



Effects of COVID-19 vaccination status, vaccine type, and vaccination interval on IVF pregnancy outcomes in infertile couples

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Abstract

Purpose This study aimed to explore whether the coronavirus disease (COVID-19) vaccination of both partners in infertile couples, different types of COVID-19 vaccines, and the interval between complete vaccination and oocyte retrieval or embryo transfer (ET) affect the quality of embryos and pregnancy rates in in vitro fertilization (IVF).

Methods This was a prospective cohort study, comprising 735 infertile couples conducted between December 6, 2021, and March 31, 2022, in a single university hospital-based IVF center. The patients were divided into different groups according to the vaccination status of both partners in infertile couples, type of vaccine, and interval between complete vaccination and IVF treatment. The embryo quality and pregnancy rates were compared among different groups.

Results The results showed that embryo quality and pregnancy rates had no significant differences among different groups. The multivariate regression model showed that the vaccination status of both infertile couples, types of vaccines, and intervals had no significant effects on the clinical pregnancy rate.

Conclusions The vaccination status of both partners in infertile couples, different types of vaccines, and time intervals have no effect on embryo quality and pregnancy rates in IVF. This is the first study to compare the vaccination status of both partners in infertile couples and the impact of different vaccine types on pregnancy rates and embryo quality in detail. Our findings provide evidence of vaccine safety for infertile couples wishing to undergo IVF treatment. This evidence is crucial for decision-making by clinicians and policymakers involved in IVF cycles.

Keywords COVID-19 vaccine · Infertile couple · IVF · Pregnancy rate · Embryo quality

Introduction

As of April 3, 2022, a total of 489,642,060 and 483,750 confirmed coronavirus disease (COVID-19) cases were reported globally and in China, respectively [1]. Due to the general

susceptibility of the population to the virus, the development and use of vaccines have become a critical strategy in controlling the spread of the virus. Currently, three types of COVID-19 vaccines are approved for use in China, including inactivated vaccine products, adenovirus vector vaccines, and recombinant subunit vaccines. As of March 31, 2022,

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China had administered 3.27 billion COVID-19 vaccine doses, with a total of 1.28 billion people vaccinated, representing 90.63% of the country's total population; 1.24 billion people have completed vaccination; and the number of people vaccinated in the whole process accounted for 88.11% of the total population of the country [2].

Based on the understanding of vaccine safety, candidates for the inactivated vaccines promoted in China also include people who are planning to become pregnant or receive assisted reproductive technology (ART) treatment [3]. The latest consensus documents published globally do not restrict COVID-19 vaccination of people of childbearing age [4, 5]. However, media doubts about vaccine safety, such as claims that the vaccine may cause female infertility [6], have emerged. These have caused concern among women who are planning to conceive, leading them to delay their conception plans [7, 8]. One reason for the vaccine safety concerns is that there may be homology between the placental syncytin-1 protein and the COVID-19 spike protein targeted by the vaccine, which could lead to infertility [9]. However, immunology experts questioned that the sequence similarity between proteins is extremely limited and unlikely to cause cross-reactivity [9, 10]. Nonetheless, because of these concerns, it is crucial to explore the vaccination status of couples who plan to get pregnant.

Vaccination rates in the population planning pregnancies are low due to concerns about reproductive function and potential offspring safety. Therefore, it is crucial to explore the impact of COVID-19 vaccination on embryo quality and pregnancy outcomes in infertile patients treated with ART. Orvieto et al. were the first to report the effect of mRNA vaccines on embryo quality and IVF outcomes [11]. A few studies on the effects of mRNA vaccines on embryo quality and pregnancy outcomes have been conducted in the USA and Israel [12–15]. To date, only one study has investigated the effect of inactivated vaccines on embryo quality and pregnancy outcomes in infertile patients treated with ART [16]. However, the study did not include vaccinations in both partners in the infertile couple. Moreover, the study only analyzed inactivated vaccines and excluded the other two types of vaccines approved for use in China [16]. Therefore, the current study aimed to investigate the (1) impact of the vaccination status of both partners in infertile couples on IVF embryo quality and pregnancy rates, (2) effect of different types of COVID-19 vaccines on embryo quality and pregnancy rates, and (3) effect of the interval between complete vaccination and oocyte retrieval on embryo quality and the interval between complete vaccination and ET on pregnancy rates.

Materials and methods

Study design

This prospective cohort study was conducted at the Reproductive Medicine Centre affiliated to a university hospital.

This study established the vaccination status of both partners in infertile couples treated with IVF and assessed its impact on embryo quality and pregnancy outcomes. A total of 735 infertile couples participated in the survey between December 6, 2021, and March 31, 2022.

The inclusion criteria were as follows: (1) women and men aged 20–44 and 20–55 years, respectively; (2) couples who were diagnosed with infertility and intended to undergo ART treatment, including IVF, intracytoplasmic sperm injection (ICSI), fresh embryo transfer (fresh ET), and frozen embryo transfer (frozen ET); and (3) the first ET cycle. The exclusion criteria were the following: (1) acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in one or both partners in a couple; (2) only one dose of vaccination; (3) uterine malformations confirmed by three-dimensional ultrasound or hysteroscopy, including septate uterus, unicornuate uterus, double uterus, submucosal uterine fibroids, or intramural fibroids larger than 5 cm; (4) intrauterine adhesions; (5) untreated hydrosalpinx visible under ultrasound; (6) using freezing and thawing eggs; (7) using sperm from a sperm bank; (8) sperm extraction through surgery; (9) chromosomal karyotype abnormalities in one or both partners in couples; (10) combined with medical diseases, such as hypertension, heart disease, diabetes, liver and kidney disease, and severe anemia, and history of venous thrombosis, pulmonary embolism, cerebrovascular events, and malignant tumor; (11) loss to follow-up or data missing; and (12) presence of any factor that could affect the evaluation of the results. All patients voluntarily participated in this study. The participants were not paid to participate in the study.

