Coronavirus disease 2019 vaccination and infertility treatment outcomes

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Objective: To assess the influence of coronavirus disease 2019 (COVID-19) messenger ribonucleic acid vaccine on ovarian response and in vitro fertilization (IVF) treatment outcomes.
Design: A retrospective cohort study.
Setting: A tertiary university-affiliated medical center and a private medical center.
Patient(s): The study included a total of 400 patients, 200 vaccinated women and 200 age-matched unvaccinated women, who underwent IVF in January–April 2021.
Intervention(s): None.
Main Outcome Measure(s): The mean number of oocytes retrieved and clinical pregnancy rates in vaccinated vs. unvaccinated patients.
Result(s): A total of 200 patients underwent oocyte retrieval 14–68 days after receiving COVID-19 vaccination. No difference was found in the mean number of oocytes retrieved per cycle (10.63 vs. 10.72) between vaccinated and unvaccinated patients. Among 128 vaccinated and 133 unvaccinated patients who underwent fresh embryos transfers, no difference was demonstrated in the clinical pregnancy rates (32.8% vs. 33.1%), with 42 and 44 clinical pregnancies, respectively. The fertilization rates and mean number of cryopreserved embryos were similar between the 2 groups in freeze-all cycles (55.43% vs. 54.29% and 3.59 vs. 3.28, respectively). Among vaccinated and unvaccinated patients who underwent fresh embryo transfers, no difference was noted in the fertilization rate (64.81% vs. 61.98%) and transferred embryos' quality. Regression models applied demonstrated no effect of the vaccine on oocyte yields and pregnancy rates.
Conclusion(s): The COVID-19 messenger ribonucleic acid vaccine did not affect the ovarian response or pregnancy rates in IVF treatment. Women should be vaccinated for COVID-19 before attempting to conceive via IVF treatments, given the higher risk of severe illness in pregnant women. (Fertil Steril® 2022;117:1291–9. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: COVID-19, mRNA vaccine, infertility treatments

Since the discovery of the first cases in December 2019 in Hubei Province, China, coronavirus disease 2019 (COVID-19) has rapidly spread worldwide, turning into a global pandemic (1). Among the first COVID-19 vaccines available was the messenger ribonucleic acid (mRNA) vaccine BNT162b2 (Pfizer-BioNTech), which was granted Emergency Use Authorization by the Food and Drug Administration in December 2020 (2). On December 20, 2020, Israel initiated a national vaccination program against COVID-19, initially prioritizing high-risk populations and healthcare workers but rapidly expanding the program to include all adults. Because early studies demonstrated that infection with COVID-19 during pregnancy increased

Received August 12, 2021; revised and accepted February 22, 2022; published online February 25, 2022.
S.A. has nothing to disclose. A.K. has nothing to disclose. H.Z. has nothing to disclose. M.Y. has nothing to disclose. O.Y. has nothing to disclose. G.M.Y. has nothing to disclose. I.G. has nothing to disclose. Y.G. has nothing to disclose. A.Hoc. has nothing to disclose. M.B. has nothing to disclose. A.Hou. has nothing to disclose. E.M. has nothing to disclose.
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Fertility and Sterility® Vol. 117, No. 6, June 2022 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2022.02.025

the risk of development of severe disease and pregnancy complications, the American Society for Reproductive Medicine recommended that pregnant women should be prioritized to receive vaccination, whether before conception or during pregnancy (3), despite the fact that the vaccine trial did not include this population. Nevertheless, a recent meta-analysis of international data (4) showed a declining tendency to be vaccinated, possibly influenced by exposure to widespread misinformation and public concerns over safety of the vaccines. Specifically, concerns were raised about a possible detrimental effect on fertility and pregnancy outcomes due to similarity between syncytin-1, a human placental fusion protein, and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein expressed after the administration of the COVID-19 vaccine. A recent study concluded it was unlikely that the vaccine protein would generate an immune response that could affect fertility and pregnancy due to very low sequence similarity between the proteins (5). Indeed, preliminary data on vaccinated pregnant women (2) have shown reassuring safety results, and a prospective study on vaccinated men suggested no effect on sperm parameters (6). A retrospective analysis on 36 patients with infertility has assessed the influence of COVID-19 vaccination on in vitro fertilization (IVF) treatment outcomes and found no differences in the stimulation characteristics and embryological variables compared with treatment before vaccination (7). In addition, a very recent prospective study demonstrated no association with fecundability among vaccinated participants trying to conceive spontaneously. The study was limited by Internet-based questioners, lack of possible infertility assessment, and lack of timed pregnancy test, which could lead to missed documentation of early pregnancy loss (8).

