7-13-2023

# Coronavirus Disease 2019 (COVID-19) Vaccination and Assisted Reproduction Outcomes: A Systematic Review and Meta-analysis.

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*Systematic Review*

# Coronavirus Disease 2019 (COVID-19) Vaccination and Assisted Reproduction Outcomes

## *A Systematic Review and Meta-analysis*

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**OBJECTIVE:** To assess the association between coronavirus disease 2019 (COVID-19) vaccination and female assisted reproduction outcomes through a systematic review and meta-analysis.

**DATA SOURCES:** We searched Medline (OVID), EMBASE, Web of Science, Cochrane Library, and ClinicalTrials.gov on January 11, 2023, for original articles on assisted reproduction outcomes after COVID-19 vaccination. The primary outcome was rates of clinical pregnancy; secondary outcomes included number of oocytes retrieved, number of mature oocytes retrieved, fertilization rate, implantation rate, ongoing pregnancy rate, and live-birth rate.

**METHODS OF STUDY SELECTION:** Two reviewers independently screened citations for relevance, extracted pertinent data, and rated study quality. Only peer-reviewed published studies were included.

**TABULATION, INTEGRATION, AND RESULTS:** Our query retrieved 216 citations, of which 25 were studies with original, relevant data. Nineteen studies reported embryo transfer outcomes, with a total of 4,899 vaccinated and 13,491 unvaccinated patients. Eighteen studies reported data on ovarian stimulation outcomes, with a total of 1,878 vaccinated and 3,174 unvaccinated patients. There were no statistically significant results among our pooled data for any of the primary or secondary outcomes: clinical pregnancy rate (odds ratio [OR] 0.94, 95% CI 0.88–1.01, $P$=.10), number of oocytes retrieved (mean difference −0.26, 95% CI −0.68 to 0.15, $P$=.21), number of mature oocytes retrieved (mean difference 0.31, 95% CI −0.14 to 0.75, $P$=.18), fertilization rate (OR 0.99, 95% CI 0.87–1.11, $P$=.83), implantation rate (OR 0.92, 95% CI 0.84–1.00, $P$=.06), ongoing pregnancy rate (OR 0.95, 95% CI 0.86–1.06, $P$=.40), or live-birth rate (OR 0.95, 95% CI 0.78–1.17, $P$=.63). A subanalysis based on country of origin and vaccine type was also performed for the primary and secondary outcomes and did not change the study results.

**CONCLUSION:** Vaccination against COVID-19 is not associated with different fertility outcomes in patients undergoing assisted reproductive technologies.

**SYSTEMATIC REVIEW REGISTRATION:** PROSPERO, CRD42023400023.

*(Obstet Gynecol 2023;00:1–9)*

*DOI: 10.1097/AOG.0000000000005310*

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*Presented at the ASRM Scientific Congress & Expo, October 22–26, 2022, Anaheim, California.*

*The authors thank Dr. Mark A. Turrentine for his assistance in designing the study and performing the analysis.*

*Each author has confirmed compliance with the journal's requirements for authorship.*

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***Financial Disclosure***

*David McCulloh was employed at NYU Langone Fertility Center during the project and directed the Andrology Laboratories for the Sperm and Embryo Bank of New York, Biogenetics Corporation, and Biogenetics Laboratory. McCulloh is the current Director of Clinical Science at ReproART: Georgian American Center for Reproductive Medicine. He was briefly the Vice President of Gameto, Inc. where he remains an advisor and was formerly a paid consultant for Buffalo IVF and Granata Bio. He was also a member of the SART Registry Committee from 2018 to 2021 and was Chair in 2020. Frederick Licciardi is a shareholder in the company that employs him, Prelude Fertility. The other authors did not report any potential conflicts of interest.*



