Original Research

In Vitro Fertilization and Early Pregnancy Outcomes After Coronavirus Disease 2019 (COVID-19) Vaccination

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OBJECTIVE: To assess whether coronavirus disease 2019 (COVID-19) mRNA vaccination is associated with controlled ovarian hyperstimulation or early pregnancy outcomes.

METHODS: This retrospective cohort study included patients who underwent controlled ovarian hyperstimulation or single euploid frozen-thawed embryo transfer at a single academic center. Patients fully vaccinated with a COVID-19 mRNA vaccine were compared with unvaccinated patients who cycled during the same time period. The primary outcome was the fertilization rate for controlled ovarian hyperstimulation and the clinical pregnancy rate for frozen-thawed embryo transfer. Secondary outcomes for controlled ovarian hyperstimulation included eggs retrieved, mature oocytes retrieved, mature oocytes ratio, blastulation rate, and euploid rate. Secondary outcomes for frozen-thawed embryo transfer included pregnancy rate, ongoing pregnancy rate, biochemical pregnancy loss rate, and clinical pregnancy loss rate.

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RESULTS: Among 222 vaccinated patients and 983 unvaccinated patients who underwent controlled ovarian hyperstimulation cycles between February and September 2021, there was no association on adjusted analysis between COVID-19 vaccination and fertilization rate ($\beta = 0.02 \pm 0.02$, P = .20) or any of the secondary outcomes assessed: eggs retrieved $(\beta = 0.01 \pm 0.57,$ P = .99), mature oocytes retrieved $(\beta = 0.26 \pm 0.47, P = .58)$, mature oocytes ratio $(\beta = 0.02 \pm 0.01,$ P=.12), blastulation rate ($\beta=0.02\pm0.02$, P=.27), or euploid rate $(\beta=0.05\pm0.03, P=.08)$. Among 214 vaccinated patients and 733 unvaccinated patients undergoing single euploid frozenthawed embryo transfer, adjusted analysis demonstrated no significant association between vaccination and clinical pregnancy (adjusted odds ratio [aOR] 0.79, 95% CI 0.54-1.16) or any of the secondary outcomes: pregnancy (aOR 0.88, 95% CI 0.58–1.33), ongoing pregnancy (aOR 0.90, 95% CI 0.61–1.31), biochemical pregnancy loss (aOR 1.21, 95% CI 0.69-2.14), or clinical pregnancy loss (aOR 1.02, 95% CI 0.51-2.06).

CONCLUSION: Administration of COVID-19 mRNA vaccines was not associated with an adverse effect on stimulation or early pregnancy outcomes after IVF. Our findings contribute to the growing body of evidence regarding the safety of COVID-19 vaccination in women who are trying to conceive.

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The dissemination of the coronavirus disease 2019 (COVID-19) vaccine has led to a gradual emergence from the global COVID-19 pandemic. Pregnant individuals may be at increased risk for morbidity and mortality from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and vaccination has been shown to be effective in pregnant women in lowering the incidence of severe disease. 1–5 Data on vaccine safety profiles in pregnancy are increasing, yet vaccination rates among pregnant women remain low. 1,6–14

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Vaccine hesitancy can be attributed in part to a concern regarding possible homology between the SARS-CoV-2 spike protein targeted by the vaccine and the placental syncitin-1 protein, potentially resulting in infertility. This theory was discredited by immunology experts, because any sequence similarity between the proteins is extremely limited and unlikely to cause cross-reactivity. 15,16

Studies to date have found no association of the COVID-19 mRNA vaccine with markers of fertility, including oocyte and embryo development; however, these included small numbers of participants. 17,18 Emerging data regarding early pregnancy outcomes among vaccinated women are reassuring, yet those studies consisted of small sample sizes or of casecontrol or observational registry data that do not fully capture fertilization rates, implantation rates, or unrecognized early pregnancy losses.^{8,19–21} One study has assessed outcomes after euploid embryo transfers among a small cohort of participants. 19 Robust clinical studies examining a relationship between the COVID-19 mRNA vaccines and in vitro fertilization (IVF) outcomes are limited. The objective of our study was to assess the association between COVID-19 mRNA vaccination and ovarian stimulation and early pregnancy outcomes in patients undergoing IVF.