IVF protocol

Clinicians chose controlled ovarian stimulation (COS) protocols, including antagonist, long, short, and microstimulation programs, according to the patient's age, ovarian function, basic hormone levels, and causes of infertility. The dose of the drug was adjusted according to serum hormone levels and follicular development under ultrasound. When two of the dominant follicles reached 18 mm or one exceeded 20 mm, the human chorionic gonadotropin (HCG) or decapeptyl trigger was used. Transvaginal ultrasound-guided oocyte retrieval was performed 36–38 h later. The method of fertilization (IVF or ICSI) was selected according to the condition of the man's semen and whether there was a history of fertilization failure. The transfer strategy (fresh ET or frozen ET) was formulated considering factors such as endometrial thickness, HCG daily serum hormone level, and ovarian hyperstimulation risk.

Data collection

First, data on the following baseline and cycle characteristics were collected: age, body mass index (BMI), type of

infertility, infertility diagnosis, serum hormone levels, COS protocol, gonadotrophin (Gn) dosage, COS duration, and fertilization methods.

Second, data on laboratory parameters and pregnancy outcomes were collected. The laboratory parameters included the number of oocytes retrieved, two pro-nuclei (2PN) embryos, cleavage, high-quality embryos, and blastocysts formation. The pregnancy outcomes included the biochemical pregnancy rate (BPR) and clinical pregnancy rate (CPR). A high-quality embryo was defined as seven or more blastomeres on day 3, equally sized blastomeres, and $\leq 10\%$ fragmentation. The blastocyst formation rate was defined as the number of blastocysts formed on days 5 and 6/number of cultured D3 cleavage stage embryos. Clinical pregnancy referred to the 4 weeks (± 2 days) after ET, where the intrauterine gestational sac, fetal pole, and fetal heartbeat could be detected by vaginal ultrasound examination. The CPR was calculated as follows: $\text{CPR} = \text{number of pregnant mothers with clinical pregnancy/women enrolled in the corresponding group who had undergone ET} \times 100\%$.

All infertile couples were screened for COVID-19 infection, including nasopharyngeal swab testing, symptom questionnaires, epidemiological investigations, and temperature checks, prior to each patient visit. The vaccine administration information, including vaccine manufacturer, type, dose, date, and batch number, were ascertained using immunization records through a mobile app (such as the client of the state council, the health codes of various provinces and cities, including Liaoshitong, Jiankangbao, Suishenma, Longjiangma, and Jijiangma) when the patients agreed to participate in this study.

Grouping criteria

- 1) Grouping according to the vaccination status of both partners in infertile couples: group A, both partners in infertile couples had received two doses of COVID-19 vaccines; group B, infertile women who were vaccinated with two doses, and the male partners were unvaccinated; group C, infertile men who received two doses of the vaccine but the female partners were unvaccinated; and group D, neither spouse had been vaccinated.
- 2) Grouping by vaccine manufacturer and type (inactivated virus vaccines, adenovirus vector vaccines, or recombinant subunit vaccines): group I, inactivated SARS-CoV-2 vaccine (Sinopharm; Beijing/Wuhan Institute of Biological Products); group II, inactivated SARS-CoV-2 vaccine (Sinovac; Beijing Sinovac Biotech Co., Ltd.); group III, recombinant tandem-repeat dimeric receptor-binding domain-based protein subunit vaccine (ZF2001; Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology, Chinese Academy of Sciences); and group IV, unvaccinated.

- 3) Grouping was done according to time interval from complete vaccination to oocyte retrieval or ET. Laboratory parameters were compared by group by time interval from complete vaccination to oocyte retrieval. Pregnancy outcomes were compared by group by time interval from complete vaccination to first ET: group 1, < 3 months; group 2, 3–6 months; group 3, > 6 months; and group 4, unvaccinated.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). Categorical variables are summarized as counts and percentages, and continuous variables are expressed as means and standard deviations (SDs). Propensity score matching (PSM) was performed to balance baseline characteristics between the vaccinated and unvaccinated groups at a ratio of 1:2. Continuous variables of baseline characteristics between vaccinated and unvaccinated groups were compared by independent samples *t* test, and categorical variables were compared by chi-square test. Differences in IVF laboratory parameters within each group were analyzed using one-way analysis of variance (ANOVA) with post hoc multiple comparisons assuming equal variances (Bonferroni) and not assuming equal variances (Dunnnett T3). In the chi-square test, *z* test was used to compare proportions (Bonferroni method). Pregnancy outcomes within each group were analyzed using the chi-square test. Effect sizes were used to evaluate the strength of each statistical analysis and were measured with η^2 for ANOVA and Cramer V for chi-square (χ^2) tests. The larger the value, the greater the difference. The critical points for the small, medium, and large effect sizes for η^2 are 0.01, 0.06, and 0.14 and for Cramer V are 0.20, 0.50, and 0.80, respectively. A multivariate regression model was used to explore the factors that affect the CPR. All tests were two-tailed, and a *p* value < 0.05 indicated statistical significance.

Results

Infertile couples' demographic characteristics

A total of 735 (221 vaccinated and 514 unvaccinated) infertile couples were included in this study. Table 1 shows the baseline characteristics of the participants. After PSM, there were 214 and 340 couples in the vaccinated and unvaccinated groups, respectively. The propensity score distributions are presented in Fig. 1. No significant differences were found in age, BMI, type of infertility, infertility

causes, hormone level, cycle characteristics, and fertilization methods between the two groups after PSM (Table 1).

Impact of the vaccination status of both partners in infertile couples on embryo quality and pregnancy rates

According to the vaccination status of both partners in infertile couples, the participants were divided into four groups: group A, 155 couples; group B, 19 couples; group C, 40 couples; and group D, 340 couples. There were no significant differences in laboratory results (number of oocytes retrieved, fertilization rate, cleavage rate, high-quality

embryos rate, and blastocyst formation rate) among the four groups ($p > 0.05$). The embryos transfer stage (cleavage or blastocyst) and type (fresh or frozen) had significant differences among the four groups ($p < 0.05$). However, no significant differences were noted in biochemical and clinical pregnancy rates among the four groups ($p > 0.05$) (Table 2).

