Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) *2022 23(8):655-665*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Research Article

https://doi.org/10.1631/jzus.B2200154

Impact of COVID-19 pandemic on the pregnancy outcomes of women undergoing assisted reproductive techniques (ARTs): a systematic review and meta-analysis

Weihuan HU[1,2*], Yuhang ZHU[1*], Yan WU[1], Fangfang WANG[1], Fan QU[1✉]

[1]*Women's Hospital, School of Medicine, Zhejiang University, Hangzhou 310006, China*
[2]*The Second Hospital of Dalian Medical University, Dalian Medical University, Dalian 116000, China*

Abstract: The global outbreak of the coronavirus disease 2019 (COVID-19) led to the suspension of most treatments with assisted reproductive technique (ART). However, with the recent successful control of the pandemic in China, there is an urgent public need to resume full reproductive care. To determine whether the COVID-19 pandemic had any adverse effects on female fertility and the pregnancy outcomes of women undergoing ART, a systematic review and meta-analysis was conducted using the electronic Chinese and English databases. Dichotomous outcomes were summarized as prevalence, and odds ratios (ORs) and continuous outcomes as standardized mean difference (SMD) with 95% confidence interval (CI). The risk of bias and subgroup analyses were assessed using Stata/SE 15.1 and R 4.1.2. The results showed that compared with women treated by ART in the pre-COVID-19 time frame, women undergoing ART after the COVID-19 pandemic exhibited no significant difference in the clinical pregnancy rate (OR 1.07, 95% CI 0.97 to 1.19; I^2=0.0%), miscarriage rate (OR 0.95, 95% CI 0.79 to 1.14; I^2=38.4%), embryo cryopreservation rate (OR 2.90, 95% CI 0.17 to 48.13; I^2=85.4%), and oocyte cryopreservation rate (OR 0.30, 95% CI 0.03 to 3.65; I^2=81.6%). This review provided additional evidence for gynecologists to guide the management of women undergoing ART treatment during the COVID-19 pandemic timeframe.

Key words: Systematic review; Coronavirus disease 2019 (COVID-19); Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Assisted reproductive technique (ART); Pregnancy outcome; Meta-analysis

1 Introduction

According to the World Health Organization (WHO), the new coronavirus disease 2019 (COVID-19) constitutes a public health emergency of international concern (PHEIC) (WHO, 2020b). As of 4:39 p.m. CET, 25 February 2022, there had been 430 257 564 confirmed cases of COVID-19 worldwide, including 5 922 047 deaths reported to WHO. As of 20 February 2022, a total of 10 407 359 583 vaccine doses had been administered (WHO, 2022). Despite of full vaccination, people are still possible to be infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and become SARS-CoV-2's carrier (UK Health Security Agency, 2022). Due to the special physiological changes and immune responses during and after the pregnancy period, pregnant women are considered as a high-risk group (Rangchaikul and Venketaraman, 2021; UK Health Security Agency, 2022), and the mental health of pregnant women during the COVID-19 pandemic has also gradually received attention (Huang et al., 2020).

Previous studies have concluded the clinical manifestations, risk factors, and maternal and perinatal outcomes of COVID-19 in pregnancy (Allotey et al., 2020). Compared with non-infected women, infected women in pregnancy are more likely to have preterm birth, and women with pre-existing comorbidities, high maternal age, and high body mass index (BMI) are more prone to develop severe COVID-19 (Allotey et al., 2020; Qiao, 2020). However, the evidence on the effect of COVID-19 pandemic on the pregnancy outcomes of women undergoing assisted reproductive techniques (ARTs) has not been systematically reviewed.

✉ Fan QU, syqufan@zju.edu.cn
* The two authors contributed equally to this work
Fan QU, https://orcid.org/0000-0003-1851-1514

Received Mar. 23, 2022; Revision accepted May 31, 2022; Crosschecked July 7, 2022

Therefore, we systematically evaluated the relevant literature to identify whether the COVID-19 infection and the changes caused by the COVID-19 pandemic, such as quarantine measures and changes in the frequency of medical visits, affect the laboratory and clinical outcomes of women undergoing ART.

2 Methods

Our systematic review was based on a prespecified protocol, which has been published on the PROSPERO website (https://www.crd.york.ac.uk/PROSPERO) under the final registration number PROSPERO CRD42022312812. The findings of our review on pregnancy outcomes in women treated with ART after the COVID-19 pandemic are in line with the preferred reporting items for systematic review and meta-analyses (PRISMA) recommendations (Table S1).

2.1 Search strategy and selection of papers

A comprehensive search strategy was used to identify articles in the following English and Chinese language databases: WHO COVID-19 Database, PubMed, Embase, the Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases from 1 December 2019 to 20 February 2022. The search strategy was provided in Method S1. In addition, to identify potential studies, we manually screened the reference lists of the included articles.

Two reviewers (WH and YW) independently assessed each study from the databases in two screening phases, namely, initial screening based on the title and abstract, followed by full-text screening of the eligible articles for final inclusion. Any discrepancies were resolved through discussion with a third investigator (FQ).

Studies were included in the second screening phase if they met all of the following inclusion criteria: (1) pregnant women who underwent ART after the COVID-19 pandemic or pregnant women who were both infected by SARS-CoV-2 and undergoing ART; (2) original full papers presenting unique data; (3) primary case reports, case series, observational studies, or randomized-controlled trials. In case of doubt, a full-text analysis was performed. We excluded studies if they met any of the following exclusion criteria: (1) duplicates; (2) not a primary study; (3) not related to the COVID-19 pandemic or ART; (4) the ART cycles were all performed before the COVID-19 pandemic; (5) no outcome of interest.