ISSN: 0029-7844/23

A fundamental component of fertility evaluation and treatment is assessing and optimizing a patient's medical, psychological, and nutritional status before attempting pregnancy. The American Society

for Reproductive Medicine's and the American College of Obstetricians and Gynecologists' joint Committee Opinion No. 762 states, "The goal of prepregnancy care is to reduce the risk of adverse health effects for the woman, fetus, and neonate by working with the woman to optimize health, address modifiable risk factors, and provide education about healthy pregnancy."[1]

An important component of prepregnancy optimization is a patient's immunization status, including immunization against, "…tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap); measles–mumps–rubella; hepatitis B; and varicella" as well as influenza, when in season.[1] The American College of Obstetricians and Gynecologists, the American Society for Reproductive Medicine, and the Society for Maternal-Fetal Medicine now also recommend coronavirus disease 2019 (COVID-19) vaccination for prepregnancy and pregnant patients.[2,3]

Pregnant women are at increased risk of severe illness from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, as well as pregnancy-related complications. They are significantly more likely than nonpregnant women to be admitted to an intensive care unit, receive invasive ventilation, receive extracorporeal membrane oxygenation, and die from COVID-19.[4] They are also at greater risk of preeclampsia, gestational diabetes, low birth weight, preterm birth, and stillbirth.[5] In addition, several large studies have demonstrated the efficacy of vaccination in preventing maternal COVID-19 and in decreasing symptom severity and rates of hospitalization in vaccinated pregnant patients who do develop illness.[6] Maternal vaccination in pregnancy also has been demonstrated to reduce the rate of infant COVID-19–associated hospitalization.[6] Despite these risks, and despite clear recommendations promoting vaccination by leading reproductive and maternal–fetal medicine societies, rates of vaccine hesitancy and refusal remain high among women in the United States, primarily due to concerns regarding its safety profile.[7]

Low utilization of vaccination among reproductive-aged women is attributed at least partially to early misinformation regarding the vaccine's safety and questions regarding its effect on fertility.[8–10] Early theories proposed that similarities between the human placental protein syncytin and the SARS-CoV-2 S protein included in the COVID-19 vaccine or produced in response to vaccination may result in an inflammatory response that conferred negative downstream effects on fertility and pregnancy.[11,12] It is therefore imperative to evaluate what effect, if any, COVID-19 vaccination may have on fertility and pregnancy outcomes.

Four predominant types of COVID-19 vaccines exist and have previously been separately evaluated in relation to reproductive outcomes. They include inactivated-virus vaccines (Sinopharm, CoronaVac), mRNA vaccines (Pfizer, Moderna), protein subunit vaccines (Zifivax), and dsDNA vaccines (Johnson & Johnson/Janssen). Inactivated vaccines are produced from dead viruses, producing a similar immune response as a viral infection but with decreased pathogenicity and no risk for viral reactivation. Double-stranded DNA and mRNA vaccines contain only the genetic material of the virus, which is translated in the vaccine recipient to elicit an immune response. Similarly, protein subunit vaccines contain only characteristic proteins of the virus antigen, which elicit an immune response in the vaccine host.[13] We conducted a systematic review and meta-analysis to assess the association between COVID-19 vaccination and reproductive outcomes in women undergoing assisted reproductive technologies.

## SOURCES

This review was conducted in accordance with MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines[14] and was considered exempt per New York University's IRB. A comprehensive electronic literature search was conducted by a certified medical librarian on January 11, 2023, using Medline (Ovid) as the primary database to develop a search strategy, which then was applied to EMBASE, Web of Science, Cochrane Library, and ClinicalTrials.gov. The strategy was developed to identify articles that reported on assisted reproduction (ovarian stimulation, in vitro fertilization [IVF], or embryo transfer) outcomes after vaccination for COVID-19, using the search terms COVID-19, SarsCov2, vaccines, bnt162 vaccines, 2019-ncov vaccine mrna-1273, IVF, egg retrieval, oocyte retrieval, and embryo transfer. The complete search strategy can be found in Appendix 1, available online at http://links.lww.com/AOG/D264. The study was registered with PROSPERO on February 16, 2023, before the results were screened or data extraction had begun. All retrieved study titles and abstracts were reviewed by two investigators (I.J.C. and L.L.T.), and those that were relevant to the study question were downloaded and reviewed in their entirety by two investigators (I.J.C. and L.L.T.). References from the final set of included articles then were hand searched

independently by two investigators (I.J.C. and L.L.T.) for additional studies.