The lack of safety data in this vulnerable population prompted us to conduct this study, aiming to evaluate the effect of COVID-19 vaccination on the results of IVF treatments, ovarian responses, embryo quality, and pregnancy rates. No significant effect on fertility treatments outcomes would allow recommending vaccination before treatments to lower the risk of severe illness during pregnancy.

MATERIALS AND METHODS

Study Design

This study is a retrospective age-matched cohort study.

Study Population

All vaccinated women aged 20–42 years who underwent IVF treatment cycles between January 1, 2021, and April 31, 2021, at Shamir Medical Center and Herzliya Medical Center, both in Israel, were included. All participants completed 2 doses of the BNT162b2 (Pfizer-BioNTech) vaccine at least 2 weeks before starting ovarian stimulation. The study group was matched by age to unvaccinated patients who underwent IVF treatments during the same period. Patients with a positive COVID-19 test in the past were excluded. The stimulation protocols and fertilization methods were chosen by the treating physician and embryologist according to the infertility cause or past cycles' performance. The study was approved by the Institutional Review Boards of both participating medical centers (ASF-0094-21 and HMC-0010-21).

Embryo and Blastocyst Scoring

The grading of embryos and blastocysts was based on the Istanbul consensus workshop (9) and adjusted to the local laboratory, resulting in 3 quality grading groups.

General Characteristics and Outcomes Measured

We recorded the demographic and baseline characteristics (including age, partner's age, smoking status, previous pregnancies and deliveries, previous IVF treatments, and infertility cause) as well as treatment protocol and cycle characteristics (total gonadotropins [GTs] administered, estradiol (E_2) levels on the day of ovulation-triggering [maximal E_2], and fertilization method). Combined protocol referred to an ultrashort flare protocol combined with an antagonist (10).

The main outcome measures were the mean number of retrieved oocytes per cycle and clinical pregnancy (≥ 1 intrauterine gestational sacs detected on ultrasound) rates. The secondary outcomes included the oocyte maturation rate (metaphase II [mature] oocytes/oocytes retrieved), fertilization rate (2 pronuclei/oocytes retrieved), mean number of embryos frozen per cycle, and chemical pregnancy rate (elevated human chorionic GT levels without a clinical pregnancy).

Cycles were further stratified and analyzed by the presence of fresh embryo transfer or "freeze-all" cycles. Freeze-all cycles referred to cycles in which all embryos were cryopreserved for various reasons, such as ovarian hyperstimulation, need for genetic analysis, and surrogacy.

Statistical Methods

The Shapiro-Wilk test was used to test for the normal distribution of continuous variables.

Continuous variables were summarized with mean and 95% confidence intervals (CIs) and compared between groups using the Mann-Whitney U test. Categorical variables were summarized using frequency and percentages. The Fisher's exact test and χ^2 test were used to compare differences between groups.

A logistic regression model was applied to identify factors related to clinical pregnancies and adjust for confounding variables. The following variables were included in the preliminary model: age; smoking; previous retrievals and transfers; body mass index (BMI); gravidity; parity; stimulation protocol; final embryo ranking; and vaccination status. The forward elimination method was applied to select the optimal model with a threshold of $P<.05$ for inclusion and $P>.15$ for exclusion. Vaccination status was forced to be included in the model. The final model included vaccination status, age, previous transfers, and final embryo rank.

A linear regression model was applied to identify factors related to the total number of oocytes retrieved. The following variables were included in the preliminary model: age; smoking; previous retrievals and transfers; BMI; gravidity, parity,

TABLE 1

Baseline characteristics and treatment outcomes of vaccinated vs. unvaccinated women.