METHODS

This retrospective cohort study was conducted at a single academic center. The study included patients who underwent controlled ovarian hyperstimulation or single euploid frozen-thawed embryo transfer. Controlled ovarian hyperstimulation cycles and frozen-thawed embryo transfer cycles were assessed separately as independent cohorts. The study groups for the controlled ovarian hyperstimulation and frozen-thawed embryo transfer cohorts consisted of fully vaccinated patients, defined as patients who received two doses of the Pfizer-BioNTech (Pfizer) or Moderna COVID-19 vaccine 14 days or more before the start of medications for their controlled ovarian hyperstimulation or frozen-thawed embryo transfer cycle. The control groups consisted of unvaccinated patients undergoing controlled ovarian hyperstimulation or frozen-thawed embryo transfer, respectively, during the same time period. Patients who started cycle medications less than 14 days from the second dose of an mRNA vaccine or who received the Johnson & Johnson/Janssen vaccine were excluded from the study. The first fully vaccinated patients began cycling in February 2021; therefore, all cycles from February through September 2021

were included. In each cohort, only the first cycle for each patient during this timeframe was included in the analysis.

The controlled ovarian hyperstimulation cohort included patients undergoing stimulation for IVF. Data collected included oocyte, fertilization, and embryo development parameters, as well as results of preimplantation genetic testing for aneuploidy among cycles in which testing was performed. Embryos from the controlled ovarian hyperstimulation cohort may have been cryopreserved or transferred fresh; embryo transfers from this cohort were not assessed. The frozenthawed embryo transfer cohort consisted of patients undergoing single embryo transfer of a tested euploid embryo that had been biopsied and cryopreserved in a prior cycle; early pregnancy outcomes were assessed among this cohort. All cycles from both cohorts underwent intracytoplasmic sperm injection. Oocyte cryopreservation cycles, in which fertilization and embryo generation were not performed, were not included. Cancelled cycles and conventional insemination cycles were excluded. Fresh embryo transfers were not included in the analysis.

Controlled ovarian stimulation was performed as previously described.^{22,23} Ovarian follicle growth was measured with transvaginal ultrasonography. Recombinant or purified human chorionic gonadotropin (hCG), leuprolide acetate, or a combination were used to induce final oocyte maturation once two or more follicles reached a mean diameter of 18 mm or more. Oocyte retrieval was performed 36 hours later under transvaginal ultrasonography guidance. Intracytoplasmic sperm injection was performed on metaphase II oocytes (mature oocytes). For cycles with preimplantation genetic testing for aneuploidy, trophectoderm biopsy was performed on days 5, 6, or 7 of embryo development once embryos achieved an adequate morphologic grade (modified Gardner morphologic score 4CC or higher), and then embryos were vitrified as described previously.²⁴ Preimplantation genetic testing for aneuploidy was performed using Next Generation Sequencing as previously described.²⁴

For frozen-thawed embryo transfer cycles, endometrial preparation was performed using oral estradiol administered twice daily for 4 days, followed by three times daily. Endometrial thickness and echotexture were assessed with transvaginal ultrasonography; when a minimum measurement of 7 mm was achieved, daily progesterone was given through intramuscular or oral and vaginal routes. Progesterone supplementation was administered for 5 days, after which embryo thawing and transfer were performed. A single euploid embryo was transferred in all cycles.

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Serum hCG levels were analyzed 8–9 days after embryo transfer and repeated 2–3 days later if positive (serum hCG 2.5 milli-international units/mL or higher). Transvaginal ultrasonography was performed 1 week after confirmed hCG rise, followed by weekly monitoring until discharge from the practice at 8–9 weeks of gestation. Clinical pregnancy was defined as visualization of an intrauterine gestational sac on transvaginal ultrasonography in the presence of a positive pregnancy test result.

Screening for SARS-CoV-2 infection was performed before each patient visit and procedure and included symptom questionnaires, temperature checks, and vaccination status once vaccines became available. Proof of vaccination was required if applicable, and vaccination type and dates were entered into the medical record. Testing for SARS-CoV-2 infection was not routinely performed.