## STUDY SELECTION

Data from randomized controlled trials, prospective and retrospective cohort studies, case–control studies, and cross-sectional studies were deemed acceptable for inclusion. Conference abstracts, case reports, and studies not published in peer-reviewed journals were excluded given their inadequate peer review and limited data available for evaluation. Only English-language articles were considered. For studies that published only median or interquartile range data or both, the corresponding author was contacted to request the mean or SD or both. If author contact was unsuccessful, the mean and SD were derived mathematically using the method developed by Wan et al[15] and the Cochrane Handbook.[16]

The primary outcome assessed was *clinical pregnancy rate*, defined as an elevated serum β-hCG level with identification of an intrauterine gestational sac on ultrasonography. Secondary outcomes were number of oocytes retrieved, number of mature (MII) oocytes retrieved, fertilization rate, implantation rate (positive serum β-hCG without ultrasound evidence of pregnancy), ongoing pregnancy rate (positive β-hCG and confirmed fetal heart tones on ultrasonography), and live-birth rate. Vaccination against COVID-19 was achieved by inoculation with a minimum of one dose of either an mRNA, dsDNA, protein subunit, or inactivated-virus COVID-19 vaccine. Descriptive variables were reported for age, vaccine type, and country of origin for the studies. Meta-analysis was performed using the random-effects model given use of studies from around the world and presumed study heterogeneity. For nominal data, odds ratios (ORs) and 95% CIs were calculated; for discrete data, mean difference and 95% CI were calculated. A subgroup analysis was conducted to evaluate whether there were differences in outcomes based on vaccine type.

Two investigators (I.J.C. and L.L.T.) independently extracted the data and used the Newcastle-Ottawa scale for cohort studies to assess the quality of the included studies. Discrepancies were resolved by discussing their point assignments. A Newcastle-Ottawa scale score of 7–9 was considered low risk of bias, a Newcastle-Ottawa scale score of 4–6 was considered intermediate risk of bias, and a Newcastle-Ottawa scale score of 0–3 was considered very high risk of bias.[17] Interrater reliability was assessed by calculating an interclass correlation coefficient.[18]

An alpha level $<0.05$ was considered statistically significant across all analyses. Heterogeneity was evaluated using the Higgins' $I^2$ statistic. A value greater than 50% was considered statistically significant. Funnel plot was used to graphically assess for publication bias. Statistical analysis was performed using RevMan 5.4.

## RESULTS

A total of 504 studies were retrieved with our initial query. Of these, 248 duplicates were removed and 216 were excluded after reviewing their titles and abstracts because they did not address the study question, with 40 studies remaining with original data on assisted reproductive outcomes after COVID-19 vaccination. Of these, 14 were conference abstracts and one was not available in English, leaving 25 original studies for inclusion in the final analysis.[19–43] A flow diagram representation of this methodology is shown in Figure 1.