We defined women with confirmed COVID-19 if they had positive laboratory test results of SARS-CoV-2 infection irrespective of the clinical signs and symptoms, such as COVID rapid detection test (RDT) and serum SARS-CoV-2 antibody (immunoglobulin G (IgG) and/or IgM) test (WHO, 2020a). The ART included all available techniques like ovarian stimulation, in vitro fertilization (IVF), fresh/frozen embryo transfer (FET), and intracytoplasmic sperm injection (ICSI). The comparative cohort studies compared the clinical outcomes (e.g., clinical pregnancy rate and miscarriage rate) and laboratory outcomes (e.g., embryo cryopreservation rate and oocyte cryopreservation rate) between pregnant women with and without SARS-CoV-2 infection or before and after the COVID-19 pandemic. The cohort studies were those in which patients were sampled on the basis of exposure and followed up over time, including both prospective and retrospective cohort studies. Finally, the outcomes were accessed, with no requirement to have a comparison group (Dekkers et al., 2012).

2.2 Study characteristics and data extraction

Two reviewers (WH and YW) independently extracted the bibliographic data from each eligible study, including the characteristics of the study design and the relevant outcomes (e.g., clinical outcomes and laboratory outcomes). If there was a disagreement, two reviewers would discuss it and arrive at a consensus with a third investigator (FQ). We considered each analysis of a specific outcome with different ART types (such as FET and IVF) as a separate comparison. Therefore, multiple comparisons were included from a single study.

The dichotomous data were collected as the number of events or total number of events, and the continuous data were collected as mean and standard deviation (SD). We extracted the number of ART cycles instead of the number of women, since this was more in line with the clinical practice and could be easily calculated. When the data were

reported as median and interquartile range (IQR), the authors were contacted for raw data. The studies with missing data, unavailable author to contact details, or no response received from the authors or remainders within six weeks, were excluded from the analyses.

2.3 Bias risk and methodological quality assessment

Two reviewers (WH and YW) independently accessed the methodological quality of included comparative cohort studies using the Newcastle-Ottawa Scale (NOS) from three board study aspects: the selection of study groups, the comparability of study groups, and the outcome ascertainment of either the exposure or interested outcomes (Wells et al., 2000). These three aspects were assessed and graded by answering nine questions: four questions pertaining the study selection, two questions for the study comparability, and another three questions regarding the outcome ascertainment. The full score for each question was 1, the answer of "Yes" scored 1, and answers of "?" and "No" scored 0. In this analysis, the studies with NOS scores of 1–3, 4–6, and 7–9 were defined as of low, median, and high quality, respectively (de Gruijter et al., 2021).

Any discrepancies were resolved among the reviewers to reach a consensus. If the evaluation team could not reach an agreement on the quality of included studies, a more conservative judgement was selected (e.g., if one reviewer made a judgement of "low quality," while another reviewer made a judgement of "median quality," the latter would be used).

2.4 Data synthesis and statistical analysis

Meta-analyses were performed using Stata 15.1, and the figure of risk of bias was obtained using R 4.1.2. If the difference of the studies were negligible, the comparative dichotomous data were combined and summarized as odds ratio (OR) with 95% confidence interval (CI), and the continuous data were combined as mean and SD. Heterogeneity was assessed as *I*-square (I^2), and we defined the significance level of the meta-analyses as $P<0.05$ or $I^2>50\%$. When significant heterogeneity was observed, we pooled the dichotomous data as proportions with 95% CI using the DerSimonian and Laird method for meta-analysis of random effects, if not, Mantel-Haenszel fixed-effects model was used.

For subgroup analyses, at least two studies per subgroup were needed. If a meta-analysis was not possible because of limited data, a descriptive summary was conducted. The assessed subgroup variables included IVF, ICSI, FET, and so on.

2.5 Sensitivity analyses

In order to eliminate the imbalance of groups, sensitivity analysis was conducted using the different ART type groups (fresh cycles, embryo warming, and oocyte warming) instead of the summary group.

3 Results

3.1 Study selection and characteristics

The selection process was provided in the flowchart (Fig. 1). A total of 342 studies were identified from the seven databases using the comprehensive electronic database search strategies. After removing 42 duplicate studies and performing the two phases of selection, seven studies of 33 883 ART cycles were finally included in this review. Five of them compared the women undergoing ARTs before and after the COVID-19 pandemic without infection with SARS-CoV-2 (Aharon et al., 2021; Chen et al., 2021; Levi-Setti et al., 2021; Shaw et al., 2021; Trawick et al., 2022), and another two studies compared women who underwent ARTs and were infected by SARS-CoV-2 with those who were not infected (Kolanska et al., 2021; Wang et al., 2021). The detailed characteristics of all included studies were presented in Table S2.

3.2 Bias risk and methodological quality assessment

Using the NOS tool, 85.7% (6/7) of the included studies scored 4–6, and 14.3% (1/7) scored 9 (Kolanska et al., 2021); therefore, the included studies had an overall median risk of bias. A total of 71.4% (5/7) scored 2 for study selection, because most of them were retrospective cohort studies. Meanwhile, 85.7% (6/7) of the included studies scored 1 for the ascertainment of outcomes, since these studies did not include the follow-up of the cohorts. However, all of the included studies had high scores for the comparability of cohorts on the basis of the design or analysis (Fig. 2; Table 1).