Impact of different types of vaccines on embryo quality and pregnancy rates

The infertile women were divided into four groups according to vaccine manufacturer and type: group I, 63 women;

Table 1 Demographic characteristics of the participants

	Before PSM		<i>p</i> value	After PSM		<i>p</i> value
	Vaccinated (<i>n</i> = 221)	Unvaccinated (<i>n</i> = 514)		Vaccinated (<i>n</i> = 214)	Unvaccinated (<i>n</i> = 340)	
Female baseline characteristics						
Age (years)	33.15 ± 3.55	32.11 ± 4.21	< 0.01**	33.04 ± 3.46	32.69 ± 4.19	0.30
BMI (kg/m ²)	23.57 ± 3.45	23.26 ± 3.56	0.21	23.57 ± 3.46	23.60 ± 3.57	0.92
Type of infertility (<i>n</i> , %)			0.94			0.21
Primary	140 (63.3)	324 (63.0)		136 (63.6)	198 (58.2)	
Secondary	81 (36.7)	190 (37.0)		78 (36.4)	142 (41.8)	
Infertility cause (<i>n</i> , %)			< 0.01**			0.24
Male factor	20 (9.0)	103 (20.0)		20 (9.3)	54 (15.9)	
Tubal factor	93 (42.1)	126 (24.5)		83 (38.8)	119 (35.0)	
Multifactor	23 (10.4)	41 (8.0)		29 (13.6)	44 (12.9)	
Endometriosis	17 (7.7)	24 (4.7)		15 (7.0)	15 (4.4)	
Couple	59 (26.7)	210 (40.9)		59 (27.6)	100 (29.4)	
Unexplained	9 (4.1)	10 (1.9)		8 (3.7)	8 (2.4)	
FSH	10.27 ± 44.63	9.18 ± 46.35	0.20	10.32 ± 45.35	10.26 ± 56.92	0.99
LH	7.60 ± 9.36	6.95 ± 6.81	0.41	7.54 ± 9.48	6.73 ± 6.78	0.24
AMH	4.01 ± 3.86	4.48 ± 3.74	< 0.01**	4.00 ± 3.77	4.14 ± 3.70	0.66
E ₂ on the trigger day	3245.36 ± 2419.23	4290.73 ± 3591.38	0.01*	3295.68 ± 2438.92	3646.43 ± 2761.86	0.13
Male baseline characteristics						
Age (years)	34.25 ± 4.33	33.49 ± 4.77	0.02*	34.20 ± 4.36	33.90 ± 4.63	0.44
BMI (kg/m ²)	26.11 ± 4.10	25.66 ± 3.65	0.30	26.02 ± 4.00	25.62 ± 3.73	0.24
Cycle characteristics						
COH protocol (<i>n</i> , %)			0.09			0.05
GnRH antagonist	143 (64.7)	331 (64.4)		139 (65.0)	208 (61.2)	
Mild stimulation	11 (5.0)	11 (2.1)		11 (5.1)	5 (1.5)	
Long agonist	37 (16.7)	117 (22.8)		36 (16.8)	81 (23.8)	
Short agonist	8 (3.6)	15 (2.9)		8 (3.7)	12 (3.5)	
Others	22 (10.0)	40 (7.8)		20 (9.3)	34 (10.0)	
Total Gn dosage (IU)	2679.30 ± 784.91	2534.17 ± 879.64	< 0.01**	2643.93 ± 751.62	2657.98 ± 908.20	0.85
COH duration (days)	9.99 ± 2.10	9.80 ± 2.00	0.111	9.93 ± 2.08	9.91 ± 1.81	0.90
Fertilization methods (<i>n</i> , %)			0.01*			0.31
IVF	119 (53.8)	222 (43.2)		117 (54.7)	172 (50.6)	
ICSI	69 (31.2)	223 (43.4)		66 (30.8)	126 (37.1)	
IVF + ICSI	33 (14.9)	69 (13.4)		31 (14.5)	42 (12.4)	

