[24] and meta-analysis of Observational Studies in

Epidemiology (MOOSE)[25]. The protocol for this review is registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number (CRD42020189856).

Inclusion/exclusion criteria for study selection

Study designs and characteristics

We will include observational studies (cohort studies, cross-sectional studies, and case-control studies), self-controlled case series designs, and randomised controlled trials if available. These studies should also report the impact of COVID-19 on female fertility, including variations in menstrual situation, gonad function, ovarian reserve function, tubal patency, endometrial receptivity, and other potential of reproduction. It is not restricted by language, publication status, geography, or medical conditions.

Participants

Female patients in puberty and adulthood (13 years old ⩽ age ⩽ 49 years old) with COVID-19; Participants were not excessively exposed to certain physical, biological, chemical, or environmental factors that affect female fertility,such as lead, cadmium, mercury, pesticides, benzene, toluene and ionizing radiation[26]; not have any gonadal injury that caused by high-dose alkylating agent chemotherapy and abdominal/pelvic radiotherapy[27]; and severe thyroid dysfunction and other diseases that affect female fertility will be excluded[28].

Exposure/Interest

The exposure factor of interest is infection with SARS-CoV-2, which is mainly diagnosed by RT-PCR with nasal swab, tracheal aspirate, or bronchoalveolar lavage (BAL) specimens[29].

Comparators

The comparator group will be population that without SARS-CoV-2 infections or with latent SARS-CoV-2 infections.

Outcome measures

The primary outcome will be at least one of the following indicators of ovarian reserve function:(1) Anti-Müllerian hormone (AMH); (2) basal follicle-stimulating hormone (FSH), basal luteinizing hormone(LH), or the ratio of FSH/LH; (3) basal estradiol (E2); (4)serum inhibin-B; (5) antral follicle count

(AFC). Secondary outcomes, if any, will be considered: (1) uterine receptivity (endometrial thickness, endometrial morphology, subendometrial blood flow, uterine spiral artery blood flow); (2) oviducts status; (3) menstruation status; (4) other female reproductive dysfunction diseases caused by COVID-19.

Exclusion criteria

Studies will be excluded when: (1) the type of research is animal experiments, short surveys, and letters; (2) the female has no potential reproduction before menarche or after menopause; (3) only suspected cases, but not yet confirmed; (4) there are factors that could affect female fertility, such as serious endocrine diseases or overexposure to certain physical and chemical elements.

Information sources and search strategy

FYL and QZ will search the following databases: Web of Science, PubMed, EMBASE, Cochrane Library, Ovid, EBSCO, WHO COVID-19 database, Chinese Biomical Databases (CBM),China National Knowledge Internet (CNKI), Chinese Scientific and Technological Journal Database (VIP), and WangFang database. To maximise the search for relevant articles, the reference lists of selected studies and relevant reviews will be searched to identify additional papers not indexed in the databases searched. A systematic search strategy will be employed to identify articles from November 2019 to 2021/06/30. No language restriction will be applied. We will translate non-English articles and conduct update searches before manuscript submission to represent more target populations. The search term will combine medical subject headings (MeSH) with free text to search for concepts such as ‘COVID-19’ and ‘fertility’ and ‘female’. 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. The search strategies will be adapted to other databases as appropriate and then be checked by another investigator.

Study selection

Citations identified from the database searches will be imported into EndNote X9.1 software, and duplicate records will be removed by QY. After removing duplicates, QY and LXQ will independently screen titles and abstracts for this first level of filtering in duplicate. Potentially eligible full-text articles passing the first level of filtering will be independently screened. The studies will be cross-checked according to the pre-determined inclusion and exclusion criteria to further determine whether to include or not. The included and excluded studies will be examined by FYL and QZ to verify the reasons for each decision. We will contact the corresponding author for additional information when a study mentions outcomes of interest

without providing estimates. If discrepancies arise, we can reach a consensus by discussing or seek an adjudication from a third reviewer.

Data extraction

Two independent researchers (FYL and TW) will use a standardised Excel spreadsheet to extract data from the included studies independently. The outcome measures will be extracted as follows:

study details: title, primary author information, year of publication, journal, study design, country/region, fund source, sample size, age, period of study, duration of follow-up.

population characteristics: mean baseline age, body weight, height, mean baseline BMI, race, associated comorbidities.

exposure: diagnostic criteria for COVID-19 as an exposure, number of exposed subjects, duration of disease, details of COVID-19 severity, treatment characteristics.

Comparators: definition of unexposed subjects, number of comparators.

Outcomes:

The primary outcome is the proportion of females with decreased fertility, the association between COVID-19 and female fertility, or any risk estimate between COVID-19 and female fertility; since ACE2 is most widely expressed in the ovaries, particular attention should be paid to the decreased ovarian reserve function (mean AMH decline, elevation of basal FSH or LH, a disorder of the FSH/LH ratio). The secondary outcomes are uterine receptivity (endometrial thickness, endometrial morphology, subendometrial blood flow, uterine spiral artery blood flow), oviducts status, menstrual status. If there is missing information or ambiguous information, we will consider contacting the corresponding author by e-mail. The accuracy and consistency of all inputs will be cross-checked by two reviewers. Any disagreement will be settled by a third reviewer.