Nineteen studies reported on embryo transfer outcomes after COVID-19 vaccination, with a total of 4,899 vaccinated and 13,491 unvaccinated women. Twelve of those studies reported data on our primary outcome, clinical pregnancy rate. Eighteen studies reported data on ovarian stimulation outcomes after

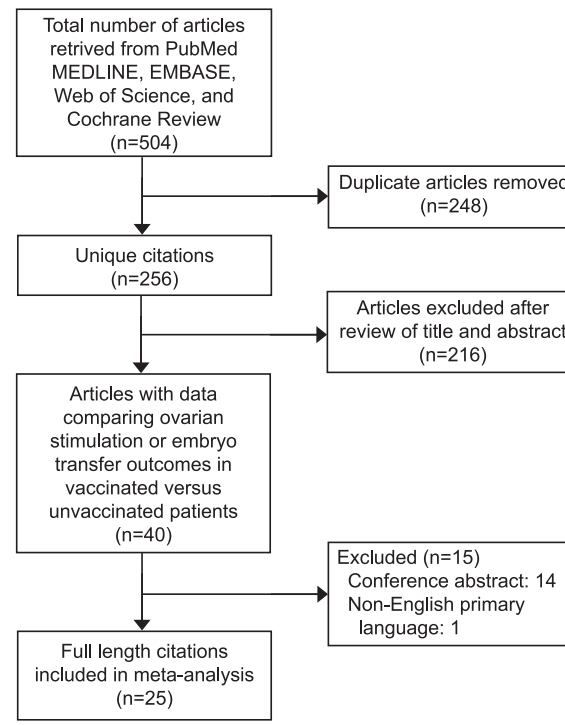


**Fig. 1.** Flowchart depicting study-selection process.
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vaccination, with a total of 1,878 vaccinated and 3,174 unvaccinated women. Ten studies were conducted in China, nine in Israel, three in the United States, two in Spain, and one in Jordan. Study characteristics are displayed in Table 1.

The quality of the studies was assessed using the Newcastle-Ottawa scale and is displayed in Table 1. There were 21 studies with a score of 7 or higher, indicating low risk for bias; four studies were rated 6, indicating intermediate risk for bias. The interrater correlation coefficient was 0.89, demonstrating a high degree of reliability.

Two studies provided median and interquartile range data.[38,40] Attempts to contact the authors to solicit the mean and SD from their study data were unsuccessful; therefore, the mean and SD were derived from the median and range using the formula developed by Wan et al.[15] Two studies reported mean and 95% CI data[19,22]; the SDs for these were derived using the method outlined by the Cochrane Handbook.[16]

Seventeen studies reported data on our primary outcome (positive β-hCG and presence of a gestational sac on ultrasonography), with no significant differences between the vaccinated and unvaccinated patients across these studies (mean rate 52.6% and 57.2%, respectively), and an aggregated OR of 0.94 and 95% CI of 0.88–1.01 ($P$=.10). Visual inspection of the funnel plot did not reveal a publication bias toward studies that yield a significant effect (Fig. 2). In addition, there were no differences among vaccinated and unvaccinated patients for our secondary outcomes, including number of oocytes retrieved (mean of means 9.6 and 10.6, respectively, mean difference −0.26, 95% CI −0.68 to 0.15, $P$=.21), number of mature oocytes retrieved (mean of means 8.9 and 9.3 respectively, mean difference 0.31, 95% CI −0.14 to 0.75, $P$=.18), fertilization rate (70.9% and 72.5%, respectively, OR 0.99, 95% CI 0.87–1.11, $P$=.83), positive β-hCG rate (51.1% and 56.7%, respectively, OR 0.92, 95% CI 0.84–1.00, $P$=.06), positive β-hCG plus fetal heart tones (52.3% and 55.5%, respectively, OR 0.95, 95% CI 0.86–1.06, $P$=.40), and live-birth rate (OR 0.95, 95% CI 0.78–1.17, $P$=.63). Detailed results for each of the outcomes, including $I^2$, ORs, CIs, and forest plots depicting the aggregated outcomes, along with which studies contributed data for each outcome, are depicted in Figure 3A–G.

A subanalysis based on country of origin and vaccine type was also performed for the primary and secondary outcomes and did not change the study results. We separated studies that used inactivated vaccines (Sinopharm and CoronaVac) from studies that primarily used mRNA or dsDNA vaccines (Pfizer, Moderna, Johnson & Johnson/Janssen) and analyzed them separately for effects on fertility. There were no significant differences across any of the measured outcomes in vaccinated compared with unvaccinated patients independent of vaccine type.