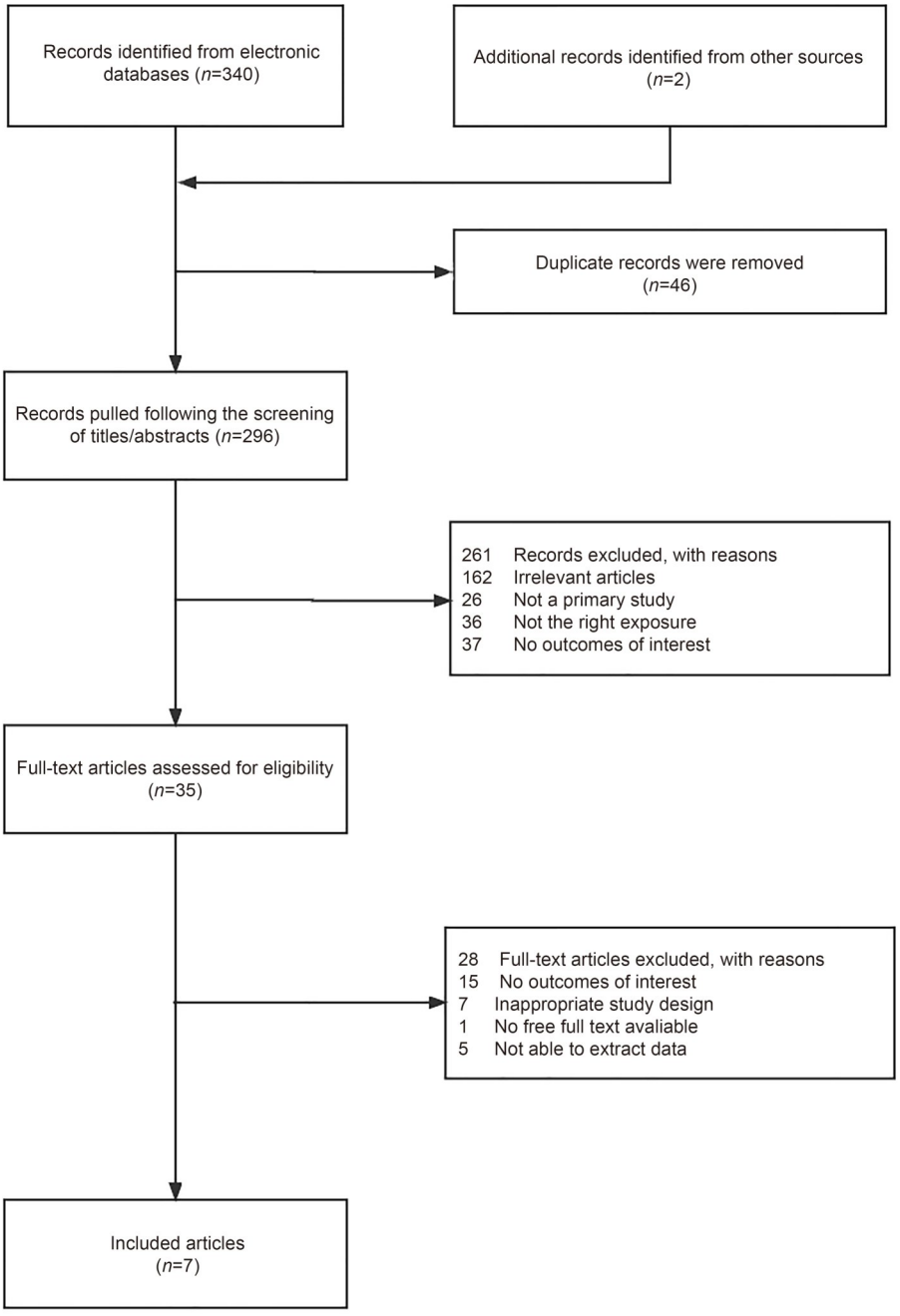

Fig. 1 Flowchart of the study selection process.

3.3 Effects of the COVID-19 pandemic on the pregnancy outcomes of women undergoing ART

3.3.1 Clinical outcomes

3.3.1.1 Clinical pregnancy rate

The clinical pregnancy rate was defined as the observed presence of a gestational sac. A total of three studies (Aharon et al., 2021; Chen et al., 2021; Levi-Setti et al., 2021) involving 10 593 ART cycles (3543 cycles after the COVID-19 pandemic and 7050 cycles before the COVID-19 pandemic) investigated the clinical pregnancy rate of women undergoing ART before and after COVID-19. Overall, there was no difference between the two groups in the clinical pregnancy rate (OR 1.07, 95% CI 0.97–1.19; I^2=0.0%; P=0.434; Fig. 3a). Meanwhile, a subgroup analysis