Note: * $p < 0.05$, ** $p < 0.01$

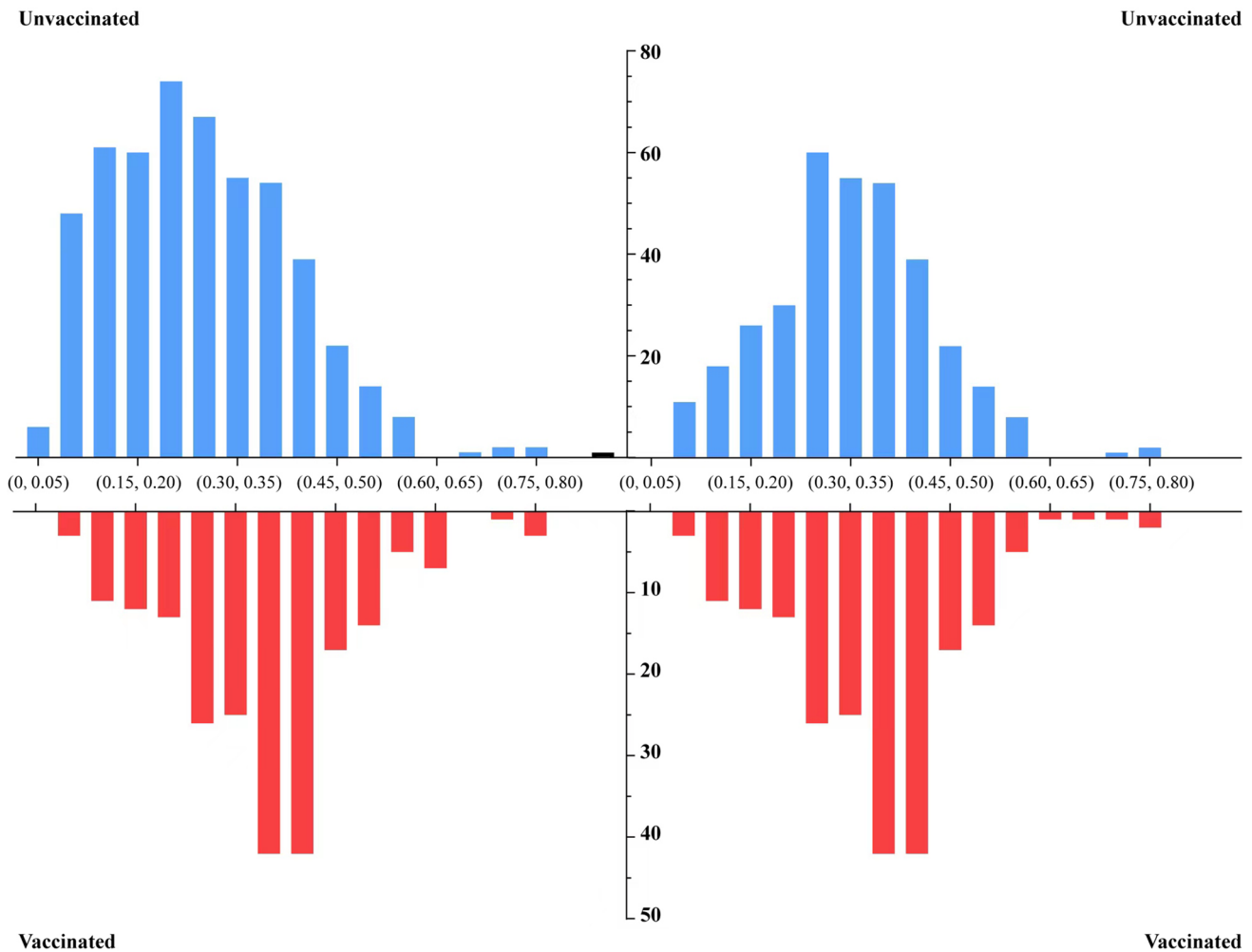


Fig. 1 Propensity score matching of vaccinated and unvaccinated couples before and after matching

group II, 100 women; group III, 11 women; and group IV, 380 women. Significant differences were observed in ET embryo quality and type (fresh or frozen) among the four groups ($p < 0.05$). No significant differences were found in other laboratory results and pregnancy outcomes among the four groups ($p > 0.05$) (Table 3).

Impact of the interval between complete vaccination and oocyte retrieval on embryo quality and the interval between complete vaccination and ET on pregnancy rates

The infertile women were then divided into four groups according to the time interval from complete vaccination to oocyte retrieval: group 1, 33 women; group 2, 103 women; group 3, 38 women; and group 4, 380 women. Significant differences were noted in cleavage rate among the four groups ($p < 0.05$). No significant differences were detected in other laboratory results among the four

groups ($p > 0.05$) (Table 4). The infertile women were further divided into four groups according to the time interval from complete vaccination to first ET: group 1, 14 women; group 2, 80 women; group 3, 42 women; and group 4, 359 women. The embryo transfer stage (cleavage or blastocyte) and type (fresh or frozen) had significant differences among the four groups ($p < 0.05$). No significant differences were found in pregnancy outcomes among the four groups ($p > 0.05$) (Table 4).

Multivariate regression analysis for the relevant factors that affect the CPR

The multivariable logistic regression models were used to analyze relevant factors that affect the CPR. The results reveal that infertile couples' age, number of embryos available, number of embryos transferred, embryo stage of ET (cleavage or blastocyte), and quality

Table 2 Impact of the vaccination status of both partners in infertile couples on IVF laboratory parameters and pregnancy outcomes

	Group A (n = 155)	Group B (n = 19)	Group C (n = 40)	Group D (n = 340)	Effect size (V or η^2)	p value
Age (female)	32.90 ± 3.29	33.00 ± 4.68	33.60 ± 3.49	32.69 ± 4.19	0.004	0.57
Age (male)	34.17 ± 4.20	33.84 ± 5.57	34.48 ± 4.42	33.90 ± 4.63	0.002	0.84
BMI (female)	23.45 ± 3.54	23.98 ± 3.28	23.83 ± 3.30	23.60 ± 3.57	0.001	0.89
BMI (male)	26.18 ± 3.90	25.97 ± 4.35	25.42 ± 4.27	25.62 ± 3.73	0.005	0.46
No. of oocytes retrieved	11.51 ± 7.72	12.74 ± 8.99	11.10 ± 7.24	11.43 ± 6.84	0.001	0.87
No. of 2PN	7.46 ± 5.28	8.16 ± 6.73	7.28 ± 5.02	7.75 ± 4.74	0.001	0.86
No. of cleaved embryos	7.44 ± 5.23	8.05 ± 6.52	7.23 ± 4.92	7.71 ± 4.68	0.001	0.87
No. of embryos available	6.35 ± 4.75	7.16 ± 6.11	6.43 ± 4.68	6.71 ± 4.50	0.002	0.81
No. of good quality embryos on day 3	4.49 ± 3.81	5.00 ± 4.61	4.88 ± 4.08	4.53 ± 3.70	0.001	0.90
Normal fertilization rate	0.68 ± 0.21	0.68 ± 0.24	0.67 ± 0.20	0.71 ± 0.20	0.006	0.34
Cleavage rate	1.00 ± 0.04	0.99 ± 0.02	1.00 ± 0.01	1.00 ± 0.02	0.001	0.95
Good quality embryo rate	0.58 ± 0.30	0.67 ± 0.22	0.65 ± 0.30	0.64 ± 0.54	0.004	0.50
Blastocyst formation rate	0.65 ± 0.27	0.73 ± 0.26	0.59 ± 0.27	0.64 ± 0.30	0.005	0.54
No. of good quality blastocyst	2.88 ± 2.69	4.15 ± 4.78	2.93 ± 2.12	2.86 ± 2.94	0.006	0.48
No. of ET cycle (n)	132	16	32	327		
Endometrial thickness of ET (mm)	10.93 ± 2.41	9.60 ± 1.62	10.53 ± 1.84	10.44 ± 2.30	0.014	0.07
No. of embryos transferred	1.48 ± 0.50	1.38 ± 0.50	1.22 ± 0.42	1.43 ± 0.50	0.015	0.05
ET cycle type, n (%)					0.182	< 0.05*
Fresh ET	70 (53.03)	8 (50.00)	14 (43.75)	108 (33.03)		
Frozen ET	62 (46.97)	8 (50.00)	18 (56.25)	219 (66.97)		
Embryo stage at ET, n (%)					0.150	< 0.05*
Cleavage	86 (65.15)	8 (50.00)	11 (34.38)	175 (53.52)		
Blastocyst	46 (34.85)	8 (50.00)	21 (65.63)	152 (46.48)		
Quality of transferred embryos, n (%)					0.110	0.06
High	107 (81.06)	14 (87.50)	29 (90.63)	287 (87.77)		
High + middle	16 (12.12)	2 (12.50)	0	16 (4.89)		
Middle	9 (6.82)	0	3 (9.38)	24 (7.34)		
Biochemical pregnancy rate, n/N (%)	89/132 (67.42)	8/16 (50.00)	21/32 (65.63)	211/327 (64.53)	0.062	0.58
Clinical pregnancy rate, n/N (%)	70/132 (53.03)	7/16 (43.75)	16/32 (50.00)	170/327 (51.99)	0.033	0.91

Note: * $p < 0.05$

of transferred embryos were significantly correlated with CPR ($p < 0.05$). However, the vaccination status of infertile couples, types of vaccines, and intervals had no significant effects on CPR ($p > 0.05$) (Table 5).

