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Investigating Impacts of CoronaVac Vaccination in Males on *In Vitro* Fertilization: A Propensity Score Matched Cohort Study

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Purpose: This study aimed to evaluate the influences of SARS-CoV-2 vaccination (CoronaVac) on male fertility and investigate the impact of a history of the CoronaVac vaccination in males on gamete and embryo development and *in vitro* fertilization (IVF) outcomes.

Materials and Methods: A prospective cohort study enrolled couples undergoing IVF cycles between June and August 2021 at Reproductive Medicine Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology in China. According to the history of SARS-CoV-2 vaccination in males, the participants were divided into the vaccination group and the non-vaccination group. A self-controlled study of semen analyses for males before and after CoronaVac vaccination was conducted. Baseline characteristics were matched using propensity score matching. Participants were categorized into the unexposed group (non-vaccination) and exposed group (vaccination), and the population was 271 for each. Semen parameters and IVF outcomes were the main outcomes.

Results: Generally, no statistically significant differences were exhibited between the matched cohorts regarding embryo developmental parameters, including fertilization rate, cleavage rate, high-quality embryo rate, blastocyst formation rate, and available blastocyst rate, as well as clinical outcomes, such as implantation rate, biochemical pregnancy rate, and clinical pregnancy rate. Moreover, males after vaccination seemed to have fluctuating semen parameters including increased semen volume, lower motility, and decreased normal forms of sperm, while the motile sperm counts were similar. In addition, all semen parameters were above the lower reference limits.

Conclusions: Our findings suggested that CoronaVac vaccinations in males may not have adverse effects on patient performance or the gamete and embryonic development potential during assisted reproductive technology (ART) treatments.

Keywords: Assisted reproductive technology; Fertility; SARS-CoV-2; Spermatozoa; Vaccine

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a serious respiratory disease mediated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and the pandemic has caused millions of confirmed cases and morbidity [1]. By the end of 2020, several vaccines against COVID-19 based on various platforms have been approved for emergency use in several countries and regions [2], while the proportion of individuals who wish to receive vaccination remains low. It has been found that the concerns about the potential negative effect of vaccines on fertility can contribute to vaccine hesitancy [3]. An Internet-based study found that there was a striking increase in fertility-related search volume after the announcement of the Emergency Use Authorization of COVID-19 vaccines [4]. Therefore, the potential influence of COVID-19 vaccines on fertility and offspring health deserves our concern and attention.

During the postpandemic era, vaccinations against COVID-19 seem to be general and essential. By 15 September 2021, it was reported that more than 1 billion individuals had been vaccinated, with a vaccination rate over 70% in China. CoronaVac, the most frequently used vaccine in China, was demonstrated to have excellent seroconversion rates of neutralizing antibodies [5]. The number of people who received the CoronaVac vaccination is large and increasing; however, none of the clinical trials have evaluated reproductive toxicity among the vaccinated population. It is necessary to perform such a study to evaluate the effect of CoronaVac on human fertility, which might help people overcome CoronaVac vaccine hesitancy about possible fertility impairment.

In this study, couples undergoing assisted reproductive technology (ART) treatments with a history of CoronaVac vaccination in males were enrolled. We collected and analyzed the data on *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) to investigate the possible impacts of CoronaVac vaccination on male fertility, gamete/embryo development, and ART outcomes.

MATERIALS AND METHODS

1. Study design

This was a single-center prospective cohort study. Couples undergoing IVF/ICSI treatments between June and August 2021 in Reproductive Medicine Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology in China were included. According to the history of SARS-CoV-2 vaccination in males, the participants were divided into the vaccination group and the non-vaccination group. We excluded participants with the following: (1) history of confirmed SARS-CoV-2 infection; (2) preimplantation genetic testing (PGT) cycles; (3) oocyte/sperm donation cycles; (4) oocyte totally or partly freezing cycles; (5) female with a history of SARS-CoV-2 vaccination; (6) administration of other types of vaccines against COVID-19 except for CoronaVac; (7) severe oligozoospermia (sperm concentration less than 1×10^6/mL); and (8) surgical sperm retrieval.

2. Administration of SARS-CoV-2 vaccines

CoronaVac (Sinovac Life Sciences, Beijing, China) was used in this study. A vaccine of 600 SU antigens of inactivated SARS-CoV-2 in 0.5 mL aluminum hydroxide diluent per dose was intramuscularly administered according to the instructions. It was a two-dose vaccine with a recommended dosing interval from 2 to 4 weeks [6].