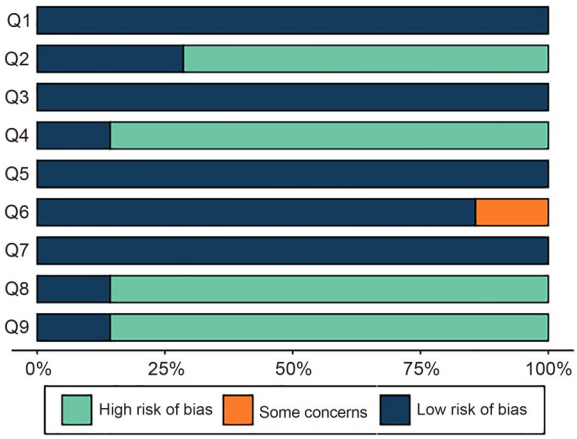

Fig. 2 Quality assessment using the Newcastle-Ottawa Scale (NOS) for the risk of bias for studies included in this review. Questions 1–4 (Q1–Q4) consider study selection; Q5 and Q6 consider study comparability; Q7–Q9 consider outcome ascertainment. Q1, What is the representativeness of the exposed cohort? Q2, How is the selection of the non-exposed cohort made? Q3, What is ascertainment of exposure? Q4, Is it demonstrated that the outcome of interest was not present at the start of the study? Q5, The comparability of cohorts on the basis of design or analysis (1): is the study controlled for the most confounding factors? Q6, The comparability of cohorts on the basis of design or analysis (2): is the study controlled for any other confounding factors? Q7, Was the assessment of outcome adequate? Q8, Was the follow-up long enough for outcomes to occur? Q9, How adequate was the follow-up of the cohorts?

according to ART type showed the same conclusion, with three studies including 4700 FET cycles (OR 1.12, 95% CI 0.97–1.29; I^2=49.9%; P=0.139; Fig. 3b). Other ART types such as embryo warming (1166 cycles, P=0.28), oocyte warming (63 cycles, P=0.975), artificial insemination by husband (AIH) (3859 cycles, P=0.917), or artificial insemination by donor's semen (AID) (795 cycles, P=0.469) could not be involved in the subgroup analyses, since only one study reported these outcomes (Fig. S1). Moreover, no significant difference was observed in the clinical pregnancy rates when comparing individual months of the two time periods, while controlling for the anti-Müllerian hormone (AMH), BMI, and endometrial thickness calculated with the multivariable logistic regression model (Aharon et al., 2021).

3.3.1.2 Miscarriage rate

The pregnant loss rate (PLR), which included biochemical or clinical pregnancy losses (Aharon et al., 2021), was is in line with the miscarriage rate (Levi-Setti et al., 2021). Two studies (Aharon et al., 2021; Levi-Setti et al., 2021) including 4938 ART cycles (1954 cycles after the COVID-19 pandemic and 2984 cycles before the COVID-19 pandemic) investigated the miscarriage rate (PLR) in women undergoing ART during the two time periods. There is no evidence that the miscarriage rate of women undergoing ART during the pandemic was affected (OR 0.95, 95% CI 0.79–1.14; I^2=38.4%; P=0.182; Fig. 3c). According to study by Aharon et al. (2021), in individual months, the COVID-19 pandemic did not significant change the PLR of women undergoing ART.

3.3.2 Laboratory outcomes

3.3.2.1 Embryo cryopreservation rate

A total of two studies (Chen et al., 2021; Trawick et al., 2022) including 13088 ART cycles (3627 cycles after the COVID-19 pandemic and 9461 cycles before the COVID-19 pandemic) investigated the embryo cryopreservation rate of women undergoing ART before and after the COVID-19 pandemic. Overall, the embryo cryopreservation rate was not significantly changed during the COVID-19 pandemic (OR 2.90, 95% CI 0.17–48.13; I^2=85.4%; P=0.009; Table 2).

3.3.2.2 Oocyte cryopreservation rate

Two studies (Shaw et al., 2021; Trawick et al., 2022) including 3088 ART cycles (1717 cycles after the COVID-19 pandemic and 1371 cycles before the COVID-19 pandemic) investigated the oocyte cryopreservation rate of women undergoing ART before and after the COVID-19 pandemic. We combined the elective oocyte cryopreservation rate and the medical oocyte cryopreservation rate in the study by Shaw et al. (2021). Overall, the COVID-19 pandemic did not significantly affect the oocyte cryopreserve rate (OR 0.30, 95% CI 0.03–3.65; I^2=81.6%; P=0.020; Table 2).

3.3.2.3 Anti-Müllerian hormone level

AMH is a biochemical marker of ovarian reserve (Visser et al., 2012), and low AMH levels may lead to infertility and the need for ART. A total of three studies (Aharon et al., 2021; Levi-Setti et al., 2021; Trawick et al., 2022) including 2972 cycles post-COVID-19 period detected the AMH levels of women undergoing ART in 2019 versus 2020. Overall, there was no significant change in AMH levels in women receiving ART during the pandemic compared to the pre-pandemic era (standardized mean difference (SMD) −0.07 ng/mL, 95% CI −0.22–0.07 ng/mL; I^2=67.0%; P=0.048; Table 3).

Table 1 Risk of bias of the included studies

Article information	Items of the "Risk of bias" tool									Score
	Selection bias				Comparability bias		Outcome ascertainment bias			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at start of the study	Comparability of cohorts on the basis of design or analysis (1)[a]	Comparability of cohorts on the basis of design or analysis (2)[b]	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of the follow-up of cohorts	
Aharon et al., 2021	Yes	No	Yes	No	Yes	?[c]	Yes	No	No	4
Kolanska et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Levi-Setti et al., 2021	Yes	No	Yes	No	Yes	Yes	Yes	No	No	5
Shaw et al., 2021	Yes	No	Yes	No	Yes	Yes	Yes	No	No	5
Trawick et al., 2022	Yes	No	Yes	No	Yes	Yes	Yes	No	No	5
Wang et al., 2021	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	6
Chen et al., 2021	Yes	No	Yes	No	Yes	Yes	Yes	No	No	5

[a] Comparability of cohorts on the basis of design or analysis (1): Is the study controlled for the most confounding factors? [b] Comparability of cohorts on the basis of design or analysis (2): Is the study controlled for any other confounding factors? (This item can be modified to illustrate the second most important factor of a particular control). [c] This study did not present other bias factors excluding age (year), body mass index (BMI), and anti-Müllerian hormone (AMH), while other studies compared life habits like smoking and comorbidities such as endometriosis. There are three aspects, including nine questions in the Newcastle-Ottawa Scale (NOS) for the risk of bias. The full score for each question is 1, the answer of "Yes" scores 1, and "?" and "No" score 0.