Discussion

This prospective cohort study showed that the vaccination status of both partners in infertile couples (both vaccinated, only one vaccinated, and neither vaccinated) had no significant effect on embryo quality and pregnancy outcomes in IVF cycles. To our best knowledge, this is the first study to report the impact of COVID-19 vaccination of infertile couples on IVF outcomes. No significant differences in IVF outcomes were found according to the vaccination status of both partners in infertile couples;

therefore, we only included infertile women in the studies of vaccine types and intervals. Our study found that the type of vaccine and the interval of vaccination had no significant effect on IVF outcomes. This is the first prospective study to compare the effects of different types of COVID-19 vaccines on pregnancy outcomes of infertile couples.

There is a paucity of studies on the impact of COVID-19 vaccination of infertile patients on IVF outcomes, and some studies conducted in reproductive centers in the USA and Israel have revealed the safety of mRNA vaccines [11–15]. However, in China, there is only one recent retrospective study of infertile women receiving inactivated vaccines [16]. The abovementioned studies included only infertile women, and the current study is the first to provide first-hand evidence on the impact of the vaccination status of both partners in infertile couples on IVF.

Table 3 IVF laboratory parameters and pregnancy outcomes according to different types of vaccines

	Group I (n=63)	Group II (n=100)	Group III (n=11)	Group IV (n=380)	Effect size (V or η^2)	p value
Age (female)	33.54 ± 3.75	32.63 ± 3.25	31.91 ± 3.18	32.78 ± 4.13	0.006	0.40
Age (male)	34.90 ± 4.25	33.84 ± 4.36	32.45 ± 4.48	33.96 ± 4.61	0.007	0.27
BMI (female)	23.98 ± 3.33	23.29 ± 3.54	22.83 ± 4.16	23.63 ± 3.54	0.004	0.56
BMI (male)	25.80 ± 3.22	26.50 ± 4.40	25.10 ± 3.13	25.60 ± 3.79	0.009	0.20
No. of oocytes retrieved	12.59 ± 8.56	10.95 ± 7.16	12.55 ± 9.65	11.39 ± 6.88	0.004	0.51
No. of 2PN	8.14 ± 5.71	7.09 ± 5.23	8.18 ± 5.86	7.70 ± 4.77	0.004	0.57
No. of cleaved embryos	8.08 ± 5.58	7.07 ± 5.18	8.18 ± 5.86	7.66 ± 4.71	0.004	0.58
No. of embryos available	6.97 ± 5.29	6.04 ± 4.62	7.09 ± 5.28	6.68 ± 4.51	0.004	0.55
No. of good quality embryos on day 3	4.95 ± 4.21	4.30 ± 3.77	4.45 ± 3.17	4.57 ± 3.74	0.002	0.64
Normal fertilization rate	0.66 ± 0.18	0.68 ± 0.23	0.70 ± 0.21	0.70 ± 0.20	0.005	0.48
Cleavage rate	1.00 ± 0.01	1.00 ± 0.05	1.00 ± 0.00	1.00 ± 0.02	0.001	0.96
Good quality embryo rate	0.58 ± 0.30	0.59 ± 0.30	0.60 ± 0.26	0.64 ± 0.52	0.003	0.50
Blastocyst formation rate	0.63 ± 0.27	0.68 ± 0.27	0.63 ± 0.23	0.64 ± 0.30	0.003	0.78
No. of good quality blastocyst	2.70 ± 2.73	3.15 ± 3.20	4.40 ± 2.30	2.87 ± 2.87	0.005	0.55
No. of ET cycle (n)	53	86	9	359		
Endometrial thickness of ET (mm)	10.52 ± 2.49	10.91 ± 2.17	11.17 ± 3.48	10.45 ± 2.26	0.007	0.33
No. of embryos transferred	1.43 ± 0.50	1.50 ± 0.50	1.44 ± 0.53	1.42 ± 0.49	0.004	0.57
ET cycle type, n (%)					0.185	<0.05*
Fresh ET	24 (45.28)	49 (56.98)	5 (55.56)	122 (33.98)		
Frozen ET	29 (54.72)	37 (43.02)	4 (44.44)	237 (66.02)		
Embryo stage at ET, n (%)					0.110	0.10
Cleavage	33 (62.26)	56 (65.12)	5 (55.56)	186 (51.81)		
Blastocyst	20 (37.74)	30 (34.88)	4 (44.44)	173 (48.19)		
Quality of transferred embryos, n (%)					0.144	<0.05*
High	47 (88.68)	68 (79.07)	6 (66.67)	316 (88.02)		
High + middle	3 (5.66)	12 (13.95)	3 (33.33)	16 (4.46)		
Middle	3 (5.66)	6 (6.98)	0	27 (7.52)		
Biochemical pregnancy rate, n/N (%)	36/53 (67.92)	57/86 (66.28)	4/9 (44.44)	232/359 (64.62)	0.062	0.58
Clinical pregnancy rate, n/N (%)	27/53 (50.94)	47/86 (54.65)	3/9 (33.32)	186/359 (51.81)	0.055	0.68