Data were collected as part of routine clinical practice and extracted from the electronic medical record. The database enforces several validation and normalization standards, including data type rules and out-of-bound triggers that prevent inaccurate data entry. Further checks on the integrity of the data were also explored as part of initial exploratory and descriptive analysis.

The primary outcome when assessing controlled ovarian hyperstimulation cycles was fertilization rate (fertilized eggs out of mature oocytes injected with sperm). Secondary outcomes included oocytes retrieved, mature oocytes retrieved, mature oocytes ratio (mature oocytes/total oocytes retrieved), blastulation rate (blastocysts out of fertilized eggs), and euploid rate (euploid embryos out of embryos biopsied). The primary outcome when assessing frozen-thawed embryo transfer was clinical pregnancy rate per transfer (clinical pregnancies out of all frozen-thawed embryo transfer). Secondary outcomes included pregnancy rate (positive hCG out of all frozen-thawed embryo transfer), ongoing pregnancy rate (discharged to obstetrician out of all frozen-thawed embryo transfer), biochemical loss rate (loss after positive hCG before detection of clinical pregnancy out of all pregnancies), and clinical pregnancy loss rate (loss after detection of clinical pregnancy out of all clinical pregnancies).

Categorical variables were compared using χ^2 tests and Fisher exact tests, and continuous variables were compared using Student's t test. Shapiro-Wilk test was used to test for normality, and nonparametric variables were assessed using Wilcoxon rank-sum test. Multivariable linear and logistic regression were used to control for confounding variables. Beta coefficients from linear regression models were examined to present the change

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in outcomes for a 1-unit change in predictor value measurements. Odds ratios from logistic regression models were used to present the strength of associations between predictors and outcomes. Potential confounders were determined a priori. For controlled ovarian hyperstimulation cycles, covariates included in the adjusted analysis were age, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), serum anti-müllerian hormone level, gravidity, parity, and stimulation type. For frozenthawed embryo transfer cycles, covariates included in the adjusted analysis were age, BMI, anti-müllerian hormone level, gravidity, parity, endometrial thickness, embryo biopsy day, expansion, inner cell mass grade, and trophectoderm grade.

For our primary outcome of fertilization rate among controlled ovarian hyperstimulation cycles, a sample size of 138 patients was required to detect an absolute difference of 15% in fertilization rates with 80% power and alpha of 0.05. This was determined with the assumption of a fertilization rate of 80% based on prior data from our center. For our primary outcome of clinical pregnancy rates among frozenthawed embryo transfer cycles, a sample size of 171 single euploid frozen-thawed embryo transfers per group was required to detect an absolute difference of 15% in clinical pregnancy rates with 80% power and alpha of 0.05, based on 64% clinical pregnancy rates in our center. All P values were two-sided, with a significance level of <.05.

Propensity score matching in a 1:1 ratio was performed to corroborate the results of adjusted analysis for each cohort. The controlled ovarian hyperstimulation cohort was matched according to age, BMI, anti-müllerian hormone level, gravidity, parity, and stimulation type. The frozen-thawed embryo transfer cohort was matched according to age, BMI, anti-müllerian hormone level, gravidity, parity, and endometrial thickness.

Further subanalyses were performed in each cohort comparing individuals who received the Pfizer and Moderna vaccines with individuals in the control group, respectively, as well as comparing the two vaccine types with one another.

SAS 9.4 and SAS Studio were used for statistical analysis. This study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai, with a waiver of consent for retrospective analysis of de-identified data.

RESULTS

A total of 1,678 individuals who underwent controlled ovarian hyperstimulation and 1,271 who underwent

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single euploid frozen-thawed embryo transfer were identified (Fig. 1). Vaccination uptake rates per month ranged from 2.7% in February 2021 to 30.7% in May 2021 and were slightly higher in the frozen-thawed embryo transfer cohort compared with the controlled ovarian hyperstimulation cohort (Appendix 1, available online at http://links.lww.com/AOG/C592).