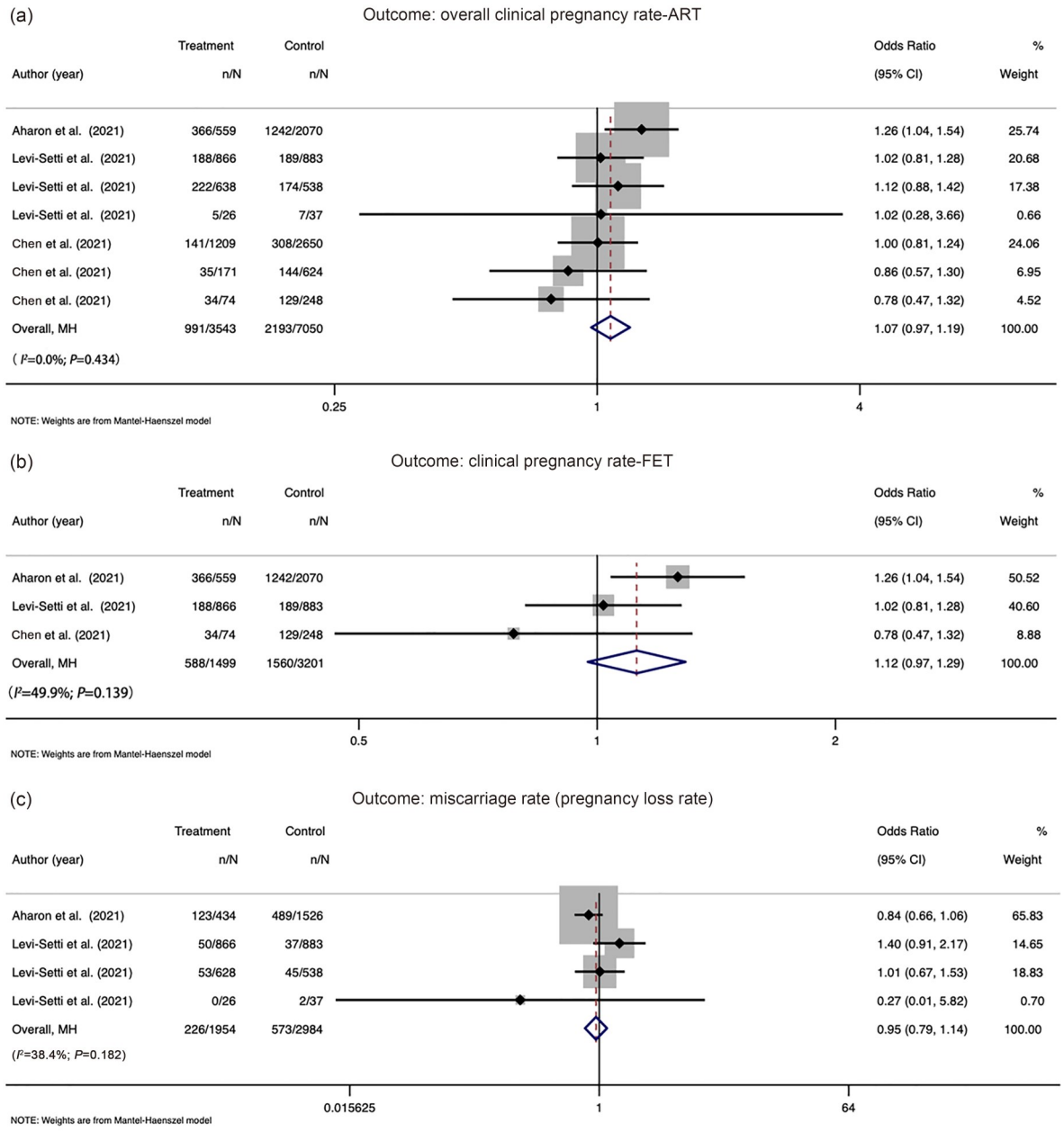

Fig. 3 Comparison of pre-COVID vs. post-COVID pregnancies. (a) Effect of the COVID-19 pandemic on the clinical pregnancy rate of women undergoing artificial reproductive technique (ART); (b) Effect of the COVID-19 pandemic on the clinical pregnancy rate of women undergoing fresh/frozen embryo transfer (FET); (c) Effect of the COVID-19 pandemic on the miscarriage rate (pregnancy loss rate) of women undergoing ART. n: the number of expected events; N: the number of total cycles; MH: the Mantal-Haenszel fixed-effects model; CI: confidence interval.