	Unvaccinated (N = 200)	Vaccinated (N = 200)	*P* value
Mean age (y)	36.11 (35.49–36.73)	36.04 (35.41–36.67)	.92
Mean partner age (y)	37.38 (36.48–38.27)	37.51 (36.38–38.64)	.54
Smoking (%)	27.0 (15.2)	23.0 (13.3)	.61
Previous retrievals	1.73 (1.44–2.01)	1.83 (1.49–2.16)	.78
Previous transfers	1.82 (1.46–2.17)	1.78 (1.43–2.13)	.48
BMI	24.36 (23.58–25.15)	24.48 (23.68–25.27)	.87
Infertility cause (%)			
Male factor	34.0 (18.8)	35.0 (19.6)	.15
Fertility preservation	26.0 (14.4)	14.0 (7.8)	
Mechanical	14.0 (7.7)	12.0 (6.7)	
Unexplained infertility	42.0 (23.2)	35.0 (19.6)	
Age-related infertility	49.0 (27.1)	55.0 (30.7)	
Other	16.0 (8.8)	28.0 (15.6)	
G (%)			
0	84.0 (51.2)	77.0 (48.4)	.26
1	46.0 (28.0)	37.0 (23.3)	
2+	34.0 (20.7)	45.0 (28.3)	
P (%)			.21
0	105.0 (62.1)	93.0 (58.1)	
1	48.0 (28.4)	43.0 (26.9)	
2+	16.0 (9.5)	24.0 (15.0)	
Days from vaccination to retrieval			
Range	-	30.63 (28.81–32.45) 14.00–68.00	
Protocol (%)			
MNC	8.0 (4.0)	4.0 (2)	.17
Antagonist	160.0 (80.4)	172.0 (87.3)	
Long luteal	14.0 (7.0)	14.0 (7.1)	
Short	7.0 (3.5)	4.0 (2.0)	
Combined	10.0 (5.0)	3.0 (1.5)	
Ovulation triggering (%)			
Dual	83.0 (42.6)	98.0 (52.4)	.15
hCG	51.0 (26.2)	42.0 (22.5)	
GnRH agonist	61.0 (31.3)	47.0 (25.1)	
Stimulation days	10.25 (9.42–11.09)	9.90 (9.32–10.47)	.62
Total gonadotropin dose (IU)	2,780.14 (2,589.71–2,970.57)	2,938.04 (2,754.47–3,121.62)	.14
E2 on the day of ovulation triggering (pmol/L)	8,070.20 (7,046.00–9,094.40)	7,388.28 (6,223.16–8,553.40)	.24
Endometrial thickness(mm)	9.72 (9.42–10.02)	9.60 (9.29–9.92)	.58
Oocytes retrieved	10.72 (9.53–11.91)	10.63 (9.82–11.43)	.93
Fertilization method (%)			
ICSI	99.0 (55.0)	106.0 (54.6)	0.94
IVF	22.0 (12.2)	26.0 (13.4)	
ICSI/IVF	59.0 (32.8)	62.0 (32.0)	
MII oocytes/oocytes retrieved (%) in cycles with ICSI	79.56% (75.07–84.04)	83.82% (79.62–88.01)	0.17

Note: Data are presented as mean and (95% confidence interval) or counts and (percentage). Mechanical factor: tubal and uterine. Age-related infertility: age of >39 years as a primary infertility indication. Combined protocol = agonist administered for 2–3 days and then replaced by an antagonist. BMI = body mass index; G = gravidity; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; MNC = modified natural cycle; P = parity; short protocol = agonist (flare-up protocol).

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protocol; and vaccination status. The forward elimination method was applied to select the optimal model with a threshold of $P<.05$ for inclusion and $P>.15$ for exclusion. Vaccination status was forced to be included in the model. The final model included vaccination status, age, previous transfers, and previous retrievals.

No imputations for missing data were applied, and each measure was reported based on the existing valid data. The logistic regression was based on 86% of cases (224/261), and the linear regression was based on 87% of cases (349/400).

Univariate analyses were conducted using R package version 3.6.3 (https://CRAN.R-project.org/package=arsenal), Jason Sinnwell, Elizabeth Atkinson, Tina Gunderson and Gregory Dougherty (2021). Arsenal: An Arsenal of 'R' Functions for Large-Scale Statistical Summaries. R package version 3.6.3. https://CRAN.R-project.org/package=arsenal. Multivariate analyses were conducted using SPSS-27 software (IBM, Armonk, NY).