Note: * $p < 0.05$

Impact of COVID-19 vaccine on pregnancy outcomes

A retrospective study conducted in the USA compared the pregnancy outcomes of 214 infertile patients vaccinated with BioNTech/Pfizer (BNT162b2) or Moderna (mRNA-1273) vaccines and 733 infertile patients who had not been vaccinated. The results showed no significant differences in CPR, BPR, and ongoing pregnancy rates between the two groups [12]. A study conducted in Israel analyzed the effect of patients' immunization after COVID-19 infection or vaccination with an mRNA vaccine on FET. The study compared the pregnancy outcomes of SARS-CoV-2-infected, vaccinated, and unvaccinated patients and found no significant difference in CPR, implantation rate, and ongoing pregnancy rate among the groups [13]. Moreover, a prospective observational cohort study also conducted in Israel compared pregnancy outcomes among 37 Pfizer-BioNTech-vaccinated and 22 unvaccinated infertile patients and found no

difference in CPR [14]. Another study conducted in the USA analyzed the effects of BioNTech/Pfizer (BNT162b2) and Moderna (mRNA-1273) vaccines on FET pregnancy outcomes. The study included 20 infected, 35 vaccinated, and 88 unvaccinated and uninfected individuals, and there was no significant difference in CPR, BPR, and ongoing pregnancy rates among the three groups [15]. A retrospective study conducted in China compared the pregnancy outcomes of 66 infertile women vaccinated with inactivated vaccines and matched 236 unvaccinated patients. The study found that CPR, BPR, and implantation rates were not significantly different between the two groups [16]. Furthermore, this was also the first study on the effects of inactivated vaccines on IVF-ET pregnancy outcomes in China [16]. However, the study had some limitations: The sample size was small, and it included only infertile women and only fresh ET. Consistent with the studies above, the current study found no effect of vaccination on pregnancy outcomes. Based on the

Table 4 IVF laboratory parameters according to the time interval between complete vaccination and oocyte retrieval

	Group 1	Group 2	Group 3	Group 4	Effect size (V or η^2)	p value
No. of oocyte retrieval cycle	33	103	38	380		
Age (female)	32.45 ± 3.84	33.00 ± 3.27	33.08 ± 3.64	32.78 ± 4.13	0.001	0.87
Age (male)	33.55 ± 3.98	34.15 ± 4.42	34.63 ± 4.53	33.96 ± 4.61	0.002	0.75
BMI (female)	23.10 ± 3.53	23.80 ± 3.65	23.09 ± 3.07	23.63 ± 3.54	0.003	0.63
BMI (male)	27.42 ± 5.12	25.65 ± 3.63	26.42 ± 3.38	25.60 ± 3.79	0.015	0.05
No. of oocytes retrieved	9.67 ± 6.44	11.81 ± 7.82	12.92 ± 8.85	11.39 ± 6.88	0.007	0.27
No. of 2PN	5.85 ± 4.45	7.71 ± 5.38	8.55 ± 6.13	7.70 ± 4.77	0.010	0.13
No. of cleaved embryos	5.85 ± 4.45	7.70 ± 5.32	8.42 ± 6.01	7.66 ± 4.71	0.010	0.15
No. of embryos available	4.97 ± 4.12	6.64 ± 4.85	7.18 ± 5.50	6.68 ± 4.51	0.009	0.19
No. of good quality embryos on day 3	3.70 ± 3.38	4.82 ± 3.98	4.55 ± 4.08	4.57 ± 3.74	0.004	0.54
Normal fertilization rate	0.64 ± 0.25	0.69 ± 0.21	0.68 ± 0.20	0.70 ± 0.20	0.006	0.35
Cleavage rate	1.00 ± 0.00	1.00 ± 0.03	0.99 ± 0.07	1.00 ± 0.02	0.019	<0.05*
Good quality embryo rate	0.64 ± 0.31	0.60 ± 0.28	0.51 ± 0.31	0.64 ± 0.52	0.006	0.34
Blastocyst formation rate	0.68 ± 0.28	0.65 ± 0.26	0.68 ± 0.30	0.64 ± 0.30	0.002	0.86
No. of good quality blastocyte	2.72 ± 2.24	2.87 ± 3.11	3.78 ± 3.10	2.87 ± 2.87	0.006	0.53
No. of ET cycle	14	80	42	359		
Age (female)	33.50 ± 3.82	32.24 ± 2.94	34.02 ± 3.96	32.74 ± 4.20	0.012	0.11
Age (male)	33.07 ± 4.58	33.59 ± 4.29	35.43 ± 4.39	33.95 ± 4.69	0.011	0.15
BMI (female)	23.23 ± 2.25	23.48 ± 3.53	23.46 ± 3.67	23.54 ± 3.50	0.001	0.99
BMI (male)	28.14 ± 5.47	25.82 ± 3.92	25.87 ± 3.56	25.61 ± 3.76	0.012	0.11
Endometrial thickness on the day of ET (mm)	12.00 ± 2.77	10.97 ± 2.44	9.92 ± 1.85	10.45 ± 2.26	0.025	<0.05*
No. of embryos transferred	1.64 ± 0.50	1.54 ± 0.50	1.38 ± 0.49	1.42 ± 0.49	0.014	0.07
ET cycle type, n (%)					0.202	<0.05*
Fresh ET	10 (71.43)	45 (56.25)	15 (35.71)	122 (33.98)		
Frozen ET	4 (28.57)	35 (43.75)	27 (64.29)	237 (66.02)		
Embryo stage at ET, n (%)					0.161	<0.05*
Cleavage	11 (78.57)	56 (70.00)	20 (47.62)	186 (51.81)		
Blastocyst	3 (21.43)	24 (30.00)	22 (52.38)	173 (48.19)		
Quality of transferred embryos, n (%)					0.103	0.11
High	12 (85.71)	65 (81.25)	35 (83.33)	316 (88.02)		
High + middle	1 (7.14)	11 (13.75)	4 (9.52)	16 (4.46)		
Middle	1 (7.14)	4 (5.00)	3 (7.14)	27 (7.52)		
Biochemical pregnancy rate, n/N (%)	11/14 (78.57)	53/80 (66.28)	24/42 (57.14)	232/359 (64.62)	0.068	0.51
Clinical pregnancy rate, n/N (%)	9/14 (64.29)	39/80 (48.75)	22/42 (52.38)	186/359 (51.81)	0.049	0.76

Note: * $p < 0.05$

abovementioned research, the current study is the first to report the effect of vaccination of both partners in infertile couples (both partners, only the woman, and only the man) on pregnancy outcomes.