Table 2 Laboratory outcomes in pregnant women undergoing artificial reproduction technique (ART) before and after COVID-19 pandemic

Outcome	No. of studies	Cycles*		OR (95% CI)	I^2 (%)	P
		After COVID-19	Before COVID-19			
Embryo cryopreservation rate	2	1343/3627 (37.0%)	3886/9461 (41.1%)	2.90 (0.17–48.13)	85.4	0.009
Oocyte cryopreservation rate	2	438/1717 (25.5%)	394/1371 (28.7%)	0.30 (0.03–3.65)	81.6	0.020

* Cycles are expressed as the number with event/the total number in group (percentage). OR: odds ratio; CI: confidence interval.

Table 3 Female fertility outcomes in women undergoing artificial reproduction techniques (ART) before and after the COVID-19 pandemic

Outcome	No. of studies (comparisons)	SMD (95% CI) (ng/mL)	I^2 (%)	P
AMH levels	3 (2972)	−0.07 (−0.22–0.07)	67.0	0.048
Antral follicle count	2 (902)	0.05 (−0.04–0.15)	0	0.602

SMD: standardized mean difference; CI: confidence interval; AMH: anti-Müllerian hormone.

3.3.2.4 Antral follicle count

A total of two studies (Levi-Setti et al., 2021; Trawick et al., 2022) (including 902 cycles after COVID-19 pandemic) investigated the antral follicle counts of women with ART treatment. Overall, the pandemic did not significantly affect the count of antral follicles (SMD 0.05 ng/mL, 95% CI −0.04–0.15 ng/mL; I^2=0%; P=0.602; Table 3). When adjusted for age, BMI, AMH, and antral follicle count, the number of oocytes retrieved did not have a significant difference between pre-COVID and post-COVID pregnancies (P=0.68) (Trawick et al., 2022).

3.4 Effects of the SARS-CoV-2 infection in women undergoing ART

3.4.1 Clinical outcomes

Two studies (Kolanska et al., 2021; Wang et al., 2021) compared the effects of the infection of SARS-CoV-2 on the pregnancy outcomes in women treated with ART with those in non-infected women. Regarding clinical outcomes, SARS-CoV-2 infection did not significantly affect the biochemical pregnancy rate, clinical pregnancy rate, early miscarriage rate, or implantation rate (Wang et al., 2021). Regarding the laboratory outcomes, the proportions of mature oocytes, damaged oocytes, fertilized oocytes, cleavage embryos, high-quality embryos, and available blastocysts were also similar between the two groups, despite a slight decrease in the blastocyst formation rate in the infected group (Wang et al., 2021).

3.4.2 Laboratory outcomes

Two studies (Kolanska et al., 2021; Wang et al., 2021) compared the effects of the infection of SARS-CoV-2 on the AMH levels in women treated with ART with those in non-infected women. The data of AMH levels in these two studies were presented as mean and IQR, which could not be analyzed by Stata 15.1. Kolanska et al. (2021) carried out a prospective observational study and identified that mild infection with SARS-CoV-2 did not alter the ovarian reserve. Meanwhile, Wang et al. (2021) included an unmatched group and a matched group in a retrospective study, and neither exhibited a difference in AMH levels between the infected and non-infected groups (P=0.789 and P=0.247, respectively). These findings were in line with other study outcomes on ovarian reserves and ovarian responses.

3.5 Sensitivity analyses

The sensitivity analyses could only be carried out among five studies that compared the related outcomes of women treated with ART pre- and post-COVID-19 pandemic. The overall effect of the pandemic on clinical pregnancy rate was not changed with the sensitivity analysis when using the summary group (I^2=4.0%, P=0.399) instead of separated groups (I^2=33.3%, P=0.186); therefore, we used the summary group in the meta-analysis due to a smaller I^2. The result was in line with the miscarriage rate (summary group: I^2=59.6%, P=0.116; separated group: I^2=38.4%, P=0.182). Therefore, we used the separated group to analyze the miscarriage rate for the same reason as mentioned above.

4 Discussion

4.1 Mini review and key results

4.1.1 Mini review

It is widely accepted that SARS-CoV-2 infection can impact the male reproductive systems (He et al., 2020). While many studies have proved that COVID-19 infection could have adverse effects on pregnant women, such as preterm birth and an increased risk of maternal death (Allotey et al., 2020; Chmielewska et al., 2021), it is also known that the COVID-19 pandemic can bring extra stress to pregnant women, leading to an increased risk of anxiety and depression (Mayeur et al., 2020; Lablanche et al., 2022). However,

for women undergoing ART, this review is the first one to perform a comprehensive investigation.

4.1.2 Key results

The findings of this review showed that the difference was not statistically significant before and after the COVID-19 pandemic for all of the studied outcomes (clinical and laboratory outcomes).

The comparison between non-COVID-infected pregnant and COVID-infected pregnant women undergoing ART treatment found no significant differences in the clinical outcomes, laboratory outcomes, ovarian reserves, or ovarian responses.

4.2 Discussion of key results

During the time frame of high COVID-19 exposure risk, the clinical pregnancy rate was not significantly affected (P=0.434), which was not in line with the reduced quality of medical services (Chen et al., 2021) and the increased psychological and financial stress during the pandemic (Kahn et al., 2021). However, the lack of increased risk for pregnancy loss rate (P=0.182) was quite reassuring. This was in agreement with the data on SARS-CoV-1 and Middle East respiratory syndrome (MERS) (Wong et al., 2004), which may be due to the quarantine strategies during the COVID-19 pandemic (Peto et al., 2020), as fewer outings mean fewer accidents (Hitosugi et al., 2006).