Quality and bias assessment

The included studies' methodological quality will be undertaken independently by two reviewers (TW and XYL) using appropriate tools. We will use the Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort and case–control studies[30]. The NOS includes 8 items grouped into three domains: Selection of study population, comparability of study groups, and exposure (case-control studies) / outcome (cohort studies).

Each study will be assigned a score of 0-9. NOS scores greater than 6 are relatively high quality, 5 to 6 are medium quality, and less than 5 are low quality. The Agency for Healthcare Research and Quality (AHRQ) methodology checklist will be applied to evaluate the quality of cross-sectional studies. Using the AHRQ checklist, each study will be judged on 11 items. The quality evaluation is as follows: high quality=8-11; moderate quality=4-7; poor quallity=0-3. 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[31].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. A summary risk of bias table in individual studies will be produced, with a short table to prove each of the judgments in the appendix. We will assess the quality of evidence and the strength of recommendations using the grading of recommendations assessment, development, and evaluation (GRADE) framework[32]. Possible discrepancies regarding bias appraisal will be solved by consensus or consulting a third reviewer.

Statistical analysis

XYL and TW will perform statistical analyses using RevMan 5.3. All statistical tests will be 2-tailed, and a P value of < 0.05 will be considered statistically significant.

Assessment of heterogeneity Heterogeneity will be tested for the results of multiple studies before merging the statistics. We will evaluate heterogeneity using the I^2 index. If the I^2 value < 50%, a non-substantial level of heterogeneity will be considered, and a fixed effect model will be applied to the meta-analysis. A random effects model will be used when I^2 value $> 50\%$ indicates substantial heterogeneity. We will investigate sources of heterogeneity by using meta-regression analysis and subgroup analysis when substantial heterogeneity is detected.

Data synthesis and analysis We will synthesize our results both narratively and quantitatively. Non-quantitative outcomes, such as study characteristics (author, year, study design, country/region, sample size, etc.), will be reported descriptively. If considerable heterogeneity can not be reduced by some methods or the source of heterogeneity cannot be explored using subgroup analysis or regression analysis, we will also conduct a systematic review with descriptive analysis. If there are sufficient studies, we will consider

combining outcome data and performing a meta-analysis where appropriate to summarise the evidence for the association between COVID-19 and female fertility.

Publication bias

Publication bias will be investigated using funnel plots, and the Egger's regression test will be applied to statistics when the funnel plots show asymmetry and there are 5 or more studies available[33].

Subgroup and sensitivity analyses

Pre-planned subgroup analyses will be conducted to explore statistical heterogeneity If sufficient data is collected: (1) subgroups based on age (female patients aged 13–35 years and female patient aged 35–49 years); (2) the time since fertility decline after COVID-19 infection; to this purpose, three subgroups will be identified: early (≤30 days); middle (<180 days); late (≥1 year); (3) Types of fertility decline: ovarian reserve function, uterine receptivity, oviducts status, menstrual status; (4) comorbidities; (5) COVID-19 stage (mild COVID-19 disease and severe COVID-19 disease). We will remove the included studies from the pooled analyses one by one and perform a sensitivity analysis to assess the robustness of the summary estimate.

Patient and Public Involvement

No patient involved.

Ethics and dissemination

Ethical approval is not required for this study, as it is a systematic review. The results will be disseminated by publication of the manuscript in a peer-reviewed journal and national and international presentations.

SUMMARY

Given the overwhelming magnitude of the COVID-19 and its worldwide prevalence, It has been a significant public health issue. Direct and indirect evidence suggests that COVID-19 could impair female fertility, and attention has grown around fertility issues in these patients. Female fertility is broadly defined as their reproductive capacity and potential. However, there is no review to explore the association between COVID-19 and female fertility comprehensively. Therefore, we will conduct a systematic review and meta-analysis to present the overall view of the current literature and further improve research regarding their relationship as the literature has been updated. By pooling the available evidence on the link of female

fertility with COVID-19, promoting fertility preservation in these patients is of high clinical and public health significance.

Sars-cov-2 may invade target cells by binding to ACE2, thereby affecting female fertility. ACE2, which is widely expressed in ovaries, uterus, vagina, and placenta, regulates the levels of angiotensin II (Ang II) and Ang-(1-7) to exert its physiological functions 8. ACE2, Ang II, and Ang-(1-7) could regulate follicular development and ovulation, regulate corpus luteum angiogenesis and degeneration, and affect endometrial tissue growth. Female fertility generally describes any form of ovarian-reserve function, uterine conditions, oviducts status, and menstrual status 8. Ovarian reserve is a key determinant of female fertility. Diminished ovarian reserve could affect fecundity by reducing egg quality[34]. In addition, ACE2 is highly expressed in the ovaries. Therefore, the ovarian reserve function should be the primary observation indicator for the impact of COVID-19 on female fertility. Routinely performed markers of ovarian reserve include a basal FSH or LH concentration, basal estradiol(E2), anti-Müllerian hormone (AMH), and assessment of antral follicle count (AFC)[35,36]. We will use endometrial receptivity, fallopian tube status, and menstrual conditions as secondary indicators. Furthermore, subgroup analyses and sensitivity analyses will be conducted to explore heterogeneity, such as age, follow-up time, the type of fertility decline, comorbidities, and severity of illness. It is generally accepted that fertility starts at (approximately) 13 years of age and is infertile at 49[37]. With aging, the female fertility naturally declines. The decline in fertility in women aged 30-35 is slow and steady; however, the decline accelerates after the age of 35 due to decreases in the ovarian reserve and oocyte quality[38]. The subgroup analysis will assess the impact of COVID-19 on the fertility of women aged <35 years and >35 years.