The controlled ovarian hyperstimulation cohort included 222 fully vaccinated patients and 983 unvaccinated patients. Baseline demographics, cycle characteristics, and cycle outcomes among the controlled ovarian hyperstimulation cohort are shown in Table 1. The control group had a higher parity compared with the vaccinated group. The vaccinated group had a higher percentage of antagonist and a lower percentage of flare protocol usage compared with the control group.

The primary outcome of fertilization rate for the controlled ovarian hyperstimulation cohort was similar between the vaccinated and unvaccinated groups (80.7% [95% CI 78.4–83.0] vs 78.7% [95% CI 77.5–80.0]). No differences were observed between vaccinated and unvaccinated patients on univariate analysis in the secondary outcomes of eggs retrieved, mature oocytes retrieved, mature oocytes retrieved, mature oocytes ratio, or blastulation rate. In cycles in which preimplantation genetic testing for aneuploidy was performed, vaccinated patients had a higher proportion of euploid embryos compared with unvaccinated patients (48.8% [95% CI 44.1–53.6] vs 42.5% [95% CI 40.2–44.9]) (Table 1).

Multivariable linear regression was performed, controlling for age, BMI, anti-müllerian hormone level, gravidity, parity, and stimulation type. No sig-

nificant association was seen on adjusted analysis between vaccination and the primary outcome of fertilization rate ($\beta = 0.02 \pm 0.02$, P = .20) or any of the secondary outcomes assessed: eggs retrieved $(\beta=0.01\pm0.57, P=.99)$; mature oocytes retrieved $(\beta = 0.26 \pm 0.47,$ P=.58); mature oocytes P=.12); $(\beta = 0.02 \pm 0.01,$ blastulation rate $(\beta = 0.02 \pm 0.02, P = .27)$; euploid rate $(\beta = 0.05 \pm 0.03, P = .27)$ P=.08).

In a sensitivity analysis in which the controlled ovarian hyperstimulation cohort was propensity score—matched, there was no association between COVID-19 vaccination and fertilization rates or any of the secondary outcomes (Appendix 2, available online at http://links.lww.com/AOG/C592). Controlled ovarian hyperstimulation cycle outcomes were assessed among patients who received the Pfizer (n=119) or Moderna (n=103) vaccine compared with the control group, respectively, as well as comparing patients who received the Pfizer or Moderna vaccine with one another. No differences were seen among the groups in the primary or secondary outcomes on adjusted analysis.

The single euploid frozen-thawed embryo transfer cohort included 214 vaccinated patients and 733 unvaccinated patients (Table 2). The control group in this cohort had higher parity and a greater endometrial thickness compared with the vaccinated group.

The primary outcome of clinical pregnancy rate in the frozen-thawed embryo transfer cohort was similar between the vaccinated and unvaccinated groups (59.5% [95% CI 52.7–66.3] vs 63.7% [95% CI 60.2–67.3]). No significant differences were seen between vaccinated and unvaccinated patients in the

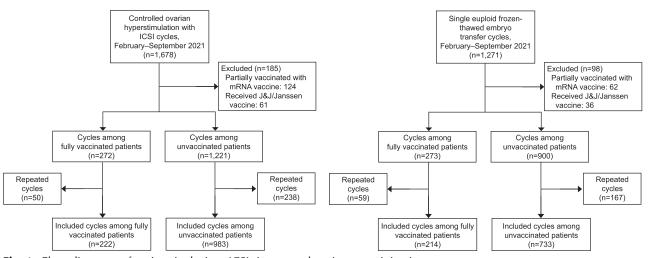


Fig. 1. Flow diagrams of patient inclusion. ICSI, intracytoplasmic sperm injection. Aharon. COVID-19 Vaccination and IVF Outcomes. Obstet Gynecol 2022.