As for the laboratory outcomes of embryo cryopreservation rate and oocyte cryopreservation rate, the results of this review showed no significant difference between before and after the COVID-19 pandemic. However, since the COVID-19 pandemic reduced the number of traditional visits to reproduction centers because of quarantine strategies (Peto et al., 2020), significantly more patients opted for embryo cryopreservation over oocyte cryopreservation in 2020 compared with the same time period in 2019 (Trawick et al., 2022), which may reflect a change in people's reproduction life plans (Lindberg et al., 2020). While these results are affirmative, more studies are needed to assess the impact of COVID-19 pandemic on pregnancy outcomes in women treated with ART.

We found that none of the relevant outcomes in infected women with ART treatment were different from those in non-infected women for the same time period in 2020, which was also proved by a recent cross-sectional study (Li et al., 2021). A plausible explanation for this result is that mild infections may not systematically affect pregnant women; to some extent, the impact of the SARS-CoV-2 on oocytes and embryos may be limited (Wang et al., 2021).

4.3 Strengths and limitations

In this review, we strictly adhered to the reporting guidelines when searching databases, selecting the eligible articles, assessing quality, and analyzing the data, despite of the urgent need for evidence on the impact of COVID-19 in ART procedures and related outcomes (Allotey et al., 2020).

The main limitation of this review is that the number of included studies was relatively small and the quality of included data was medium because of their retrospective nature. Therefore, many related outcomes such as pregnancy rate and implantation rate could not be fully investigated. Moreover, there was a high heterogeneity of laboratory outcomes (I^2>50%, Table 2). Since we could establish the original heterogeneity, in order to account for the heterogeneity, we used the random effect model for these outcomes.

The included studies only performed subgroup analyses of ART types, whereas other influencing factors, like region, race, severity of symptoms (mild and severe), government response stringency index (Dell'Utri et al., 2020), and WHO healthcare efficiency index (Greene et al., 2020), should also be fully explored in the future.

5 Conclusions

SARS-CoV-2 infection and the ramifications of COVID-19 pandemic did not seem to exert adverse effects on the pregnancy outcomes of women undergoing ART treatment. However, additional studies with better design are needed to further confirm this finding.

Acknowledgments

This study was supported by the Health High-Level Talent Training Project (Innovative Talents), the Health Commission of Zhejiang Province (File [2021] 40), and the 151 Talent Project (Second Level), Zhejiang Province Human Resources and Social Security Department (File [2018] 126), China.

Author contributions

Weihuan HU performed the study design and data analysis, wrote and edited of the manuscript. Yuhang ZHU performed the data analysis. Yan WU visualized the data. Fangfang WANG contributed to the study design and project administration. Fan QU contributed to the study design, funding acquisition, and supervision. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Weihuan HU, Yuhang ZHU, Yan WU, Fangfang WANG, and Fan QU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Aharon D, Gounko D, Lee JA, et al., 2021. The impact of the coronavirus disease 19 pandemic on early pregnancy outcomes among patients undergoing *in vitro* fertilization treatment. *Womens Health Rep*, 2(1):473-478. https://doi.org/10.1089/whr.2021.0054

Allotey J, Fernandez S, Bonet M, et al., 2020. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*, 370:m3320. https://doi.org/10.1136/bmj.m3320

Chen LX, Wu HP, Li R, et al., 2021. Impacts and prompts of COVID-19 outbreaking on assisted reproductive technology services in Beijing. *Chin J Reprod Contracept*, 41(1):12-17 (in Chinese). https://doi.org/10.3760/cma.j.cn101441-20200831-00468

Chmielewska B, Barratt I, Townsend R, et al., 2021. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health*, 9(6):e759-e772. https://doi.org/10.1016/S2214-109X(21)00079-6

de Gruijter NM, Naja M, Peckham H, et al., 2021. A systematic review exploring the bidirectional relationship between puberty and autoimmune rheumatic diseases. *Pediatr Rheumatol*, 19:47. https://doi.org/10.1186/s12969-021-00528-y

Dekkers OM, Egger M, Altman DG, et al., 2012. Distinguishing case series from cohort studies. *Ann Intern Med*, 156(1):37-40. https://doi.org/10.7326/0003-4819-156-1-201201030-00006

Dell'Utri C, Manzoni E, Cipriani S, et al., 2020. Effects of SARS CoV-2 epidemic on the obstetrical and gynecological emergency service accesses. What happened and what shall we expect now? *Eur J Obstet Gynecol Reprod Biol*, 254:64-68. https://doi.org/10.1016/j.ejogrb.2020.09.006

Greene NH, Kilpatrick SJ, Wong MS, et al., 2020. Impact of labor and delivery unit policy modifications on maternal and neonatal outcomes during the coronavirus disease 2019 pandemic. *Am J Obstet Gynecol MFM*, 2(4):100234. https://doi.org/10.1016/j.ajogmf.2020.100234

He WH, Liu XQ, Feng L, et al., 2020. Impact of SARS-CoV-2 on male reproductive health: a review of the literature on male reproductive involvement in COVID-19. *Front Med*, 7:594364. https://doi.org/10.3389/fmed.2020.594364

Hitosugi M, Motozawa Y, Kido M, et al., 2006. Traffic injuries of the pregnant women and fetal or neonatal outcomes. *Forensic Sci Int*, 159(1):51-54. https://doi.org/10.1016/j.forsciint.2005.06.006