Sample Size Calculation

Based on an assumed pregnancy rate of 30% in the control group, a sample size of 200 patients per group would be needed to detect a reduction to a pregnancy rate of 19% using a χ^2 test

TABLE 2

Clinical outcomes of vaccinated vs. unvaccinated patients in freeze-all embryo cycles.

	Unvaccinated (N = 47)	Vaccinated (N = 66)	*P* value
Days from vaccination to retrieval	—	29.44 (26.68–32.19)	—
Range		14.00–62.00	
Protocol (%)			
MNC	1.0 (2.1)	0 (0)	.10
Antagonist	39.0 (83.0)	61.0 (93.8)	
Long luteal	4.0 (8.5)	4.0 (6.2)	
Short	0 (0)	0 (0)	
Combined	3.0 (6.4)	0 (0)	
Ovulation triggering (%)			
Dual	13.0 (28.3)	21.0 (34.4)	.78
hCG	7.0 (15.2)	8.0 (13.1)	
GnRH agonist	26.0 (56.5)	32.0 (52.5)	
Stimulation days	10.67 (9.44–11.90)	9.80 (9.20–10.39)	.26
Overall Gonadotropins dose (IU)	3,103.24 (2,709.68–3,496.81)	2,857.72 (2,520.08, –3,195.36)	.27
E2 on the day of ovulation triggering (pmol/L)	10,157.74 (7,975.79–12,339.69)	11,249.20 (7,689.82–14,808.58)	.82
Endometrial thickness(mm)	9.49 (8.93–10.04)	9.39 (8.83–9.95)	.67
Oocytes retrieved	13.62 (10.89–16.34)	14.88 (12.07–17.69)	.95
Fertilization method (%)			
ICSI	32.0 (71.1)	38.0 (59.4)	.43
IVF	3.0 (6.7)	7.0 (10.9)	
ICSI/IVF	10.0 (22.2)	19.0 (29.7)	
MII oocytes/oocytes retrieved (%) - ICSI	77.66 (70.55–84.76)	86.01 (79.64–92.38)	.06
Fertilization rate (pronuclei/total oocytes) (%)	54.29 (46.50–62.08)	55.43 (48.91–61.96)	.73
Frozen embryos per cycle			
Total	3.28 (2.43–4.13)	3.59 (2.77–4.41)	.80
Day 2/3	2.72 (1.96–3.48)	2.68 (2.00–3.36)	.88
Day 5	2.61 (1.54–3.67)	2.73 (1.98–3.48)	.71
Day 6	0.58 (0.08–1.09)	1.92 (0.75–3.08)	.025

Note: Data are presented as mean and (95% confidence interval) or counts and (percentage). Combined protocol = agonist administered for 2–3 days and then replaced by an antagonist. E2 = estradiol; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; MII = metaphase II; MNC = modified natural cycle; short protocol = agonist (flare-up protocol).

Avraham. COVID-19 vaccination and infertility. Fertil Steril 2022.

with a one-sided type 1 error of 5% and 80% power and a reduction of 1.4 oocytes assuming an SD of 5.5 with a one-sided type 1 error of 5% and 80% power, applying an independent Student's *t* test. To detect a reduction to a 25% pregnancy rate, 985 patients per group would be needed. Our study was powered to detect only a major reduction in pregnancy rate. However, the study demonstrated similar pregnancy rates among vaccinated and unvaccinated patients (32.8% vs. 33.1%). To enable confirmation of our results that show no harmful effect on the clinical pregnancy rate with a lesser reduction, a larger group would be needed. Our study was powered to detect a difference of 1.4 oocytes retrieved and demonstrated negligible differences between groups in all comparisons.

RESULTS

A total of 200 patients met the inclusion criteria and were matched to 200 control patients of similar age that were not vaccinated or previously infected with COVID-19. The mean (range) time from the second vaccination to oocyte retrieval was 30.63 (14–68) days. The mean participant's age was similar between the study and control groups (36.04 vs. 36.11, respectively; $P=.92$), as were the mean partner's age (37.51 vs. 37.38, $P=.54$), smoking rates (13.3% vs. 15.2%, $P=.61$), and mean BMI (24.48 vs. 24.36, $P=.87$). No differences were observed regarding obstetric history, infertility cause, and number of prior IVF treatments.