A substantial degree of heterogeneity was noted among fertilization rate ($I^2$=89%) and number of retrieved oocytes ($I^2$=56%). A subanalysis was performed in which studies were sequentially removed from the calculation to determine the effect on the overall heterogeneity; however, this did not identify any single study with a significant contribution.

## DISCUSSION

We conducted a systematic review and meta-analysis of the available literature comparing assisted reproduction outcomes in patients vaccinated against COVID-19 with those who were not vaccinated. There does not appear to be any difference in clinical pregnancy rate, number or total or mature oocytes retrieved, fertilization rate, implantation rate, and live-birth rate between vaccinated and unvaccinated women undergoing IVF.

All studies included in this analysis, except for one (Shi et al[38]) demonstrated no significant difference in clinical pregnancy rates between vaccinated and unvaccinated patients undergoing IVF. Furthermore, they demonstrate no differences in relevant secondary outcomes (oocytes retrieved, MII oocytes retrieved, fertilization rates, positive β-hCG, positive β-hCG plus fetal heart tones, and live-birth rates) between vaccinated and unvaccinated patients undergoing IVF. Our subanalysis based on vaccine type also demonstrated no significant differences in outcomes.

A single study evaluated assisted reproduction outcomes after administration of two doses of inactivated COVID-19 vaccine and reported a reduced number of oocytes retrieved, number of oocytes fertilized, and rates of biochemical, clinical, and ongoing pregnancy in patients undergoing IVF within 60 days of COVID-19 vaccination.[38] This effect was not noted in patients who initiated fertility treatment 60 days after vaccination. Significant study limitations include a significantly older population age in those undergoing treatment less than 60 days from vaccination, use of only inactivated COVID-19 vaccine, inclusion of only fresh embryo transfer cycles, and administration of the first vaccine dose near IVF initiation, with many patients