There are few large randomized studies in the literature on the impact of COVID-19 on female fertility. The majority of the relevant studies may come from cohort studies, cross-sectional studies, and case-control studies), and self-controlled case series designs. Nevertheless, we will conduct a systematic review and meta-analysis based on the existing evidence and constitute an update of literature to explore the immediate, medium, and long-term effects of COVID-19 on female fertility. It is of great significance to plan and take action to protect female fertility when there is a negative impact on fertility.

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Abbreviations

COVID-19 = coronavirus disease 2019, ACE2 = , SARS-CoV-2 = severe acute respiratory syndrome -CoV . Coronavirus 2 , WHO = World Health Organization, CBM = Chinese Biomedical Databases, CNKI = China National Knowledge Internet, VIP = Chinese Scientific and Technological Journal Database, 2019-nCoV = 2019 Novel Coronavirus, PRISMA-P = Preferred Reporting Items for Systematic Reviews and

Meta-Analyses Protocol, MOOSE = meta-analysis of Observational Studies in Epidemiology, BAL = bronchoalveolar lavage, AMH = Anti-Müllerian hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone,E2 = estradiol, AFC = antral follicle count, BMI = Body Mass Index, NOS = Newcastle-Ottawa Quality Assessment Scale, AHRQ = Agency for Healthcare Research and Quality, ROB = Risk of Bias, GRADE = grading of recommendations assessment, development, and evaluation, Ang = angiotensin.

Contributors

The study concept was developed by FYL. The manuscript of the protocol was drafted by FYL and critically revised by QZ and XYL. HL developed and provided feedback for all sections of the review protocol and approved the final manuscript. The search strategy was developed by FYL and QZ. Study selection will be performed by QY and LXQ. Data extraction and quality assessment will be performed by FYL and TW, with QCL as a third party in case of disagreements. All authors have approved the final version of the manuscript.

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Competing interests

None declared.

Patient consent and Ethics approval

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Supplementary information

Table S1:Searching strategy in PubMed

Theme	Number	Searching terms
exposures	#1	*"COVID-19" [Supplementary Concept,Mesh]*
	#2	*"2019 novel coronavirus disease"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "covid 19 pandemic"[Title/Abstract] OR "sars cov 2 infection"[Title/Abstract] OR "covid 19 virus disease"[Title/Abstract] OR "2019 novel coronavirus infection"[Title/Abstract] OR "2019 ncov infection"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "coronavirus disease 19"[Title/Abstract] OR "2019 ncov disease"[Title/Abstract] OR "covid 19 virus infection"[Title/Abstract]*
outcomes	#3	*"fertility"[MeSH Terms]*
	#4	*"Fecundability"[Title/Abstract] OR "Fecundity"[Title/Abstract] OR "differential fertility"[Title/Abstract] OR "fertility differential"[Title/Abstract] OR "fertility determinants"[Title/Abstract] OR "determinant fertility"[Title/Abstract] OR "determinants fertility"[Title/Abstract] OR "fertility determinant"[Title/Abstract] OR "Subfecundity"[Title/Abstract] OR "fertility preferences"[Title/Abstract] OR "fertility preference"[Title/Abstract] OR "preference fertility"[Title/Abstract] OR "preferences fertility"[Title/Abstract] OR "fertility below replacement"[Title/Abstract] OR "below replacement fertility"[Title/Abstract] OR ("Martal"[All Fields] AND "Fertility"[Title/Abstract]) OR "fertility marital"[Title/Abstract] OR "natural fertility"[Title/Abstract] OR "fertility natural"[Title/Abstract] OR "world fertility survey"[Title/Abstract] OR (("fertiles"[All Fields] OR "Fertility"[MeSH Terms] OR "Fertility"[All Fields] OR "fertile"[All Fields] OR "fertilities"[All Fields]) AND "survey world"[Title/Abstract]) OR (("fertiles"[All Fields] OR "Fertility"[MeSH Terms] OR "Fertility"[All Fields] OR "fertile"[All Fields] OR "fertilities"[All Fields]) AND "surveys world"[Title/Abstract]) OR (("survey s"[All Fields] OR "surveyed"[All Fields] OR "surveying"[All Fields] OR "surveys and questionnaires"[MeSH Terms] OR ("Surveys"[All Fields] AND "questionnaires"[All Fields]) OR "surveys and questionnaires"[All Fields] OR "Survey"[All Fields] OR "Surveys"[All Fields]) AND "world fertility"[Title/Abstract]) OR*