The groups had similar treatment protocols and ovulation-triggering and fertilization methods. Patients in the study and control groups had similar cycle characteristics in terms of total GT use (2,938.04 vs. 2,780.14 IU, $P=.14$), days of stimulation (9.90 vs. 10.25, $P=.62$), maximal E2 levels (7,388 vs. 8,070 pmol/L, $P=.24$), and endometrial thickness on the day of ovulation triggering (9.60 vs. 9.72 mm, $P=.58$).

The mean number of oocytes retrieved per cycle (10.63 vs. 10.72, $P=.93$) and the maturation rate in intracytoplasmic sperm injection cycles (83.82% vs. 79.56%, $P=.17$) were similar between groups. Data are presented in Table 1.

Freeze-All Cycles

A total of 113 patients (66 in the study group and 47 in the control group) underwent freeze-all cycles due to fertility preservation (medical or social), need for genetic analysis, surrogacy, or ovarian hyperstimulation. There were no differences in age (34.61 vs. 35.36, $P=.28$), partner's age

TABLE 3

Clinical outcomes of vaccinated vs. unvaccinated patients in embryo transfer cycles.

	Unvaccinated (N = 133)	Vaccinated (N = 128)	*P* value
Days from vaccination to retrieval	—	30.38 (28.05, 32.71)	—
Range		14.00–68.00	
Protocol (%)			
MNC	7.0(5.3)	4.0 (3.2)	.93
Antagonist	109.0 (82.6)	107.0 (84.9)	
Long luteal	10.0 (7.6)	10.0 (7.7)	
Short	5.0 (3.8)	4.0 (3.2)	
Combined	1.0 (0.8)	1.0 (0.8)	
Ovulation triggering (%)			
Dual	70.0 (54.3)	76.0 (63.3)	.31
hCG	42.0 (32.6)	33.0 (27.5)	
GnRH agonist	17.0 (13.2)	11.0 (9.2)	
Stimulation days	9.59 (9.05, 10.12)	9.73 (8.94, 10.52)	.83
Total Gonadotropins dose	2,634.90 (2,406.74, 2,863.06)	2,980.45 (2,749.12, 3,211.77)	.01
E2 on the day of ovulation triggering pmol/L	6,199.54 (5,358.01, 7,041.07)	5,896.69 (5,113.34, 6,680.04)	.70
Endometrial thickness (mm)	9.80 (9.41, 10.20)	9.67 (9.28, 10.06)	0.72
Oocytes retrieved	8.32 (7.38, 9.27)	8.47 (7.52, 9.42)	0.78
Fertilization method (%)			
ICSI	64.0 (48.5)	65.0 (51.2)	.85
IVF	19.0 (14.4)	19.0 (15.0)	
ICSI/IVF	49.0 (37.1)	43.0 (33.9)	
MII oocytes/oocytes retrieved (%) - ICSI	80.07 (74.09–86.04)	84.63 (79.62–89.65)	.35
Fertilization rate (pronuclei/total oocytes)	61.98 (57.37–66.60)	64.81 (60.69–68.93)	.51
Frozen embryos per cycle			
Total	1.22 (0.91–1.53)	1.53 (1.16–1.91)	.42
Day 2/3	1.07 (0.74–1.41)	1.43 (0.91–1.95)	.51
Day 5	1.07 (0.74–1.40)	1.41 (1.08–1.74)	.11
Day 6	0.45 (0.14–0.75)	0.48 (0.15–0.82)	.75
Embryos transferred per cycle (%)			
1	73.0 (54.9)	70.0 (54.7)	.96
2	54.0 (40.6)	53.0 (41.4)	
3	6.0 (4.5)	5.0 (3.9)	
Day of transfer/total transfers (%)			
Day 2	31.0 (25.4)	16.0 (13.7)	.07
Day 3	70.0 (56.9)	76.0 (65.0)	
Day 5	22.0 (17.9)	25.0 (21.4)	
Top transferred embryo grade (grade/total cycles) (%)			
A	77.0 (57.9)	71.0 (55.5)	.89
B	39.0 (29.3)	41.0 (32.0)	
C	17.0 (12.8)	16.0 (12.5)	
Clinical pregnancy rate (%)	44.0 (33.1)	42.0 (32.8)	.96
Chemical pregnancy rate (%)	13.0 (9.8)	6.0 (4.7)	.11