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Table 1. Baseline Demographics, Cycle Characteristics, and Cycle Outcomes Among Vaccinated and Unvaccinated Patients Undergoing Controlled Ovarian Hyperstimulation

Variable	Vaccinated (n=222)	Unvaccinated (n=983)	P
Age (y)	36.7±4.4	37.1±4.5	.19
BMI (kg/m²)	24.3 ± 4.6	24.9±5.0	.30
AMH (ng/mL)	2.9 ± 2.9	2.7 ± 2.6	.38
AFC	14.9 ± 10.1	13.9±8.5	.33
Gravidity	0.0 (0.0–7.0)	0.0 (0.0–8.0)	.30
Parity	0.0 (0.0–3.0)	0.0 (0.0–4.0)	.01
Stimulation protocol			.02
Antagonist	92.3	86.2	.01
Flare	6.3	12.8	.005
Down-regulation	1.4	1.0	.71
Cumulative gonadotropin dosage (international units)	$3,954.0\pm1,392.5$	$3,927.3\pm1,317.9$.78
Estradiol at trigger (pg/mL)	2,559.4±1,371.2	2,513.7±1,256.1	.91
Embryo biopsy for PGT-A	79.7	78.6	.72
Average biopsy day*			.28
5	59.9	54.2	
6	36.7	40.1	
7	3.4	5.7	
Fertilization rate (%)	80.7 [78.4–83.0]	78.7 [77.5–80.0]	.39
No. of eggs retrieved	15.9 [14.4–17.5]	15.0 [14.4–15.6]	.64
No. of mature oocytes retrieved	12.2 [11.0–13.3]	11.2 [10.7–11.7]	.20
Mature oocytes ratio (%)	77.2 [75.0–79.3]	74.7 [73.5–75.8]	.18
Blastulation rate (%)	62.9 [59.4–66.4]	60.0 [58.2–61.7]	.30
Euploid rate (%)*	48.8 [44.1–53.6]	42.5 [40.2–44.9]	.02

BMI, body mass index; AMH, anti-müllerian hormone; AFC, antral follicle count; PGT-A, preimplantation genetic testing for aneuploidy. Data are mean ±SD, median (range), %, or mean [95% confidence limit] unless otherwise specified.

* Among cycles with embryo biopsy for PGT-A.

secondary outcomes of pregnancy rate, ongoing pregnancy rate, biochemical loss rate, or clinical pregnancy loss rate (Table 2, Fig. 2).

An adjusted analysis controlling for age, BMI, anti-müllerian hormone level, gravidity, parity, endometrial thickness, biopsy day, expansion, inner cell mass grade, and trophectoderm grade demonstrated no significant association between vaccination and the odds of clinical pregnancy (adjusted odds ratio [aOR] 0.79, 95% CI 0.54–1.16) or with any of the secondary outcomes assessed: pregnancy (aOR 0.88, 95% CI 0.58–1.33), ongoing pregnancy (aOR 0.90, 95% CI 0.61–1.31), biochemical pregnancy loss (aOR 1.21, 95% CI 0.69–2.14), or clinical pregnancy loss (aOR 1.02, 95% CI 0.51–2.06) (Table 3).

In a sensitivity analysis, after propensity score matching for the frozen-thawed embryo transfer cohort, there was no association between COVID-19 vaccination and clinical pregnancy rates (vaccinated vs unvaccinated: 59.5% [95% CI 52.7–66.3] vs 63.2% [95% CI 56.7–69.8], P=.44; odds ratio 0.86, 95% CI 0.58–1.27) or any of the secondary outcomes (Appendix 3, available online at http://links.lww.com/AOG/C592). No differences were seen in primary or secondary frozen-thawed embryo transfer

outcomes among patients who received the Pfizer (n=119) or Moderna (n=95) vaccine when compared with the control group, respectively, or when compared with one another, on multivariate analysis.

DISCUSSION

Patients vaccinated with the Pfizer or Moderna COVID-19 vaccine had similar responses to ovarian stimulation and similar pregnancy outcomes compared with unvaccinated patients. These findings provide reassurance that reproductive potential does not appear to be affected by COVID-19 mRNA vaccination in patients who undergo IVF.