		(("survey s"[All Fields] OR "surveyed"[All Fields] OR "surveying"[All Fields] OR "surveys and questionnaires"[MeSH Terms] OR ("Surveys"[All Fields] AND "questionnaires"[All Fields]) OR "surveys and questionnaires"[All Fields] OR "Survey"[All Fields] OR "Surveys"[All Fields]) AND "world fertility"[Title/Abstract]) OR "world fertility surveys"[Title/Abstract] OR "fertility incentives"[Title/Abstract] OR "fertility incentive"[Title/Abstract]
population	***#5***	*"female"[MeSH Terms]*
	#6	*"Females"[Title/Abstract] OR "Female"[Title/Abstract]*
Search	*#7*	*(#1 OR #2)* ***AND*** *(#3 OR #4)****AND****(#5 OR #6)*

Table S2: Data extraction tool for the characteristics of the studies.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
title	primary author	year of publication	journal	study design	country/region	fund source	sample size	age	duration of follow-up	age	weight	height	race	comorbidities	diagnostic criteria for COVID-19	number of exposed subjects	duration of disease	severity	treatment	risk estimate between COVID-19 and female fertility	association between COVID-19 and female fertility	ovarian reserve function declines	uterine receptivity	oviducts status	menstrual status

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item		
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	✓	P1(Title Page)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	✓	P2
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓	P1(Title Page)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓	P14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-	-
Support:				
Sources	5a	Indicate sources of financial or other support for the review	✓	P14
Sponsor	5b	Provide name for the review funder and/or sponsor	✓	P14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-	-
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	✓	P3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓	P4
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	✓	P4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	✓	P6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	supplementary appendix 1
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	P6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	✓	P6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓	P6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	✓	P7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	P7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓	P7-8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	✓	P8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	✓	P8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	✓	P8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓	P8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	✓	P8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	✓	P7-8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology, Reproductive medicine
Keywords:	COVID-19, GYNAECOLOGY, Epidemiology < INFECTIOUS DISEASES

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The impact of COVID-19 on female fertility: a systematic review and meta-analysis protocol

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Word Count: 3032 words

ABSTRACT

Introduction

The increased social and economic burden caused by the novel COVID-19 outbreak is gradually becoming a worrisome issue for the health sector. The novel coronavirus invades the target cell by binding to ACE2, which is widely expressed in the ovaries, uterus, vagina, and placenta. Significantly, the SARS-CoV-2 is said to interrupt female fertility through regulating ACE2. Thus, 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.

Methods and analysis

We will systematically search cohort studies, cross-sectional studies, case-control studies, and self-controlled case series designs in the following databases: Web of Science, PubMed, EMBASE, Cochrane Library, Ovid, EBSCO, WHO COVID-19 database, CBM, CNKI, VIP, and WanFang database. Medical subject headings and free text terms for "COVID-19" AND "female" AND "fertility" will be performed. Eligibility criteria are as follows: population (female patients aged 13-49 years); exposure (infection with SARS-CoV-2); comparison (population without SARS-CoV-2 infections or latent SARS-CoV-2 infections); and outcome (female fertility, such as ovarian reserve function, uterine receptivity, oviducts status, and menstruation status). Article screening and data extraction will be undertaken independently by two reviewers, and discrepancies will be resolved through discussion. We will use the I^2 statistics to assess the heterogeneity and perform a meta-analysis when sufficiently homogeneous studies are provided. Otherwise, a narrative synthesis will be performed. We will explore the potential sources of heterogeneity using subgroup analyses and meta-regression.

Ethics and dissemination

Formal ethical approval is not required, and findings will be published in a peer-reviewed journal.

PROSPERO registration number

CRD42020189856

Keywords: novel coronavirus, COVID-19, female fertility, systematic review

Strengths and limitations of this study

The present systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines.

The present study has an established aim, stringent inclusion and exclusion criteria, and a precise quality evaluation and quantitative synthesis.

It will assess the evidence for differential impact of COVID-19 on reduced fertility risk in different population subgroups, for example, by different ages, the severity of disease through subgroup analysis.

Two reviewers will independently screen for eligibility, data extraction, with a third reviewer mediating when a disagreement arises, thus ensuring that reviewer bias is minimized.

The lack of uniformity in measures of fertility may yield significant heterogeneity.

INTRODUCTION

The national and global spread of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has made it one of the most severe public health threat. 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[1]. SARS-CoV-2 infection disrupts normal immune responses[2], leading to the local and systematic damage of tissues[3]. Local tissue damage primarily affects the lower respiratory tract and presents as pneumonia, including fever, cough, expectoration, and haemoptysis[4]. Extrapulmonary damage of COVID-19 includes acute kidney injury, hepatocellular injury, neurologic illnesses, myocardial dysfunction and arrhythmia, and gastrointestinal symptoms[5].