**Table 1. Study Characteristics**

| Study | Country | Study Design | NOS Score | Vaccine Type | No. of Doses | Vaccination–ART Time Interval | Age (y) (Vaccinated vs Unvaccinated) |
|---|---|---|---|---|---|---|---|
| Aharon et al[19] | United States | Retrospective cohort | 8 | Pfizer, Moderna | 2 | More than 14 d (after 2nd dose) | 37 vs 37 |
| Aizer et al[20] | Israel | Retrospective cohort | 7 | Pfizer, Moderna | 2 | 79±46 d (after 2nd dose) | 30 vs 31 |
| Albeitawi et al[21] | Jordan | Retrospective cohort | 7 | Pfizer, AstraZeneca, Sinopharm | NS | NS | 31 vs 36 |
| Avraham et al[22] | Israel | Retrospective age-matched cohort | 8 | Pfizer | 2 | 30.63 d (28.81–32.45 d) (after 2nd dose) | 36 vs 36 |
| Bentov et al[23] | Israel | Prospective cohort | 7 | Pfizer | 1 or 2 | 32.2±22.1 d (after 1st dose) | 35 vs 33 |
| Brandão et al[24] | Spain | Retrospective cohort | 7 | Pfizer, Moderna | 1 0r 2 | 32.2±22.1 d (after 1st dose) | 39 vs 38 |
| Cao et al[25] | China | Retrospective cohort | 6 | Sinopharm, CoronaVac, Convidecia | 1 or 2 | NS | 32 vs 33 |
| Dong et al[26] | China | Prospective cohort | 8 | Sinopharm, SinoVac, Zifivax | 2 | Less than 3, 3–6, more than 6 mo | 33 vs 33 |
| Huang, Xia, Tian et al[29] | China | Retrospective cohort | 8 | Sinopharm, Sinovac | 2 | 126.5±64.0 d (after 2nd dose) | 38 vs 38 |
| Huang, Xia, Zhao et al[28] | China | Retrospective cohort | 7 | CoronaVac, Sinopharm | 2 | More or less than 2 mo | 31 vs 31 |
| Huang, Xia, Lin et al[27] | China | Retrospective cohort | 8 | Sinopharm, Sinovac | 2 | Less than 1, 1–2, and more than 2 mo | 34 vs 33 |
| Jacobs 2022[43] | United States | Retrospective cohort | 8 | Pfizer, Moderna, Janssen | 1 or 2 | 93±65 d (after last dose) | 34 vs 33 |
| Karavani et al[30] | Israel | Retrospective cohort | 8 | Pfizer | 2 or 3 | Less than 3, 3–6, 6–9, and 9–13 mo | 35 vs 36 |
| Lazarovits et al[31] | Israel | Prospective cohort | 7 | Pfizer | 2 or 3 | 43.3±30.9 | 35 vs 37 |
| Morris[32] | United States | Prospective cohort | 6 | Pfizer, Moderna | NS | NS | 36 vs 35 |
| Odeh-Natour et al[33] | Israel | Prospective cohort | 7 | Pfizer | 2 | 14–60 d (after 2nd dose) | 34 vs 36 |
| Orvieto et al[34] | Israel | Prospective cohort crossover | 8 | Pfizer | 2 | 32.6±17.5 d (after 2nd dose) | 37 |
| Requena et al[35] | Spain | Retrospective cohort crossover | 8 | Pfizer, AstraZeneca, Moderna | 2 | 2 mo | 35 vs 34 |
| Safrai et al[36] | Israel | Retrospective crossover cohort | 8 | Pfizer | 2 | 57.3±24.7 d (after 1st dose) | 37 |
| Safrai et al[37] | Israel | Retrospective cohort | 7 | Pfizer | 2 | 131.8±43.1 d (after 1st dose) | 32 vs 35 |
| Shi et al[38] | China | Prospective cohort | 7 | Inactivated | 1 or 2 | Less than 30, 31–60, 61–90, more than 91 d | 31 vs 31 |
| Wang et al[39] | China | Retrospective cohort | 6 | Inactivated | 2 | NS | 33 vs 33 |
| Wu et al[40] | China | Retrospective cohort | 8 | CoronaVac, Sinopharm | 1 or 2 or 3 | Less than 30, 31–60, more than 61 d | 34 vs 33 |
| Xia et al[41] | China | Retrospective cohort | 7 | SinoVac, Sinopharm | 2 | NS | 32 vs 32 |
| Zhao et al[42] | China | Retrospective cohort | 6 | Inactivated | 2 | More or less than 3 mo | NS |

NOS, Newcastle-Ottawa scale; ART, assisted reproductive technology; NS, not supplied.

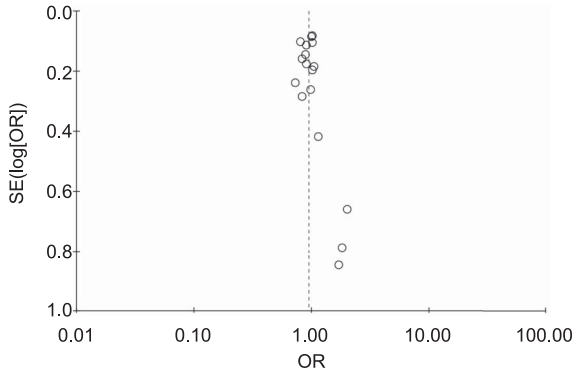


**Fig. 2.** Funnel plot of clinical pregnancy rate in vaccinated vs unvaccinated patients. SE, standard error; OR, odds ratio.