3. Semen analysis and semen preparation

A combination of manual Papanicolaou sperm staining and a computer-assisted sperm analysis (CASA) system (BEION S3-3, V4.20; BEION, Shanghai, China) was applied in semen analysis. Quality control of CASA was conducted every day to avoid any possible biases, and a standard semen analysis according to the World Health Organization (WHO) Semen Analysis Manual 2010 [7] was performed before CASA. The lower reference limits of semen parameters were based on the WHO criteria (fifth edition), namely semen volume (1.5 mL), sperm concentration (15×10^6/mL), total sperm count (39×10^6 per ejaculate), total motility (40%), progressive motility (32%), and normal forms (4%) [7].

Semen preparation for IVF was selected using standard density-gradient centrifugation. Up to 3 mL semen was added to 3 mL 45%/90% gradient media (1:1; Vitrolife, Gothenburg, Sweden) and centrifuged at 200 g for 20 minutes. After washing, the pellet was resuspended in 0.5 mL sperm washing medium (Vitrolife) to allow for a 30 to 60 minutes swim-up. The top 0.3 mL was collected for optimized analysis and insemination.

Normally, IVF was performed when the optimized sperm had a concentration above 5×10^6/mL; otherwise, the sperm were subjected to ICSI.

4. IVF/ICSI procedure and embryo culture

Controlled ovarian hyperstimulation (COH) protocols were well described in previous studies [8]. When 2–3 dominant follicles with a diameter no less than 18 mm were observed, recombinant human chorionic gonadotropin (HCG) was intramuscularly administered for triggering. Oocyte retrieval was performed 36 to 38 hours later for fertilization.

Morphological assessments were performed by two independent embryologists. When no consensus could be reached, the dispute was arbitrated by a third one. The existence of 2 pronuclei (2PN) was thought to be normal fertilization, while multiple PN was a sign of abnormal fertilization. Fertilized embryos were cultured in G1-plus medium (Vitrolife) until day 3 for cleavage assessment. Single or double high-quality embryos were freshly transferred on day 3 under ultrasound guidance, and the surplus embryos were either cryopreserved or cultured in G2-plus medium (Vitrolife) until D5 or D6 for blastocyst assessment and cryopreservation. The morphological evaluation criteria for PN, cleavage embryos, high quality embryos, and blastocysts were described in detail as previously [9,10]. Available blastocysts referred to those with a morphologic score of 3BC or higher on day 5 or 6 based on the Gardner scoring system.

Serum HCG levels were measured 14 days after embryo transfer, and transvaginal ultrasound was performed 4 to 6 weeks after embryo transfer. In this study, biochemical pregnancy was defined as an elevated serum HCG level without a sonographic gestational sac, and clinical pregnancy was confirmed by the presence of an intrauterine gestational sac.

5. Outcome assessment

For semen evaluation, males experiencing semen analyses before and after SARS-CoV-2 vaccination were selected to have a comparison of semen parameters. The main semen analysis outcomes included semen volume, semen concentration, total number per ejaculate, total motility, progressive motility, and normal forms.

The ART outcomes of the current study included laboratory outcomes and clinical outcomes. The laboratory outcomes referred to embryo developmental parameters. The primary outcomes were the normal fertilization rate and available blastocyst rate, and the secondary outcomes were as follows: mature oocyte rate, abnormal fertilization rate, cleavage rate, high-quality embryo rate, and blastocyst formation rate. For the clinical outcomes, the clinical pregnancy rate was the primary outcome, and the secondary outcomes included the implantation rate and biochemical pregnancy rate. The computations were previously described with minor modifications [8,11].

6. Statistical analyses

SPSS (version 26.0; IBM Corp., Armonk, NY, USA) was utilized for statistical analyses. Continuous variables not obeying a normal distribution are presented as medians (interquartile range [IQR]), and the categorical variables are presented as % (n/N). Statistical differences between the groups were compared utilizing the Mann–Whitney U rank-sum test (for continuous variables) or chi-squared test (for categorical variables) as appropriate. The Wilcoxon rank test was used to evaluate alterations in semen parameters before and after vaccination in the same individuals. A two-tailed p-value <0.05 was considered statistically significant.