Besides, sperm are also susceptible to viral attack[6] and SARS-CoV-2 infection may most likely to cause male infertility[7]. SARS-CoV-2 appears to have shown adverse effects on the reproductive system. Some studies have shown that SARS-CoV-2 might affect female fertility and disturb female reproductive functions[8,9]. Given the scale of the COVID-19 pandemic, there appears to be a potential decline in fertility[10].

A study reported that many young adults have sexual and reproductive health problems due to COVID-19 pandemic and related containment measures[11]. 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[12]. An epidemiological study demonstrated that coronaviruses could have adverse effects on fetuses and infants, including preterm delivery, intrauterine growth restriction, spontaneous abortion, and even death[13]. Moreover, studies have documented the presence of SARS-COV-2 across the placenta even in pregnant patients with mild COVID-19 disease, potentially leading to fetal growth restriction and other pregnancy complications[14]. Accumulating evidence now suggests that 2019-nCoV/ACE2 may interfere with the female reproductive functions, leading to menstrual disorder, infertility, and fetal distress8.

Angiotensin-converting enzyme 2 (ACE2) is a receptor for SARS-CoV[15]. SARS-CoV-2, as a subgenus Sarbecovirus of the genus Betacoronavirus, shares a 76% amino acid sequence homology with SARS-CoV[16]. The protein expression profile of ACE2 is also considered to be the host receptor of SARS-COV-2[17]. Thus SARS-CoV-2 can invade target host cells by using the ACE2 as the primary receptor binding site[18-20] and regulate the expression of ACE2 in host cells8. ACE2 expression has been assessed in various human organs, such as respiratory tracts, heart, kidney, ovary, uterus, testis, vagina and placenta, and gastrointestinal system8,21. Notably, ACE2 is highly expressed in the ovaries[22]. Published reports suggest that ACE2 is expressed in stromal cells, granulosa cells, and oocytes in immature rat ovaries[23]. ACE2 regulates follicular development and ovulation, regulates luteal angiogenesis and degeneration, and affects the regular changes of endometrial tissue and embryo development8. Significantly, ACE2 plays a regulatory role in reproduction7. Considering these factors, SARS-CoV-2 may interrupt female fertility by attacking ovarian tissue and granulosa cells or damaging endometrial epithelial cells9. Basigin (BSG) is also one of the most crucial receptors for COVID-19 that mediates its entry to host cells[24]. BSG is expressed not only in the uterus but also in the stroma and granulosa cells of the ovary24,25. BSG may play a role during follicle development, corpus luteum formation, and embryo implantation[26]. Besides, COVID-19, impairing the immune system might alter the function of the hypothalamic-pituitary-gonadal axis2,27. Sex steroids are potent immune modulators, different progesterone (P) and androgen concentrations are likely to influence the immune response and inflammatory outcomes of COVID-1927. Notwithstanding, the magnitude of the association between COVID-19 and female fertility remains unclear. With the overwhelming magnitude of

COVID-19 and its worldwide prevalence, the associated health burden, and social and economic costs, might be a massive loss around the world.

To our knowledge, there is no systematic review of the potential role of COVID-19 on female fertility. One of the most critical questions that remain to be answered is if or how COVID-19 affects female fertility. Hence, we decided to carry out a systematic review and meta-analysis to improve our understanding of the relationship between COVID-19 and female fertility and facilitate the development of prevention strategies at individual and population levels.

METHODS AND ANALYSIS

The study will be reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) statement[28] and meta-analysis of Observational Studies in Epidemiology (MOOSE)[29]. This review's protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number (CRD42020189856).

Inclusion/exclusion criteria for study selection

Study designs and characteristics

We will include observational studies (cohort studies, cross-sectional studies, and case-control studies), and self-controlled case series designs. These studies should also report the impact of COVID-19 on female fertility, including variations in menstrual situation, gonad function, ovarian reserve function, tubal patency, and endometrial receptivity. It is not restricted by language, publication status, geography, or medical conditions.

Participants

Female patients in puberty and adulthood (13 years old ≤ age≦49 years old) with COVID-19; females were not excessively exposed to certain physical, biological, chemical, or environmental factors that affect female fertility,such as lead, cadmium, mercury, pesticides, benzene, toluene and ionizing radiation[30]; not have any gonadal injury that caused by high-dose alkylating agent chemotherapy and abdominal/pelvic radiotherapy[31]; and severe thyroid dysfunction and other diseases that affect female fertility will be excluded[32].

Exposure/Interest

The exposure factor of interest is infection with SARS-CoV-2, primarily diagnosed by RT-PCR with a nasal swab, tracheal aspirate, or bronchoalveolar lavage (BAL) specimens[33].

Comparators

The comparator group will be the population without SARS-CoV-2 infections or with latent SARS-CoV-2 infections.

Outcome measures

The primary outcome will be at least one of the following indicators of ovarian reserve function:(1) Anti-Müllerian hormone (AMH); (2) basal follicle-stimulating hormone (FSH), basal luteinizing hormone(LH), or the ratio of FSH/LH; (3) basal estradiol (E2); (4)serum inhibin-B; and (5) antral follicle count (AFC). Secondary outcomes, if any, will be considered: (1) uterine receptivity (endometrial thickness, endometrial morphology, subendometrial blood flow, uterine spiral artery blood flow); (2) oviducts status; (3) menstruation status; and (4) other female reproductive dysfunction diseases caused by COVID-19.