Impact of COVID-19 vaccine on embryo quality

The findings of our study were consistent with those of Huang et al. [16] who found that COVID-19 vaccination had no effect on the quality of IVF embryos. A self-controlled before-and-after study which included 36 infertile patients has found that the number of oocytes retrieved, MII oocyte, fertilization rate, and embryo quality did not

decrease after two doses of an mRNA vaccine, compared with the previous cycle without vaccination [11]. This suggests that the vaccine has no adverse effect on the patient's ovarian reserve and gamete/embryo development. Orvieto et al. [11] believe that since IVF treatment is performed 7–85 days after vaccination, gametes obtained at this stage are exposed to a vaccine-induced generalized inflammatory response rather than an active infection-induced inflammatory response. However, neither of these responses interferes with the complex process of follicle formation and spermatogenesis [11]. Another study compared oocyte and embryo quality in 9 patients with COVID-19, 9 patients vaccinated with the BNT162b2 mRNA vaccine, and 14

Table 5 Multivariate regression analysis for the relevant factors that affect the CPR (1 = pregnant, 0 = nonpregnant)

Items	OR	95% CI	<i>p</i> value
Age (female)	1.08	1.00–1.17	0.04*
Age (male)	0.93	0.87–0.99	0.03*
BMI (female)	1.01	0.95–1.06	0.82
BMI (male)	0.98	0.93–1.03	0.36
FSH	0.98	0.92–1.03	0.41
AMH	1.02	0.95–1.09	0.59
Fertilization methods			
IVF	1.00		
ICSI	1.08	0.70–1.66	0.73
IVF+ICSI	0.88	0.47–1.62	0.67
Endometrial thickness on the day of ET	1.01	0.93–1.10	0.83
No. of embryos available	0.93	0.88–0.99	0.01*
Good quality embryo rate	0.69	0.34–1.40	0.30
No. of embryos transferred			
One	1.00		
Two	0.39	0.19–0.76	0.01*
ET cycle type			
Fresh ET	1.00		
Frozen ET	0.99	0.64–1.53	0.97
Embryo stage at ET			
Cleavage	1.00		
Blastocyst	0.44	0.21–0.90	0.03*
Quality of transferred embryos			
High	1.00		
High + middle	2.70	1.15–6.35	0.02*
Middle	4.50	1.60–12.65	<0.01*
Vaccination status of both partners in infertile couples			
Neither vaccinated	1.00		
Only infertile men vaccinated	1.04	0.47–2.30	0.92
Only infertile women vaccinated	0.59	0.12–2.82	0.51
Both partners vaccinated	0.48	0.13–1.82	0.28
Vaccine manufacturer and type			
Unvaccinated	1.00		
ZF2001	1.00	-	-
Sinovac	0.75	0.34–1.64	0.47
Sinopharm	1.78	0.35–9.17	0.49
Time interval from complete vaccination to ET			
Unvaccinated	1.00		
< 3 months	1.00	-	-
3–6 months	2.45	0.66–9.03	0.18
> 6 months	2.34	0.58–9.503	0.24

Note: * $p < 0.05$

unvaccinated patients. The results showed no significant differences among the three groups. Although the study sample was small, the study provides first-hand evidence on the impact of vaccination and infection on oocyte quality. The study assessed oocyte quality by follicular fluid HSPG2 concentration and found that anti-COVID-19 IgG was present in serum and follicular fluid 13 days after the first dose of the vaccine [17].

Controversy exists regarding gamete and embryo quality studies in SARS-CoV-2-infected and vaccinated individuals. An observational study has evaluated the impact of SARS-CoV-2 infection on gamete and embryo quality. The study has found no significant differences in the number of MII oocytes in women, the semen parameters in men, and fertilization rate after infection with SARS-CoV-2 (two men, seven women). However, COVID-19 influenced the high-quality embryo rate [18]. Moreover, a

retrospective cohort study also conducted in Israel compared IVF fresh cycle outcomes in 121 SARS-CoV-2-infected patients with 121 unvaccinated and uninfected infertile patients. The study found no significant differences in mature oocytes, fertilization, freezing per cycle, and CPR between the two groups. However, the number of oocytes retrieved was affected in patients with the infection for more than 180 days [19].

Effects of vaccination interval on embryo quality and pregnancy outcomes

The time interval between vaccination and IVF-ET is not consistent among different national organizations. In China, guidelines recommend IVF-ET treatment 1 month after vaccination [4]; the European Society of Human Reproduction and Embryology recommends IVF-ET treatment after 2 months of vaccination [20]; the American Society of Reproductive Medicine recommends that patients should be vaccinated as soon as possible, but oocyte retrieval or ET should be avoided at least 3 days before and after vaccination [21]. Huang et al. [16] divided infertile patients into groups according to the vaccination interval (≤ 1 month ($n=37$), 1–2 months ($n=42$), > 2 months ($n=71$)) and have found no significant differences in laboratory parameters and pregnancy outcomes among the groups. In the current study, the interval between vaccination and IVF of our patients was consistent with the recommended guidelines in China. We divided the patients into groups based on time interval (1–3 months, 3–6 months, and > 6 months) from complete vaccination to oocyte retrieval or ET and found no significant differences in embryo quality and pregnancy outcomes among the groups. This also provides evidence of vaccine safety for infertile patients who want to undergo IVF treatment as soon as possible after vaccination.

Strengths and limitations

This was the first study to compare the effects of vaccination on embryo quality and pregnancy outcomes in infertile couples. Furthermore, this study compared embryo quality and pregnancy outcomes after vaccination with different types of vaccines, which has not been previously explored. Most of the previous studies were conducted in the USA and Israel and included only mRNA vaccines. Prospective studies make data more objective, less expensive, and more accurate. This study provides strong evidence for the safety of COVID-19 vaccines and strongly complements previous studies.

This study had some limitations. First, the sample size was small. Second, this was a single-center study; thus, the findings should be further confirmed by a multicenter large-sample study. Third, this safety data is limited to people using the inactivated vaccine produced in China. Moreover, it is limited to vaccines taken 1 month or more away from egg retrieval or embryo transfer.