Propensity score matching was performed to eliminate the imbalance of baseline characteristics and sample sizes between the groups. The propensity scores were estimated by a logistic regression model, and the demographic characteristics, which were considered as potential confounding variables affecting ART outcomes, were included in the model and matched in a 1:1 fashion to create a highly comparable control cohort, including male age, female age, female body mass index, basal follicle stimulation hormone (FSH), basal anti-Müllerian hormone (AMH), basal antral follicle counting, experienced ART times, infertility type, infertility duration, infertility causes, operation types, COH protocols, gonadotropin (Gn) duration, Gn dosage, number of large follicles, estradiol level on HCG day, progesterone level on HCG day, endometrium thickness on HCG day, and number of oocytes retrieved. Nearest neighbor matching without replacement (random order, caliper=0.1) was utilized.

7. Ethics statement

This study was approved by the Ethical Committee of Tongji Medical College (approval number: [2020]

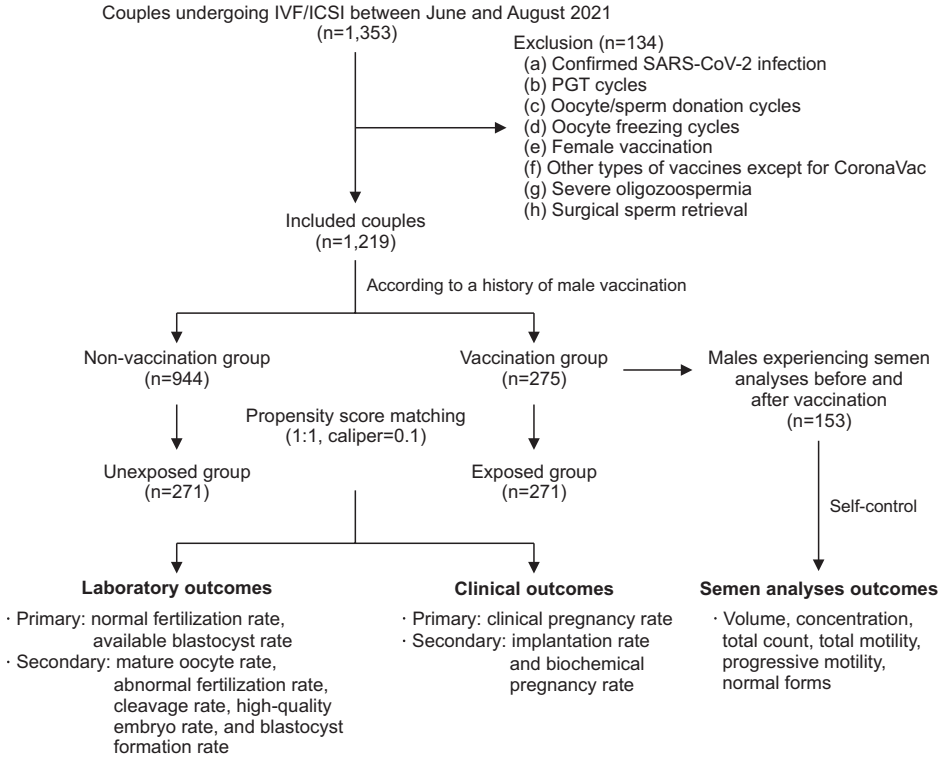

Fig. 1. Flow chart of the study. IVF: *in vitro* fertilization, ICSI: intracytoplasmic sperm injection, PGT: preimplantation genetic testing.

S066) with written informed consent provided by the participants.

RESULTS

A total of 1,353 couples undergoing IVF/ICSI treatments between June and August 2021 were enrolled in this study. Based on the inclusion and exclusion criteria, 1,219 couples were included for analysis. Subsequently, the participants were divided into the vaccination group (n=275) and the non-vaccination group (n=944) according to a history of SARS-CoV-2 vaccination (Fig. 1) in males. Obvious significant differences were observed in the demographic characteristics of the included couples, such as female age, basal AMH level, Gn dosage, number of large follicles, and number of oocytes retrieved ($p<0.05$, Table 1). Propensity score matching was then performed to eliminate the imbalance of baseline characteristics (Fig. 1). Two hundred seventy-one matched pairs remained in the unexposed group (non-vaccination) and the exposed group (vaccination) after matching, and there were no significant differences between the matched cohorts in terms of the characteristics (Table 1). The distributions of propensity scores and standard deviations are presented through visualization. The density curves of propensity scores almost completely coincided after matching, and the distribution of standard deviations after matching was much more concentrated, verifying the effectiveness of the matching (Fig. 2).