Exclusion criteria

Studies will be excluded when: (1) the type of research are animal experiments, short surveys, and letters; (2) the female has no potential reproduction before menarche or after menopause; (3) only suspected cases, but not yet confirmed; (4) factors that could affect female fertility, such as severe endocrine diseases or overexposure to certain physical and chemical elements.

Information sources and search strategy

FYL and QZ will search the following databases: Web of Science, PubMed, EMBASE, Cochrane Library, Ovid, EBSCO, WHO COVID-19 database, Chinese Biomedical Databases (CBM), China National Knowledge Internet (CNKI), Chinese Scientific and Technological Journal Database (VIP), and WanFang database. The reference lists of selected studies and relevant reviews will be searched to search for relevant articles and identify additional papers not indexed in the databases searched. A systematic search strategy will be employed to identify articles from November 2019 to 2021/06/30, with no language restriction. We will translate non-English articles and conduct update searches before manuscript submission to represent more target populations. The search term will combine medical subject headings (MeSH) with free text to search for concepts such as ‘COVID-19’ and ‘fertility’ and ‘female’. A detailed search strategy is described

in Table S1 of Supplementary Appendix 1, using PubMed as an example. The search strategies will be adapted to other databases as appropriate and then be checked by another investigator.

Study selection

Citations identified from the database searches will be imported into EndNote X9.1 software, and QY will remove duplicate records. After removing duplicates, QY and LXQ will independently screen titles and abstracts for this first level of filtering duplicates. Potentially eligible full-text articles passing the first level of filtering will be independently screened. The studies will be cross-checked according to the pre-determined inclusion and exclusion criteria to determine their final inclusion. FYL and QZ will examine the included and excluded studies, and verify the reasons for each decision. We will contact the corresponding author for additional information when a study mentions impressive outcomes without providing estimates. If discrepancies arise, we can reach a consensus by discussing or seeking adjudication from a third reviewer.

Data extraction

Two independent researchers (FYL and TW) will use a standardized Excel spreadsheet to independently extract data from the included studies. The outcome measures will be extracted as follows:

Study details: Title, primary author information, year of publication, journal, study design, country/region, fund source, sample size, age, the period of study, and duration of follow-up.

Population characteristics: Mean baseline age, body weight, height, mean baseline BMI, race, and associated comorbidities.

Exposure: Diagnostic criteria for COVID-19 as an exposure, number of exposed subjects, duration of disease, details of COVID-19 severity, and treatment characteristics.

Comparators: Definition of unexposed subjects, and the number of comparators.

Outcomes:

The primary outcomes are the proportion of females with decreased fertility, the association between COVID-19 and female fertility, or any risk estimate between COVID-19 and female fertility; since ACE2 is most widely expressed in the ovaries, particular attention should be paid to the decreased ovarian reserve function (mean AMH decline, the elevation of basal FSH or LH, a disorder of the FSH/LH ratio). The

secondary outcomes are uterine receptivity (endometrial thickness, endometrial morphology, subendometrial blood flow, and uterine spiral artery blood flow), oviducts status, and menstrual status.

Quality and bias assessment

The included studies' methodological quality will be undertaken independently by two reviewers (TW and XYL) using appropriate tools. We will use the Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort and case–control studies[34]. The NOS includes eight items grouped into three domains: selection of study population, comparability of study groups, and exposure (case-control studies) / outcome (cohort studies). Each study will be assigned a score of 0-9. NOS scores greater than 6 are relatively high quality, 5 to 6 are medium quality, and less than 5 are low quality. The Agency for Healthcare Research and Quality (AHRQ) methodology checklist will be applied to evaluate the cross-sectional studies' quality. Using the AHRQ checklist, each study will be judged on 11 items. The quality evaluation is as follows: high quality=8-11; moderate quality=4-7; poor quallity=0-3. A summary risk of bias table in individual studies will be produced, with a short table to prove each of the judgments in the appendix. We will assess the quality of evidence and the strength of recommendations using the grading of recommendations assessment, development, and evaluation (GRADE) framework[35]. Possible discrepancies regarding bias appraisal will be solved by consensus or consulting a third reviewer.

Statistical analysis

XYL and TW will perform statistical analyses using RevMan 5.3. All statistical tests will be 2-tailed, and a P value of < 0.05 will be considered statistically significant.

Assessment of heterogeneity: Heterogeneity will be tested for results reported by multiple studies before merging the statistics. We will evaluate heterogeneity using the I^2 index. If the I^2 value is $< 50\%$, a non-substantial level of heterogeneity will be considered, and a fixed effect model will be applied to the meta-analysis. A random effects model will be used when the I^2 value is $> 50\%$, indicating substantial heterogeneity. We will investigate sources of heterogeneity by using meta-regression analysis and subgroup analysis when substantial heterogeneity is detected.