Our data contribute to the ever-increasing evidence that COVID-19 vaccines do not negatively affect fertility or pregnancy. Clinical trials have generated reassuring observations, including the rates of pregnancies among vaccinated and unvaccinated women during the original vaccine trials. ¹⁵ Data from the Centers for Disease Control and Prevention's V-safe COVID vaccine registry and the Vaccine Adverse Event Reporting System have demonstrated similar incidences of pregnancy loss and other adverse pregnancy and neonatal outcomes in vaccinated patients compared with a historical control group. ^{7,8} Similarly,

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Table 2. Baseline Demographics, Cycle Characteristics, and Pregnancy Outcomes Among Vaccinated and Unvaccinated Patients Undergoing Single Euploid Frozen Embryo Transfer

Variable	Vaccinated (n=214)	Unvaccinated (n=733)	Р
Age (y)	36.5±3.7	36.5±4.1	.99
Oocyte age (y)	35.7 ± 3.6	35.5 ± 4.1	.54
BMI (kg/m ²)	24.0 ± 4.3	24.9 ± 5.0	.06
AMH (ng/mL)	3.3 ± 2.9	3.3 ± 3.0	.83
AFC	14.4 ± 9.4	13.9 ± 9.7	.54
Gravidity	1.0 (0.0–7.0)	1.0 (0.0–9.0)	.07
Parity	0.0 (0.0-3.0)	0.0 (0.0-4.0)	.01
Endometrial thickness (mm)	9.6±2.2	10.0±2.4	.02
Embryo biopsy day			.64
5	55.1	52.0	
6	40.2	42.1	
7	4.7	5.9	
Expansion			.93
4	46.7	45.3	
5	25.7	26.5	
6	27.6	28.2	
ICM grade			.84
A	75.8	76.4	
В	19.4	18.1	
C	4.8	5.5	
TE grade		3.5	.90
A	41.0	42.7	.50
В	39.5	38.2	
C	19.5	19.1	
Clinical pregnancy rate (%)	59.5 [52.7–66.3]	63.7 [60.2–67.3]	.27
Pregnancy rate (%)	73.8 [67.9–79.8]	74.9 [71.8–78.0]	.75
Ongoing pregnancy rate (%)	47.5 [40.4–54.5]	53.6 [49.7–57.4]	.13
Biochemical loss rate (%)	17.1 [11.2–23.0]	13.8 [10.9–16.7]	.30
Clinical loss rate (%)	18.0 [11.1–24.9]	12.0 [9.0–15.0]	.08

BMI, body mass index; AMH, anti-müllerian hormone; AFC, antral follicle count; ICM, inner cell mass; TE, trophectoderm. Data are mean ±SD, median (range), %, or mean [95% confidence limit] unless otherwise specified.

two large case–control studies found no association between vaccination and spontaneous abortion. ^{20,21} Those studies may be limited by assessing only clini-

cally recognized pregnancies and pregnancy losses. Pregnancies after IVF are closely tracked; this study therefore captures early implantation and biochemical

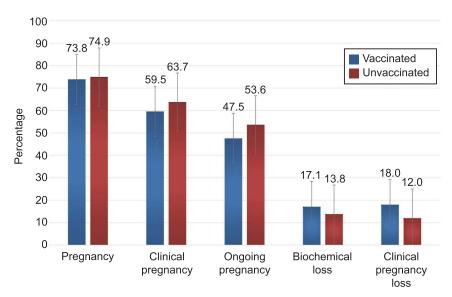


Fig. 2. Single euploid frozen-thawed embryo transfer outcomes between fully vaccinated and unvaccinated patients. *Error bars* represent 95% Cls.

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Table 3. Association of Vaccination With Single Euploid Frozen Embryo Transfer Outcomes on Unadjusted and Adjusted Analysis*

Outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Clinical pregnancy	0.84 (0.61–1.15)	0.79 (0.54–1.16)
Pregnancy	0.95 (0.67–1.34)	0.88 (0.58–1.33)
Ongoing pregnancy	0.78 (0.57–1.08)	0.90 (0.61–1.31)
Biochemical pregnancy loss	1.28 (0.79–2.07)	1.21 (0.69–2.14)
Clinical pregnancy loss	1.61 (0.94–2.76)	1.02 (0.51–2.06)

OR, odds ratio.

pregnancies in addition to clinical pregnancy losses that may be unrecognized or underreported in the general population or in registry studies.