Note: Data are presented as mean (95% confidence interval) or counts (percentage). MNC- modified natural cycle. Combined protocol = agonist administered for 2–3 days and then replaced by an antagonist. E2 = estradiol; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; MII = metaphase II; MNC = modified natural cycle; short protocol = agonist administered from day 1 of menstruation.

Avraham. COVID-19 vaccination and infertility. Fertil Steril 2022.

(35.21 vs. 36.89, *P*=.13), smoking rates (11.3%, 14.0%, *P*=.69), or mean BMI (24.0 vs. 23.51, *P*=.70) between groups or in obstetric histories, infertility cause, and prior number of IVF treatments. The number of previous transfers was significantly higher in the control group but was not considered clinically relevant. Data are shown in Supplemental Table 1 (available online).

The mean (range) number of days from vaccination to oocyte retrieval was 29.44 (14–62) days. There were no differences in the type of protocol, ovulation trigger, and fertilization method between both groups.

Patients in the study and control groups were administered similar GT dosages during stimulation (2,857.72 vs. 3,103.24 IU, *P*=.27), reached similar maximal E2 levels

TABLE 4

Logistic regression model for pregnancy rate in fresh embryo transfer cycles.

Variable name	OR	Lower limit		Upper limit	*P* value
Age (y)	0.92	0.86		0.98	.02
Number of previous transfers	0.91	0.80		1.04	.18
Embryo grade	—	—		—	.05
C			*Reference*		
A	3.85	1.25		11.89	.01
B	2.79	0.85		9.11	.09
Vaccination	—	—		—	*.49*
No			*Reference*		
Yes	1.22	0.68		2.19	—

Note: A = top-quality embryo; B = good-quality embryo; C = impaired-quality embryo; OR = odds ratio.

Avraham. COVID-19 vaccination and infertility. Fertil Steril 2022.

(11,249 vs. 10,157 pmol/L, *P*=.82), and had comparable endometrial thickness on the day of ovulation triggering (9.39 vs. 9.49 mm, *P*=.67).

The mean number of oocytes retrieved per cycle was 14.88 in the study group compared with 13.62 in the control group (*P*=.95), with similar maturation and fertilization rates (86.01% vs. 77.66%, *P*=.06, and 55.43% vs. 54.29%, *P*=.73, respectively). The mean number of frozen embryos per cycle was similar both overall (3.59 vs. 3.28, *P*=.80) and for cleavage embryos or day 5 blastocysts individually. Significantly more day 6 blastocysts were frozen per cycle in the study group (1.92 vs. 0.58, *P*=.02) (Table 2).

Cycle Outcomes After Fresh Embryo Transfer

A total of 261 transfer cycles were analyzed, 128 from vaccinated women and 133 from unvaccinated women. There were no differences between groups in age (36.70 vs. 36.39, *P*=.55), partner's age (38.72 vs. 37.60, *P*=.64), smoking rates (13.9%, 15.5%, *P*=.73), or mean BMI (24.87 vs. 24.64, *P*=.73) as well as in obstetric history, infertility cause, and number of prior IVF treatments (Supplemental Table 2, available online).

The mean (range) number of days from vaccination to oocyte retrieval was 30.38 (14–68) days. No difference was demonstrated in the type of protocol, ovulation trigger, and fertilization method between both groups. Patients in the study group consumed higher total dosages of GTs (2,980.45 vs. 2,634.90 IU, *P*=.01), needed similar periods of stimulation (9.73 vs. 9.59 days, *P* =.83), and reached similar maximal E2 levels (5,896 vs. 6,199 pmol/L, *P*=.7) and similar endometrial thickness on the day of ovulation triggering (9.67 vs. 9.80 mm, *P*=.72). The number of embryos transferred per cycle and the day of transfer were similar in both groups (*P*=.96 and *P*=.07), as were the grades of transferred cleavage embryos and blastocysts (*P*=.89) and mean number of surplus embryos frozen per cycle (1.53 vs. 1.22, *P*=.42),

Importantly, there were no differences in the clinical pregnancy rate (32.8% vs. 33.1%, *P*=.96) or chemical pregnancy rate (4.7% vs. 9.8%, *P*=.11) between the study and control groups, respectively. Furthermore, no difference was observed in the number of oocytes retrieved per cycle (mean, 8.47 vs. 8.32, *P*=.78), with similar maturation and fertilization rates (84.63% vs. 80.07%, *P*=.35, and 64.81% vs. 61.98%, *P*=.51, respectively) (Table 3).