The laboratory outcomes of the included IVF/ICSI cycles are presented in Table 2. It has shown that embryo developmental parameters were similar between the groups after matching, including the mature oocyte rate, normal fertilization rate, abnormal fertilization rate, normal cleavage rate, high-quality embryo rate, blastocyst formation rate, and available blastocyst rate ($p>0.05$).

Similarly, the data on clinical outcomes are shown in Table 3. Single embryo transfer was conducted in most of these cycles, and the proportion of single embryo transfer was similar in the groups after matching (91.3% *vs.* 94.2%, p=0.387). A total of 128 embryos were transferred in the exposed group and 125 embryos in the control group. Likewise, regardless of a history of male vaccination, no significant differences were observed in the matched groups regarding implantation rate, biochemical pregnancy rate, and clinical pregnancy rate ($p>0.05$).

Among the 275 males with a history of SARS-CoV-2 vaccination, 153 of them had ever undergone semen analyses before and after vaccine administration. The

Table 1. Baseline characteristics of participants before and after matching

Variable	Unmatched			Matched		
	Unexposed (n=944)	Exposed (n=275)	p-value	Unexposed (n=271)	Exposed (n=271)	p-value
Age, y						
Male	34 (31–37)	34 (32–37)	0.178	34 (32–37)	34 (32–37)	0.712
Female	32 (29–35)	32 (30–35)	0.014	32 (30–35)	32 (30–35)	0.729
Female BMI, kg/m^2	21.8 (20.0–24.0)	22.0 (20.0–24.4)	0.291	22.0 (20.1–24.4)	22.0 (20.0–24.4)	0.857
FSH, mIU/mL	7.1 (5.9–8.7)	7.3 (5.8–8.9)	0.531	7.1 (6.0–8.7)	7.3 (5.8–8.9)	0.610
AMH, ng/mL	2.9 (1.5–4.8)	2.5 (1.3–4.2)	0.022	2.6 (1.4–4.5)	2.5 (1.3–4.3)	0.939
AFC	11 (7–18)	10 (6–16)	0.060	10 (7–16)	10 (6–16)	0.947
Experienced ART times	1 (1–2)	1 (1–2)	0.321	1 (1–2)	1 (1–2)	0.419
Infertility duration, y	3 (2–4)	3 (2–4)	0.879	3 (2–5)	3 (2–4)	0.551
Infertility type			0.094			0.793
Primary	65.1 (615)	59.6 (164)		58.7 (159)	59.8 (162)	
Secondary	34.9 (329)	40.4 (111)		41.3 (112)	40.2 (109)	
Infertility causes			0.168			0.512
Female factors	59.4 (561)	54.5 (150)		53.1 (144)	55.4 (150)	
Male factors	10.0 (94)	8.7 (24)		10.7 (29)	8.9 (24)	
Mixed factors	25.2 (238)	32.0 (88)		28.8 (78)	31.0 (84)	
Unexplained	5.4 (51)	4.7 (13)		7.4 (20)	4.8 (13)	
Operation types			0.533			0.473
IVF	63.8 (602)	65.8 (181)		62.7 (170)	65.7 (178)	
ICSI	36.2 (342)	34.2 (94)		37.3 (101)	34.3 (93)	
COH protocol			0.091			0.372
GnRH-agonist	43.8 (413)	36.4 (100)		34.7 (94)	36.9 (100)	
GnRH-antagonist	41.1 (388)	46.2 (127)		50.9 (138)	45.4 (123)	
Others[a]	15.1 (143)	17.5 (48)		14.4 (39)	17.7 (48)	
Gn duration, d	10 (9–11)	10 (9–11)	0.949	10 (9–11)	10 (9–11)	0.900
Gn dosage, IU	2,355 (1,763–3,000)	2,550 (1,823–3,263)	0.028	2,550 (1,898–3,225)	2,550 (1,800–3,225)	0.667
No. of large follicles	10 (6–13)	9 (5–12)	0.047	9 (6–13)	9 (5–12)	0.531
Estradiol on HCG day, pg/mL	2,137 (1,394–3,667)	2,155 (1,398–3,496)	0.652	2,131 (1,382–3,555)	2,161 (1,398–3,496)	0.941
Progesterone on HCG day, ng/mL	0.8 (0.5–1.1)	0.8 (0.5–1.1)	0.985	0.9 (0.5–1.2)	0.8 (0.5–1.1)	0.255
Endometrium thickness on HCG day, mm	11.0 (9.0–12.7)	10.8 (8.9–12.6)	0.401	10.5 (9.0–12.5)	10.8 (8.9–12.6)	0.712
No. of oocytes retrieved	12 (7–16)	10 (6–15)	0.032	11 (6–16)	10 (6–15)	0.343