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receiving the "second dose during time of embryo implantation." All these variables can independently affect outcomes and limit the study's broader generalizability. Alternatively, the statistical difference found in this single study could represent a type I error, which would be expected when assessing approximately 20 studies and using an alpha level of 0.05. In addition, other studies did not find any differences in outcomes based on the time interval from vaccination to reproductive therapy.[26,27,30,42,44] Finally, when aggregating the Shi et al results together with all the other published literature, or even with only the other studies on inactivated COVID-19 vaccine, there was no significant aggregated effect across any of the outcomes.

A previous systematic review was conducted by Zace et al.[45] Their literature search was conducted earlier than ours, on June 8, 2022, and they therefore included only 10 studies in their analysis. Furthermore, although their analysis reports biochemical and clinical pregnancy outcomes, several other parameters are not addressed, such as oocyte yield, ongoing pregnancy, and live-birth rates. A more recent study by Huang et al,[46] however, did include a greater number of more recent studies. Their analysis included 21 studies and did find a statistically significant increase in mature oocytes but not in any other outcomes. A significant limitation to their work, however, is their exclusion of the study by Shi et al,[38] which notably was unique for finding several statistically significantly poorer outcomes among vaccinated patients, as discussed above. Although their rationale for doing so was due to the significantly older age differences reported in vaccinated compared with unvaccinated patients in Shi et al study, we believe it is important to include their results in the final meta-analysis to demonstrate that there is no aggregated effect on assisted reproductive technology outcomes in vaccinated patients among all the available literature. We additionally did not find any statistically significant differences in MII oocyte results in our analysis.

Our study's strengths include a prospectively disclosed protocol, a methodical and thorough search strategy, use of the latest literature on a rapidly developing area of investigation, and inclusion of both oocyte and embryo transfer outcomes, as well as inclusion and analysis of different vaccine types from around the world. Limitations to our study include a lack of randomized controlled studies, a variable interval period between vaccination and assisted reproduction, limited information regarding partner vaccination status and natural immunity, and limited live-birth data presently available. These present opportunities for additional research. Some of the elevated heterogeneity we discovered in two of our outcomes (fertilization rate and number of oocytes) may be due to the global representation of the included studies and the differing laboratory protocols and practices in different parts of the world. In addition, although the majority of the studies were located within the expected funnel plot, there were three smaller studies that were located outside the area of symmetry. Each of these studies, however, showed no significant effect, which makes this asymmetry unlikely to be the result of publication bias.

There are several potential physiologic mechanisms by which recent vaccination theoretically can result in poorer reproductive outcomes. Vaccination-induced elevations in serum levels of activated T cells,[47] production of autoantibodies (eg, antiphospholipid antibody),[48] and temporary immune-mediated disruptions to the hypothalamic-pituitary-ovarian axis[49] can lead to menstrual or ovarian dysfunction as well as impaired embryo implantation.[50] Our study reinforces COVID-19 vaccine safety by demonstrating similarities in key reproductive outcomes between vaccinated and unvaccinated patients undergoing IVF. As COVID-19 continues to be a part of modern life, with the potential formation of novel mutations of varying infectivity and virulence, vaccination remains a critical component of health maintenance. This is particularly true for susceptible members of the population, including pregnant patients. These data provide reassurance to clinicians as well as patients regarding the reproductive safety of COVID-19 vaccination and further adherence