In a logistic regression model, variables that were related to pregnancy rates were age (*P*=.02) and embryo quality (*P*=.05). Vaccination status had no effect on pregnancy rates (*P*=.49). A linear regression model demonstrated no effect of vaccination status on oocyte yield (*P*=.84), whereas age remained a significant factor, reducing the number of oocytes by 0.6 for every additional year of age (*P*<.001) (Tables 4 and Supplemental Table 3, available online). The same models were applied to cycles of vaccinated patients only and found no association between the number of days from vaccination and pregnancy rates (odds ratio, 1.02 [95% CI, 0.98–1.05, *P*=.35]) or oocyte yields (slope, 0.02 [95% CI, −0.07to 0.11, *P*=.64).

In a subanalysis of the main outcomes stratified by age (≥39 years), vaccination status had no effect on pregnancy rates or oocyte yield in both age groups (Supplemental Table 4, available online).

DISCUSSION

In this retrospective cohort study of patients who underwent IVF treatments, the ovarian response and pregnancy rates were similar in patients who were vaccinated with the COVID-19 mRNA vaccine before IVF treatment compared with those in unvaccinated women. Concerns that the vaccine may affect fertility treatment outcomes were not supported. The theoretical concept of the supposed similarity between the SARS-CoV-2 spike protein and the syncytin protein that is speculated to take part in the fertilization process and the formation of the placenta has led to the assumption that the vaccine may induce an immune response that would affect implantation and pregnancy (5). Our results confirm the findings of an earlier small study that showed similar treatment outcomes in terms of oocyte yield and embryo quality in 36 women who underwent ovarian stimulation after vaccination in comparison with their prior treatment (7). Moreover, despite concerns (11, 12) that the virus itself may harm steroidogenesis and folliculogenesis through the ovarian renin-angiotensin axis or through creating a systematic cytokine storm (7), to our knowledge, only 1 study has been published regarding the effect of COVID-19 on ovarian function and demonstrated

no detrimental effect on function of the ovarian follicle among 9 patients who recovered from COVID-19 infection. The study was limited by the small sample size and long interval from infection, which may have missed short-term effect on ovarian function (13). Our results demonstrate similar oocyte yields and fertilization rates among vaccinated and unvaccinated women. These results are also supported by a very recent study that showed similar antimullerian hormone levels before and 3 months after the COVID-19 vaccination (14). Although antimullerian hormone is considered the test of choice for ovarian reserve estimation (14), it has some limitations (15), and our study's strength is that it demonstrated that the vaccine did not harm ovarian function during IVF treatments in practice. Therefore, taking into account the potential harm of the infection itself on fertility, the already proven worse pregnancy outcomes (16) among pregnant women with COVID-19 infection, and the higher risk of infection among unvaccinated pregnant women (17), it seems reasonable to reduce infection risk through vaccination.

Our study examined pregnancy rates that have not been previously published in a controlled study and found similar chemical and clinical pregnancy rates. Preliminary reports on vaccine safety in pregnant women found similar miscarriage rates among vaccinated women compared with historical data from the literature. However, concern has been raised with regard to the proportion of miscarriages in the vaccinated group since it may not reflect true postvaccination occurrence. It is possible that early pregnancy losses were not recognized (2) because they were not followed up from menstruation, as were the pregnancies followed in our study, and as a consequence, early placentation failures may have been missed. The results of our study strengthen the notion that it is unlikely that the vaccine would generate a response that may interfere with placentation. Further studies are needed to evaluate the safety of the vaccine beyond the eighth week of pregnancy because long-term pregnancy outcomes were beyond the scope of this study and require further follow-up.