This study's results are also consistent with studies to date of IVF outcomes in vaccinated patients. No differences were observed among 32 patients in follicular steroidogenesis, response to IVF trigger medications, and oocyte quality biomarkers when comparing individuals with anti-SARS-CoV-2 immunoglobulin G from vaccination or prior infection and seronegative individuals in a control group.¹⁸ Outcomes of IVF stimulation, including oocytes and mature oocytes retrieved, fertilization rate, and ratio of top-quality embryos per fertilized oocyte, were similar among 36 couples assessed before and after COVID-19 mRNA vaccination.¹⁷ One study assessing 55 patients with anti-SARS-CoV-2 spike immunoglobulin G reactivity compared with nonreactive patients found no differences in chemical, clinical, or ongoing pregnancy rates after frozen embryo transfer. 19

Our study provides further evidence indicating the safety of COVID-19 vaccination for patients who are planning pregnancy or are currently pregnant. By analyzing controlled ovarian hyperstimulation outcomes, we can assess a potential association of vaccination with markers of oocyte and embryo quality and development. By evaluating only euploid frozen-thawed embryo transfers, our study excludes a number of confounding variables that may affect pregnancy and pregnancy loss rates. Our control group cycled during the same time period, using the same protocols and techniques. Both the study and control groups were subject to the same environmental exposures, including exposure to SARS-CoV-2 in the community. The inclusion of only the first cycle for each patient served to minimize potential bias from repeated frozen-thawed embryo transfer cycles, which would necessarily be due to failed transfer cycles during this short timeframe, and to remove partial crossover between the groups.

This study is not without its limitations, including its retrospective design. We did not assess

antibody levels or test for SARS-CoV-2 infection in our patient population as part of our routine clinical practice; therefore, we do not know how many patients in the control group may have been exposed to SARS-CoV-2 and developed natural antibodies. Additionally, owing to the recent availability of vaccination, data on live birth rates and neonatal outcomes are currently limited and were not assessed as part of this study but will be an important focus of future studies.

The administration of COVID-19 mRNA vaccines was not associated with oocyte or embryo development, implantation, or early pregnancy loss in patients undergoing IVF in our study. These findings provide additional reassuring data that COVID-19 vaccination does not adversely affect fertility or early pregnancy outcomes and contribute to the growing body of evidence that the risk-to-benefit ratio supports vaccination in women who are pregnant or trying to conceive.

REFERENCES

- Chen F, Zhu S, Dai Z, Hao L, Luan C, Guo Q, et al. Effects of COVID-19 and mRNA vaccines on human fertility. Hum Reprod 2021;37:5–13. doi: 10.1093/humrep/deab23
- Badr DA, Mattern J, Carlin A, Cordier AG, Maillart E, El Hachem L, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol 2020;223:764–8. doi: 10.1016/j.ajog.2020.07.045
- Zambrano LD, Ellington S, Strid P, Galang R, Oduyebo T, Tong V, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69: 1641-7. doi: 10.15585/mmwr.mm6944e3
- Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. CMAJ 2021;193:E540-e8. doi: 10.1503/cmaj. 202604
- Dagan N, Barda N, Biron-Shental T, Makov-Assif M, Key C, Kohane I, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nat Med 2021;27:1693–5. doi: 10.1038/s41591-021-01490-8

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^{*} Adjusted for age, body mass index, anti-müllerian hormone level, gravidity, parity, endometrial thickness, biopsy day, expansion, inner cell mass grade, and trophectoderm grade.