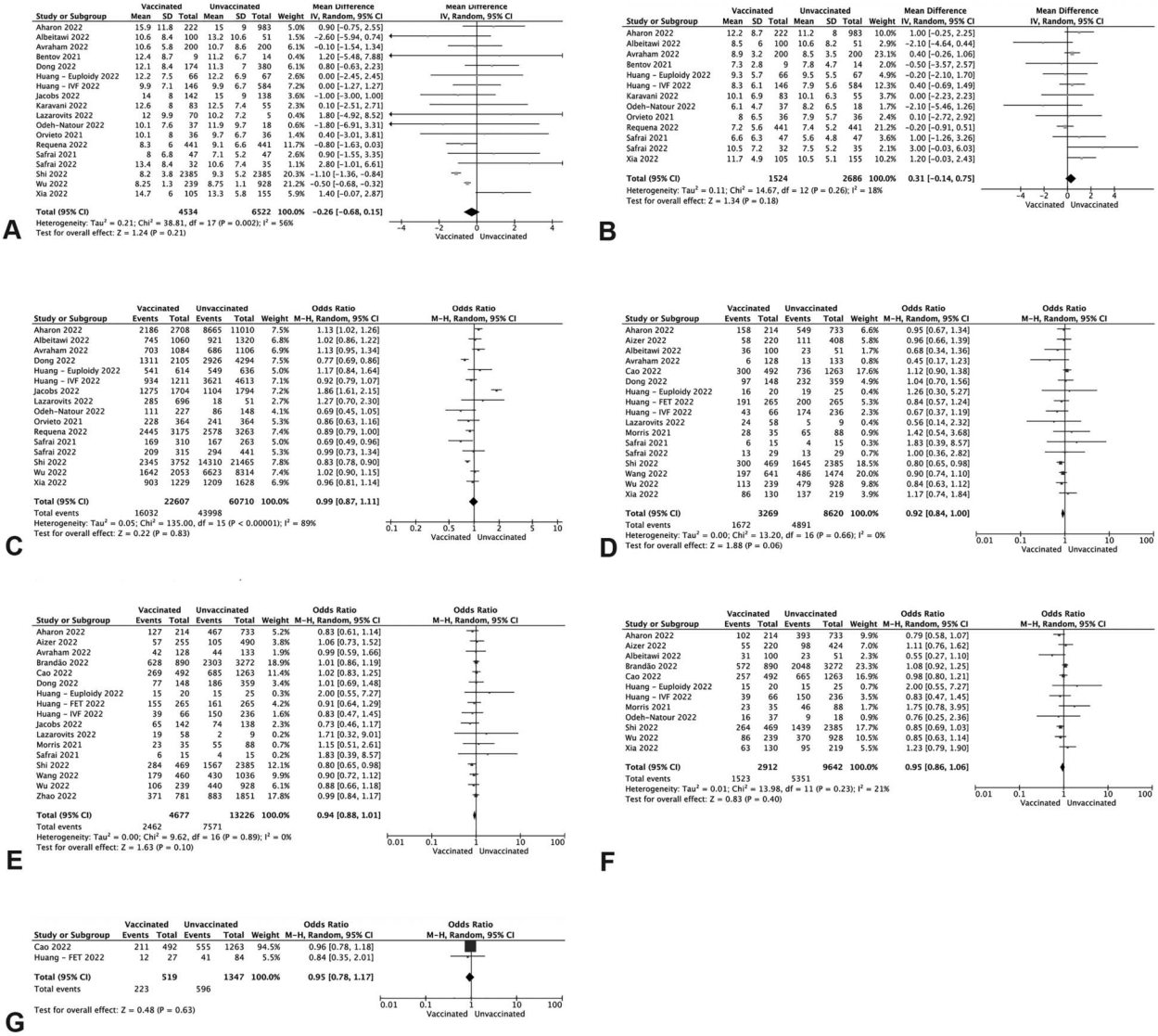


**Fig. 3.** Forrest plots depicting included studies and aggregated results for the number of retrieved oocytes (**A**), number of mature oocytes (**B**), fertilization rates (**C**), positive human chorionic gonadotropin (hCG) results (**D**), positive hCG and gestational sac (**E**), positive hCG and fetal heart tones (**F**), live birth rates (**G**). SD, standard deviation; IV, independent variable; df, degrees of freedom; M-H: Mantel-Haenszel.

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among pregnant women and those undergoing fertility treatment.

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## PEER REVIEW HISTORY

Received May 18, 2023. Received in revised form June 7, 2023. Accepted June 15, 2023. Peer reviews and author correspondence are available at http://links.lww.com/AOG/D265.