The limitations of our study include its retrospective nature and the different treatment protocols used. However, our sample size was sufficient to control for this variable, and vaccination status was found to have no effect on pregnancy rates and oocyte yield when regression models were applied. Thus, our interpretation of treatment outcomes should be valid regardless of treatment protocol. An additional limitation is the lack of information about vaccination or past-infection status of the male partners. One would assume that if unbalanced, the proportion of vaccinated males would be higher in the study group because partners tend to make similar choices with regard to vaccine administration, thus only strengthening our conclusion that the vaccine had no detrimental effect on fertility (18). Furthermore, although more research is needed, preliminary data have shown that vaccination has no effect on sperm parameters (6). Some studies have suggested that the infection itself can have an impact on sperm parameters (19), but data are still lacking regarding the severity and infection status at the time of semen collection.

The wide range of time from vaccination to oocyte retrieval (14–68 days), similar number of oocytes retrieved, and increased risk of complications when infected with COVID-19 during pregnancy strengthen the recommendation to administer the vaccine before IVF treatments. The similar outcomes in vaccinated and unvaccinated women aged >39 years are reassuring inasmuch as the vaccine had no influence on treatment outcomes even in a population with reduced ovarian reserve.

The results from the current study add valuable information to the ongoing debate concerning timing of vaccination (20) during the fertility treatment process. Delaying vaccination until conception may lead to missed opportunities to receive the vaccine because its availability may change over time (18).

CONCLUSION

In conclusion, this study found no effect of COVID-19 mRNA vaccine on oocyte yield during hormonal stimulation or on pregnancy rates during IVF treatments. Thus, we recommend considering COVID-19 vaccination before commencing IVF treatments to reduce the risk of SARS-CoV-2 infection during pregnancy.

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/33674

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Vacunación contra la enfermedad del coronavirus 2019 y resultados de tratamientos de infertilidad.

Objetivo: Evaluar la influencia de la vacuna de ácido ribonucleico mensajero contra la enfermedad por coronavirus 2019 (COVID-19) en la respuesta ovárica y los resultados de tratamientos de fecundación in vitro (FIV).

Diseño: Estudio de cohorte retrospectivo.

Lugar: Centro médico terciario adscrito a una universidad y a un centro médico privado.

Paciente(s): El estudio incluyó un total de 400 pacientes, 200 mujeres vacunadas y 200 mujeres no vacunadas de la misma edad, que se sometieron a tratamientos de FIV desde enero a abril de 2021.

Intervención(es): Ninguna.

Medida(s) de resultado principal: El número medio de ovocitos recuperados y las tasas de embarazo clínico en pacientes vacunadas frente a no vacunadas.

Resultado(s): Un total de 200 pacientes se sometieron a la extracción de ovocitos entre 14 y 68 días después de recibir la vacuna contra la COVID-19. No se encontraron diferencias en el número medio de ovocitos recuperados por ciclo (10,63 frente a 10,72) entre pacientes vacunadas y no vacunadas. Entre las 128 pacientes vacunadas y las 133 no vacunadas que se sometieron a transferencias de embriones frescos, no se observó diferencias en las tasas de embarazo clínico (32,8% frente a 33,1%), con 42 y 44 embarazos clínicos, respectivamente. Las tasas de fecundación y la media del número de embriones criopreservados fue similar entre los 2 grupos en los ciclos de congelación total (55,43 % frente a 54,29 % y 3,59 frente a 3,28, respectivamente). Entre las pacientes vacunadas y no vacunadas que se sometieron a transferencias de embriones frescos, no se observaron diferencias en la tasa de fecundación (64,81% frente a 61,98%) ni en la calidad de los embriones transferidos. Los modelos de regresión aplicados no demostraron ningún efecto de la vacuna sobre el rendimiento de los ovocitos y las tasas de embarazo.

Conclusión(es): La vacuna de ácido ribonucleico mensajero COVID-19 no afectó a la respuesta ovárica ni a las tasas de embarazo en los tratamientos de FIV. Las mujeres deben vacunarse contra COVID-19 antes de intentar concebir a través de tratamientos de FIV, dado el mayor riesgo de enfermedad grave en mujeres embarazadas.