- Rasmussen SA, Kelley CF, Horton JP, Jamieson DJ. Coronavirus disease 2019 (COVID-19) vaccines and pregnancy: what obstetricians need to know. Obstet Gynecol 2021;137:408–14. doi: 10.1097/AOG.0000000000004290
- Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary findings of mRNA covid-19 vaccine safety in pregnant persons. N Engl J Med 2021;384:2273–82. doi: 10.1056/NEJMoa2104983
- Zauche LH, Wallace B, Smoots AN, Olson CK, Oduyebo T, Kim SY, et al. Receipt of mRNA Covid-19 vaccines and risk of spontaneous abortion. N Engl J Med 2021;385:1533–5. doi: 10. 1056/NEJMc2113891
- Wainstock T, Yoles I, Sergienko R, Sheiner E. Prenatal maternal COVID-19 vaccination and pregnancy outcomes. Vaccine 2021;39:6037–40. doi: 10.1016/j.vaccine.2021.09.012
- Bookstein Peretz S, Regev N, Novick L, et al. Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. Ultrasound Obstet Gynecol 2021;58:450– 6. doi: 10.1002/uog.23729
- American Society for Reproductive Medicine. Statement from the ASRM COVID-19 task force. Accessed January 7, 2022. https:// www.asrm.org/news-and-publications/news-and-research/pressreleases-and-bulletins/statement-from-the-asrm-covid-19-task-force/
- American College of Obstetricians and Gynecologists. COV-ID-19 vaccination considerations for obstetric-gynecologic care. Accessed January 7, 2022. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/covid-19-vaccination-considerations-for-obstetric-gynecologic-care
- Society for Maternal-Fetal Medicine. Provider considerations for engaging in COVID-19 vaccine counseling with pregnant and lactating patients. Accessed January 7, 2022. https://s3.amazonaws.com/cdn.smfm.org/publications/390/downloadbd041e52c3af99c51223153fc7325a20.pdf
- 14. Centers for Disease Control and Prevention. COVID-19 vaccination among pregnant people aged 18-49 years overall, by race/ethnicity, and date reported to CDC Vaccine Safety Datalink,* United States. Accessed Nov 11, 2021. https://covid.cdc.gov/covid-data-tracker/#vaccinations-pregnant-women
- Male V. Are COVID-19 vaccines safe in pregnancy? Nat Rev Immunol 2021;21:200-1. doi: 10.1038/s41577-021-00525-y
- Kloc M, Uosef A, Kubiak JZ, Ghobrial RM. Exaptation of retroviral syncytin for development of syncytialized placenta, its limited homology to the SARS-CoV-2 spike protein and

- arguments against disturbing narrative in the context of COVID-19 vaccination. Biology (Basel) 2021;10:238. doi: 10. 3390/biology10030238
- Orvieto R, Noach-Hirsh M, Segev-Zahav A, Haas J, Nahum R, Aizer A. Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? Reprod Biol Endocrinol 2021;19:69. doi: 10.1186/s12958-021-00757-6
- Bentov Y, Beharier O, Moav-Zafrir A, Kabessa M, Godin M, Greenfield CS, et al. Ovarian follicular function is not altered by SARS-CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination. Hum Reprod 2021;36:2506–13. doi: 10. 1093/humrep/deab182
- Morris RS. SARS-CoV-2 spike protein seropositivity from vaccination or infection does not cause sterility. F S Rep 2021;2: 253–5. doi: 10.1016/j.xfre.2021.05.010
- Kharbanda EO, Haapala J, DeSilva M, Vazquez-Benitez G, Vesco KK, Naleway AL, et al. Spontaneous abortion following COVID-19 vaccination during pregnancy. JAMA 2021;326: 1629–31. doi: 10.1001/jama.2021.15494
- Magnus MC, Gjessing HK, Eide HN, Wilcox AJ, Fell DB, Håberg SE. Covid-19 vaccination during pregnancy and firsttrimester miscarriage. N Engl J Med 2021; 385:2008–10. doi: 10.1056/NEJMc2114466
- Rodriguez-Purata J, Lee J, Whitehouse M, Duke M, Grunfeld L, Sandler B, et al. Reproductive outcome is optimized by genomic embryo screening, vitrification, and subsequent transfer into a prepared synchronous endometrium. J Assist Reprod Genet 2016;33:401–12. doi: 10.1007/s10815-016-0647-y
- Sekhon L, Lee JA, Flisser E, Copperman AB, Stein D. Blastocyst vitrification, cryostorage and warming does not affect live birth rate, infant birth weight or timing of delivery. Reprod Biomed Online 2018;37:33–42. doi: 10.1016/j.rbmo.2018.03. 023
- 24. Hernandez-Nieto C, Lee JA, Slifkin R, Sandler B, Copperman AB, Flisser E. What is the reproductive potential of day 7 euploid embryos? Hum Reprod 2019;34:1697–706. doi: 10.1093/humrep/dez129

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