Continuous variables are presented as the median (interquartile range). Categorical variables are presented as % (number).
BMI: body mass index, FSH: follicle stimulation hormone, AMH: anti-Müllerian hormone, AFC: antral follicle counting, ART: assisted reproductive technology, IVF: *in vitro* fertilization, ICSI: intracytoplasmic sperm injection, COH: controlled ovarian hyperstimulation, GnRH: gonadotropin releasing hormone, Gn: gonadotropin, HCG: human chorionic gonadotropin.
[a]Others: including mild stimulation and luteal phase stimulation protocols.
$p<0.05$ was considered statistically significant.

median time interval between the two semen analyses was 244 days (IQR, 133–476 d), and for the time interval between the last vaccine administration and the semen analysis after vaccination, the median was 71 days (IQR, 38–102 d). As Table 4 shows, there was a slight increase in semen volume after vaccination ($p<0.001$), while sperm concentration and total sperm count were similar between the compared cohorts. Moreover, although progressive motility and total motility decreased after vaccination, there were no significant differences in terms of progressive and total motile sperm counts. In addition, the percentage and count of sperm with normal morphology were higher before vaccination.

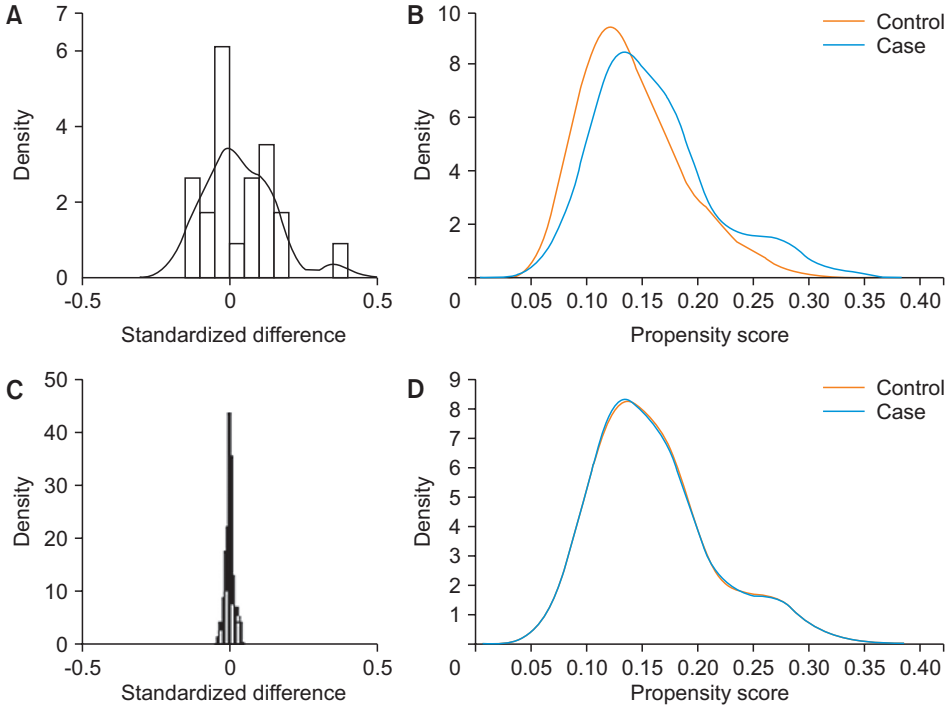

Fig. 2. The distributions of propensity scores and standard deviations before and after matching. (A) Standardized differences before matching. (B) Propensity scores before matching. (C) Standardized differences after matching. (D) Propensity scores after matching.