Conclusions

There were no significant differences in IVF embryo quality and pregnancy outcomes among infertile couples in which both, only one, and neither of the partners was vaccinated against COVID-19. Additionally, the type of vaccine used among infertile women and time interval between vaccination and IVF had no effect on pregnancy outcomes. Our findings provide evidence of vaccine safety for infertile couples wishing to undergo IVF treatment. This evidence is crucial for decision-making by clinicians and policymakers involved in IVF cycles.

Author contribution All authors have seen and approved the final version of this article. DM: designed and executed the study, gathered, analyzed the data, drafted the manuscript, and contributed to the critical discussion. WSS: analyzed and interpreted the data and contributed to the critical discussion. ZX, ZN, QJ, ZDD, and SY: collected the data. TJC: supervisor, contributed to the study design, study execution, critical discussion, revised the manuscript, and approved the final submitted version.

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Data availability The datasets used and/or analyzed during the current study are available from the first author or corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics approval The Hospital Institutional Review Board for Research on Human Subjects approved this study (2021PS020F).

Consent to participate All participants provided written informed consent.

Consent for publication All the authors in this paper consent to the publication of the work.

Conflict of interest The authors declare no competing interests.

References

1. World Health Organization. World Health Organization coronavirus disease (COVID-19) dashboard. Available from: <https://covid19.who.int/>. Accessed 3 April 2022.
2. National Health Commission of the People's Republic of China. COVID-19 vaccination status. Available from: <http://www.nhc.gov.cn/>. Accessed 3 March 2022.
3. Bureau of Disease Control Prevention, National Health Commission of the People's Republic of China. Technical guidelines for new coronavirus vaccination (First Edition) [In Chinese]. *Chin J Viral Dis.* 2021; 11: 161–162.

4. Expert Group for Beijing Human Assisted Reproductive Technology Center For Quality Control and Improvement. COVID-19 vaccination strategy for planning pregnancy and assisted reproductive technology treatment: expert recommendations [In Chinese]. *Chin J Reprod Contracep.* 2021; 41:296–299.
5. European Society of Human Reproduction and Embryology (ESHRE). COVID-19 vaccination and assisted reproduction [EB/OL]. (publication date 08 June 2021) <https://www.eshre.eu/Home/COVID19WG>.
6. Blake EM, Alexander C, Barnard E, Max EM, Hill MJ, Hoyos E, et al. COVID-19 vaccine and infertility: baseless claims and unfounded social media panic. In ASRM, *Fertil Steril* 2021; <https://www.fertstertdialog.com/posts/covid-19-vaccine-and-infertility-baseless-claims-and-unfounded-social-media-panic>
7. Flynn AC, Kavanagh K, Smith AD, Poston L, White SL. The impact of the COVID-19 pandemic on pregnancy planning behaviors. *Womens Health Rep (New Rochelle)*. 2021;2:71–7. <https://doi.org/10.1089/whr.2021.0005>.
8. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. CDC COVID-19 response pregnancy and infant linked outcomes team. 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; 69:1641–1647. <https://doi.org/10.15585/mmwr.mm6944e3>
9. Male V. Are COVID-19 vaccines safe in pregnancy? *Nat Rev Immunol.* 2021;21:200–1. <https://doi.org/10.1038/s41577-021-00525-y>.
10. 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. 10.3390/biology10030238.
11. 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. <https://doi.org/10.1186/s12958-021-00757-6>.
12. Aharon D, Lederman M, Ghofranian A, Hernandez-Nieto C, Canon C, Hanley W, et al. In vitro fertilization and early pregnancy outcomes after coronavirus disease 2019 (COVID-19) vaccination. *Obstet Gynecol.* 2022;139:490–7. <https://doi.org/10.1097/AOG.0000000000004713>.
13. Aizer A, Noach-Hirsh M, Dratviman-Storobinsky O, Nahum R, Machtinger R, Yung Y, et al. The effect of coronavirus disease 2019 immunity on frozen-thawed embryo transfer cycles outcome. *Fertil Steril.* 2022;10: S0015–0282(22)00022-X. <https://doi.org/10.1016/j.fertnstert.2022.01.009>.
14. Odeh-Natour R, Shapira M, Estrada D, Freimann S, Tal Y, Atzmon Y, et al. Does mRNA SARS-CoV-2 vaccine in the follicular fluid impact follicle and oocyte performance in IVF treatments? *Am J Reprod Immunol.* 2022; e13530. <https://doi.org/10.1111/aji.13530>
15. Morris RS. SARS-CoV-2 spike protein seropositivity from vaccination or infection does not cause sterility. *F S Rep.* 2021;2:253–5. <https://doi.org/10.1016/j.xfre.2021.05.010>.
16. Huang J, Xia L, Lin J, Liu B, Zhao Y, Xin C, et al. No effect of inactivated SARS-CoV-2 vaccination on in vitro fertilization outcomes: a propensity score-matched study. *J Inflamm Res.* 2022;15:839–49. <https://doi.org/10.2147/JIR.S347729>.
17. Bentov Y, Beharier O, Moav-Zafirir 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. <https://doi.org/10.1093/humrep/deab182>.
18. Orvieto R, Segev-Zahav A, Aizer A. Does COVID-19 infection influence patients' performance during IVF-ET cycle?: an observational study. *Gynecol Endocrinol.* 2021;37:895–7. <https://doi.org/10.1080/09513590.2021.1918080>.
19. Youngster M, Avraham S, Yaakov O, Landau RM, Gat I, Yerushalmi G, et al. IVF under COVID-19: treatment outcomes of fresh ART cycles. *Hum Reprod.* 2022;37:947–53. <https://doi.org/10.1093/humrep/deac043>.
20. ESHRE COVID-19 Working Group. ESHRE statement on COVID-19 vaccination and medically assisted reproduction. Available from: <https://www.eshre.eu/Europe/Position-tatements/COVID19/vaccination>. Accessed 3 October 2021.
21. Coronavirus/COVID-19 Task Force of the American Society for Reproductive Medicine. ASRM patient management and clinical recommendations during the (coronavirus COVID-19) pandemic: update no. 13—variants, vaccines, and vaccination; February 22, 2021. Available from: <https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate13.pdf>. Accessed 3 October 2021.

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