Huang JW, Zhou XY, Lu SJ, et al., 2020. Dialectical behavior therapy-based psychological intervention for woman in late pregnancy and early postpartum suffering from COVID-19: a case report. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 21(5):394-399. https://doi.org/10.1631/jzus.B2010012

Kahn LG, Trasande L, Liu ML, et al., 2021. Factors associated with changes in pregnancy intention among women who were mothers of young children in New York City following the COVID-19 outbreak. *JAMA Netw Open*, 4(9):e2124273. https://doi.org/10.1001/jamanetworkopen.2021.24273

Kolanska K, Hours A, Jonquière L, et al., 2021. Mild COVID-19 infection does not alter the ovarian reserve in women treated with ART. *Reprod BioMed Online*, 43(6):1117-1121. https://doi.org/10.1016/j.rbmo.2021.09.001

Lablanche O, Salle B, Perie MA, et al., 2022. Psychological effect of COVID-19 pandemic among women undergoing infertility care, a French cohort-PsyCovART Psychological effect of COVID-19: PsyCovART. *J Gynecol Obstet Hum Reprod*, 51(1):102251. https://doi.org/10.1016/j.jogoh.2021.102251

Levi-Setti PE, Cirillo F, Immediata F, et al., 2021. First trimester pregnancy outcomes in a large IVF center from the Lombardy County (Italy) during the peak COVID-19 pandemic. *Sci Rep*, 11:16529. https://doi.org/10.1038/s41598-021-96134-9

Li KZ, Chen G, Hou HY, et al., 2021. Analysis of sex hormones and menstruation in COVID-19 women of childbearing age. *Reprod BioMed Online*, 42(1):260-267. https://doi.org/10.1016/j.rbmo.2020.09.020

Lindberg LD, VandeVusse A, Mueller J, et al., 2020. Early impacts of the COVID-19 pandemic: findings from the 2020 Guttmacher Survey of Reproductive Health Experiences. Guttmacher Institute, New York. https://www.guttmacher.org/report/early-impacts-covid-19-pandemic-findings-2020-guttmacher-survey-reproductive-health [Accessed on Mar. 1, 2021].

Mayeur A, Binois O, Gallot V, et al., 2020. First follow-up of art pregnancies in the context of the COVID-19 outbreak. *Eur J Obstet Gynecol Reprod Biol*, 253:71-75. https://doi.org/10.1016/j.ejogrb.2020.07.050

Peto J, Alwan NA, Godfrey KM, et al., 2020. Universal weekly testing as the UK COVID-19 lockdown exit strategy. *Lancet*, 395(10234):1420-1421. https://doi.org/10.1016/S0140-6736(20)30936-3

Qiao J, 2020. What are the risks of COVID-19 infection in pregnant women? *Lancet*, 395(10226):760-762. https://doi.org/10.1016/s0140-6736(20)30365-2

Rangchaikul P, Venketaraman V, 2021. SARS-CoV-2 and the immune response in pregnancy with Delta variant considerations. *Infect Dis Rep*, 13(4):993-1008. https://doi.org/10.3390/idr13040091

Shaw J, Tozour J, Blakemore JK, et al., 2021. Universal SARS-CoV-2 polymerase chain reaction screening and assisted reproductive technology in a coronavirus disease 2019 pandemic epicenter: screening and cycle outcomes from a New York City fertility center. *Fertil Steril*, 116(4):980-987. https://doi.org/10.1016/j.fertnstert.2021.05.109

Trawick E, Babayev E, Potapragada N, et al., 2022. Fertility preservation during the COVID-19 pandemic: modified but uncompromised. *Womens Health Rep*, 3(1):31-37. https://doi.org/10.1089/whr.2021.0107

UK Health Security Agency, 2022. Living safely with respiratory infections, including COVID-19. https://www.gov.uk/guidance/covid-19-coronavirus-restrictions-what-you-can-and-cannot-do#covid-19-remains-a-risk [Accessed on Apr. 1, 2022].

Visser JA, Schipper I, Laven JSE, et al., 2012. Anti-Müllerian hormone: an ovarian reserve marker in primary ovarian insufficiency. *Nat Rev Endocrinol*, 8(6):331-341. https://doi.org/10.1038/nrendo.2011.224

Wang M, Yang QY, Ren X, et al., 2021. Investigating the impact of asymptomatic or mild SARS-CoV-2 infection on female fertility and *in vitro* fertilization outcomes: a retrospective cohort study. *eClinicalMedicine*, 38:101013. https://doi.org/10.1016/j.eclinm.2021.101013

Wells G, Shea BJ, O'Connell D, et al., 2000. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. https://www.researchgate.net/publication/261773681 [Accessed on Mar. 1, 2021].

WHO (World Health Organization), 2020a. Global surveillance for COVID-19 caused by human infection with COVID-19 virus: interim guidance, 20 March 2020. https://apps.who.int/iris/handle/10665/331506 [Accessed on Mar. 1, 2021].

WHO, 2020b. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). https://www.who.int/zh/news-room/detail/01-05-2020-statement-on-the-third-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-coronavirus-disease-(covid-19) [Accessed on Mar. 1, 2021].

WHO, 2022. WHO coronavirus (COVID-19) dashboard. https://covid19.who.int [Accessed on Mar. 1, 2021].

Wong SF, Chow KM, Leung TN, et al., 2004. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol*, 191(1):292-297. https://doi.org/10.1016/j.ajog.2003.11.019

Supplementary information

Tables S1 and S2; Method S1; Fig. S1