Table 2. Laboratory outcomes before and after matching

Variable	Unmatched			Matched		
	Unexposed (n=1,639)	Exposed (n=275)	p-value	Unexposed (n=271)	Exposed (n=271)	p-value
No. of oocytes retrieved	11,398	3,146		3,150	3,117	
Mature oocyte rate	84.2 (9,596/11,398)	85.3 (2,682/3,146)	0.146	84.3 (2,656/3,150)	85.1 (2,653/3,117)	0.381
Normal fertilization rate	63.1 (7,197/11,398)	62.9 (1,978/3,146)	0.782	61.7 (1,944/3,150)	62.9 (1,960/3,117)	0.341
Abnormal fertilization rate	9.0 (1,031/11,398)	9.6 (302/3,146)	0.340	9.5 (300/3,150)	9.6 (299/3,117)	0.926
Normal cleavage rate	97.6 (7,026/7,197)	97.7 (1,933/1,978)	0.793	97.9 (1,903/1,944)	97.7 (1,915/1,960)	0.691
High-quality embryo rate	51.8 (3,637/7,026)	50.3 (973/1,933)	0.266	50.2 (955/1,903)	50.4 (965/1,915)	0.898
No. of embryos extended culture on day 3	6,116	1,651		1,639	1,635	
Blastocyst formation rate	74.9 (4,578/6,116)	74.1 (1,224/1,651)	0.553	74.5 (1,221/1,639)	74.3 (1,214/1,635)	0.872
Available blastocyst rate	50.9 (3,115/6,116)	50.8 (839/1,651)	0.934	49.3 (808/1,639)	50.8 (831/1,635)	0.382

Categorical variables are presented as % (n/N).

Table 3. Clinical outcomes before and after matching

Variable	Unmatched			Matched		
	Unexposed (n=1,639)	Exposed (n=275)	p-value	Unexposed (n=274)	Exposed (n=274)	p-value
Fresh embryo transfer cycles	445	123		115	121	
No. of embryos transferred	469	130	0.898	125	128	0.387
1	94.6 (421/445)	94.3 (116/123)		91.3 (105/115)	94.2 (114/121)	
2	5.4 (24/445)	5.7 (7/123)		8.7 (10/115)	5.8 (7/121)	
Gestational sacs	226	56		59	56	
Implantation rate	48.1 (226/469)	43.1 (56/130)	0.302	47.2 (59/125)	43.8 (56/128)	0.582
Biochemical pregnancy rate	7.9 (35/445)	6.5 (8/123)	0.613	7.0 (8/115)	5.8 (7/121)	0.712
Clinical pregnancy rate	50.3 (224/445)	45.5 (56/123)	0.345	50.4 (58/115)	46.3 (56/121)	0.523

Categorical variables are presented as % (n/N).

Table 4. Sperm analyses before and after vaccination

Variable	Lower reference limits	Self-controlled patients (n=153)			
		Before vaccination	After vaccination	D-value[a]	p-value
Age, y	-	33 (29–37)	34 (31–38)	-1.0	<0.001
Sperm volume, mL	1.5	3.2 (2.5–4.5)	3.8 (2.9–4.8)	-0.4	<0.001
Sperm concentration, $\times 10^6$/mL	15	47.9 (31.8–77.0)	47.0 (27.0–78.0)	1.2	0.420
Total sperm count, $\times 10^6$	39	167.5 (97.9–274.7)	174.8 (105.3–272.4)	-9.2	0.401
Progressive motility, %	40	47.9 (37.7–60.7)	46.0 (32.0–55.0)	3.2	0.002
Progressive motile sperm count, $\times 10^6$	-	72.6 (40.5–136.6)	70.4 (31.4–129.8)	1.8	0.407
Total motility, %	32	54.3 (41.6–65.8)	49.0 (35.5–58.0)	5.2	<0.001
Total motile sperm count, $\times 10^6$	-	83.0 (48.9–149.6)	77.5 (34.2–128.3)	3.0	0.300
Normal forms, %	4	5.4 (4.0–7.0)	4.0 (4.0–5.0)	1.0	<0.001
Normal forms sperm count, $\times 10^6$	-	8.8 (4.4–15.8)	7.2 (4.1–11.8)	0	0.01

Continuous variables are presented as the median (interquartile range).
-: not available.
[a]D-value referred to the difference of medians before and after vaccination.
p<0.05 was considered statistically significant.