Data synthesis and analysis: We will synthesize our results both narratively and quantitatively. Non-quantitative outcomes, such as study characteristics (author, year, study design, country/region, and

sample size), will be reported descriptively. If considerable heterogeneity can not be reduced by some methods or the source of heterogeneity cannot be explored using subgroup analysis or regression analysis, we will also conduct a systematic review with descriptive analysis. If there are sufficient studies, we will consider combining outcome data and performing a meta-analysis where appropriate to summarise the evidence for the association between COVID-19 and female fertility.

Publication bias

Publication bias will be investigated using funnel plots, and Egger's regression test will be applied to statistics when the funnel plots show asymmetry and there are five or more studies available[36].

Subgroup and sensitivity analyses

Pre-planned subgroup analyses will be conducted to explore statistical heterogeneity. If sufficient data is collected: (1) subgroups based on age (13–35 years and 35–49 years old); (2) the time since fertility decline after COVID-19 infection; to this purpose, three subgroups will be identified: early (≤30 days); middle (<180 days); late (≥1 year); (3) Types of fertility decline: ovarian reserve function, uterine receptivity, oviducts status, menstrual status; (4) comorbidities; and (5) COVID-19 stage (mild COVID-19 disease and severe COVID-19 disease). We will remove the included studies from the pooled analyses one by one and perform a sensitivity analysis to assess the robustness of the summary estimate.

Patient and Public Involvement

No patient involved.

Ethics and dissemination

Ethical approval is not required for this study, as it is a systematic review. The results will be disseminated by the publication of the manuscript in a peer-reviewed journal and national and international presentations.

SUMMARY

COVID-19 has been a significant public health issue, given its overwhelming magnitude and worldwide prevalence. Direct and indirect evidence suggests that COVID-19 could impair female fertility, which has gained much broader attention. Female fertility is broadly defined as their reproductive capacity and

potential. However, there are no comprehensive reviews to explore the association between COVID-19 and female fertility comprehensively. Hence, we will conduct a systematic review and meta-analysis to improve our understanding of the relationship between COVID-19 and female fertility and facilitate prevention strategies at individual and population levels. The study will also establish the current overall view of COVID-19 and female fertility, given the literature has been updated. By pooling the available evidence on the link of female fertility with COVID-19, promoting fertility preservation in these patients is of high clinical and public health significance.

SARS-CoV-2 may invade target cells by binding to ACE2, thereby affecting female fertility. ACE2, which is widely expressed in ovaries, uterus, vagina, and placenta, regulates the levels of angiotensin II (Ang II) and Ang-(1-7) to exert its physiological functions [8]. ACE2, Ang II, and Ang-(1-7) could regulate follicular development and ovulation, regulate corpus luteum angiogenesis and degeneration, and affect endometrial tissue growth. Ovarian reserve is a key determinant of female fertility. Diminished ovarian reserve could affect fecundity by reducing egg quality[37]. Besides, ACE2 is highly expressed in the ovaries. Therefore, the ovarian reserve function should be the primary observation indicator for the impact of COVID-19 on female fertility. Routinely performed markers of the ovarian reserve include a basal FSH or LH concentration, basal estradiol(E2), anti-Müllerian hormone (AMH), and assessment of antral follicle count (AFC)[38,39]. We will use endometrial receptivity, fallopian tube status, and menstrual conditions as secondary indicators. Furthermore, subgroup analyses and sensitivity analyses will be conducted to explore heterogeneity, such as age, follow-up time, the type of fertility decline, comorbidities, and severity of illness. It is generally accepted that fertility starts at (approximately) 13 years of age, and females begin infertile at age 49[40]. With aging, the female fertility naturally declines. The decline in fertility in women aged 30-35 is slow and steady; however, the decline accelerates after the age of 35 due to decreases in the ovarian reserve and oocyte quality[41]. The subgroup analysis will assess the impact of COVID-19 on the fertility of women aged <35 years and >35 years.

The majority of the relevant studies may come from cohort studies, cross-sectional studies, case-control studies, and self-controlled case series designs. Nevertheless, we will conduct a systematic review and meta-analysis based on the existing evidence to explore the immediate, medium, and long-term effects of COVID-19 on female fertility. It is of great significance to plan and take action to protect female fertility when there is a negative impact on fertility.

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Abbreviations

COVID-19 = coronavirus disease 2019, ACE2 = angiotensin-converting enzyme 2, SARS-CoV-2 = severe acute respiratory syndrome Coronavirus 2, BSG = Basigin, WHO = World Health Organization, CBM = Chinese Biomedical Databases, CNKI = China National Knowledge Internet, VIP = Chinese Scientific and Technological Journal Database, 2019-nCoV =2019 Novel Coronavirus, PRISMA-P = Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol, MOOSE = meta-analysis of Observational Studies in Epidemiology, BAL = bronchoalveolar lavage, AMH = Anti-Müllerian hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone,E2 = estradiol, AFC = antral follicle count, BMI = Body Mass Index, NOS = Newcastle-Ottawa Quality Assessment Scale, AHRQ = Agency for Healthcare Research and Quality, ROB = Risk of Bias, GRADE = grading of recommendations assessment, development, and evaluation, Ang = angiotensin.

Contributors

The study concept was developed by FYL. The manuscript of the protocol was drafted by FYL and critically revised by QZ and XYL. HL developed and provided feedback for all sections of the review protocol and approved the final manuscript. The search strategy was developed by FYL and QZ. Study selection will be performed by QY and LXQ. Data extraction and quality assessment will be performed by FYL and TW, with QCL as a third party in case of disagreements. All authors have approved the final version of the manuscript.

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Competing interests

None declared.

Patient consent and Ethics approval

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Supplementary information

Table S1:Searching strategy in PubMed

Theme	Number	Searching terms
exposures	***#1***	*"COVID-19" [Supplementary Concept,Mesh]*
	#2	*"2019 novel coronavirus disease"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "covid 19 pandemic"[Title/Abstract] OR "sars cov 2 infection"[Title/Abstract] OR "covid 19 virus disease"[Title/Abstract] OR "2019 novel coronavirus infection"[Title/Abstract] OR "2019 ncov infection"[Title/Abstract] OR "coronavirus disease 2019"[Title/Abstract] OR "coronavirus disease 19"[Title/Abstract] OR "2019 ncov disease"[Title/Abstract] OR "covid 19 virus infection"[Title/Abstract]*
outcomes	***#3***	*"fertility"[MeSH Terms]*
	#4	*"Fecundability"[Title/Abstract] OR "Fecundity"[Title/Abstract] OR "differential fertility"[Title/Abstract] OR "fertility differential"[Title/Abstract] OR "fertility determinants"[Title/Abstract] OR "determinant fertility"[Title/Abstract] OR "determinants fertility"[Title/Abstract] OR "fertility determinant"[Title/Abstract] OR "Subfecundity"[Title/Abstract] OR "fertility preferences"[Title/Abstract] OR "fertility preference"[Title/Abstract] OR "preference fertility"[Title/Abstract] OR "preferences fertility"[Title/Abstract] OR "fertility below replacement"[Title/Abstract] OR "below replacement fertility"[Title/Abstract] OR ("Martal"[All Fields] AND "Fertility"[Title/Abstract]) OR "fertility marital"[Title/Abstract] OR "natural fertility"[Title/Abstract] OR "fertility natural"[Title/Abstract] OR "world fertility survey"[Title/Abstract] OR (("fertiles"[All Fields] OR "Fertility"[MeSH Terms] OR "Fertility"[All Fields] OR "fertile"[All Fields] OR "fertilities"[All Fields]) AND "survey world"[Title/Abstract]) OR (("fertiles"[All Fields] OR "Fertility"[MeSH Terms] OR "Fertility"[All Fields] OR "fertile"[All Fields] OR "fertilities"[All Fields]) AND "surveys world"[Title/Abstract]) OR (("survey s"[All Fields] OR "surveyed"[All Fields] OR "surveying"[All Fields] OR "surveys and questionnaires"[MeSH Terms] OR ("Surveys"[All Fields] AND "questionnaires"[All Fields]) OR "surveys and questionnaires"[All Fields] OR "Survey"[All Fields] OR "Surveys"[All Fields]) AND "world fertility"[Title/Abstract]) OR (("survey s"[All Fields] OR "surveyed"[All Fields] OR "surveying"[All Fields] OR "surveys*

		and questionnaires"[MeSH Terms] OR ("Surveys"[All Fields] AND "questionnaires"[All Fields]) OR "surveys and questionnaires"[All Fields] OR "Survey"[All Fields] OR "Surveys"[All Fields]) AND "world fertility"[Title/Abstract]) OR "world fertility surveys"[Title/Abstract] OR "fertility incentives"[Title/Abstract] OR "fertility incentive"[Title/Abstract]
population	***#5***	*"female"[MeSH Terms]*
	#6	*"Females"[Title/Abstract] OR "Female"[Title/Abstract]*
Search	*#7*	*(#1 OR #2)* ***AND*** *(#3 OR #4)****AND****(#5 OR #6)*

Table S2: Data extraction tool for the characteristics of the studies.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z
title	primary author	year of publication	journal	study design	country/region	fund source	sample size	age	duration of follow-up	age	weight	height	race	comorbidities	diagnostic criteria for COVID-19	number of exposed subjects	duration of disease	severity	treatment	risk estimate between COVID-19 and female fertility	association between COVID-19 and female fertility	ovarian reserve function declines	uterine receptivity	oviducts status	menstrual status

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item		
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	✓	P1(Title Page)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	✓	P2
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓	P1(Title Page)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓	P14/15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-	-
Support:				
Sources	5a	Indicate sources of financial or other support for the review	✓	P15
Sponsor	5b	Provide name for the review funder and/or sponsor	✓	P15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-	-
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	✓	P3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓	P4
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	✓	P5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	✓	P6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	supplementary appendix 1
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	P6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	✓	P6-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓	P7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	✓	P7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	P7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓	P7-8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	✓	P8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	✓	P8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	✓	P8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	✓	P8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	✓	P8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	✓	P8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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