DISCUSSION

In the current study, we presented laboratory and clinical outcomes during ART treatments in infertilite couples with CoronaVac vaccinations in males as well as semen assessment. The results suggested no adverse impact of CoronaVac vaccination on gamete/embryonic development and implantation potential among the infertility population.

To date, the impact of SARS-CoV-2 infection on male fertility has been debated. Many studies have demonstrated that angiotensin-converting enzyme 2 (ACE2), an essential molecule for the pathogenesis of SARS-CoV-2 infection, is predominantly enriched in the male reproductive system such as spermatogonia, Leydig cells, and Sertoli cells [12,13], making testicles at a high risk of viral damage. Moreover, the expression of ACE2 in testicular cells was reported to be associated with male age, and males of reproductive age were likely to be more susceptible to testicular damage caused by COVID-19 [12]. In addition, persistent high fever, as a common symptom of COVID-19, can damage the blood-testis barriers [14], subsequently allowing for the entry of viruses from the circulation into the testicular. The damage caused by COVID-19 to the testis may also be secondary to vasculitis-like orchitis [15], which was supported by the reported testicular pain and epididymo-orchitis in hospitalized COVID-19 patients [16]. Furthermore, due to the high plasma viral load, the elevated secondary inflammatory response, which might induce oxidative stress [17] and alter the host epigenome [18-20], could also mediate testicular damage and impair male fertility. Some clinical trials reported sperm quality impairment to varying degrees, such as azoospermia and oligozoospermia, in confirmed cases during the recovery stage [21], while some other studies demonstrated that COVID-19 might not greatly affect semen quality and male fertility [22]. A previous study found that SARS-CoV-2 infection might not negatively affect fertility and ART outcomes by analyzing ART data [11]. However, all these studies were case reports or observational studies with a follow-up period that was too short, and no real randomized clinical trial has ever been conducted. It should also be noted that the alterations in semen parameters were compatible with the expected transient alteration caused by fever or other pathological conditions. Therefore, the potential fertility impairment of infected males deserves long-term follow-up, and more relevant high-quality studies are urgently needed.

Vaccination is effective in protecting against SARS-CoV-2 infection. CoronaVac is the most commonly used COVID-19 inactivated vaccine in China, which contains antigens of live viruses and has shown excellent immunogenicity in animals [23], and phase 3 clinical trials [19,24] through the induction of robust systemic inflammation and the production of neutralizing antibodies against SARS-CoV-2. Nevertheless, in consideration of the characteristics of inactivated vaccines, CoronaVac-induced immune responses may be similar

to those caused by live viruses, which can potentially damage human fertility. Furthermore, concerns about the potential negative effect of vaccines on human fertility and offspring health have been increasing, which was reported to account for one of the top reasons for vaccine hesitancy [4]. Investigations into the impacts of CoronaVac on fertility are imminent.

To date, the impact of COVID-19 vaccines on reproductive systems has not been fully investigated. A preclinical animal study announced a lack of reproductive toxicity of BNT162b2, an mRNA vaccine produced by Pfizer/BioNTech, in rats, and no significant impairments were observed in embryonic and neonatal development [25]. Similarly, another study reported the developmental and reproductive safety of AZD1222, a recombinant replication-deficient adenovirus vaccine, in mice [26]. Currently, studies investigating the effect of COVID-19 vaccines on human fertility have mainly focused on BNT162b2. A cohort study found that anti-SARS-CoV-2 IgG antibodies can be detected in follicular fluids of BNT162b2-vaccinated IVF patients, yet parameters for ovarian follicle quality were similar among confirmed COVID-19 patients in the recovery stage, vaccinated couples, and controls [27]. Due to a lack of studies on other types of vaccines, future studies with longer follow-up periods using different vaccines are needed.

Semen analysis is the most frequently used method for male fertility status prediction. In the current study, we enrolled 153 males experiencing semen analyses before and after CoronaVac vaccination and compared their semen quality. Similar clinical trials conducted in the USA reported no significant decreases in any sperm parameter before and after mRNA vaccination among 45 healthy volunteers [28]. Similarly, there was no obvious adverse effect of the mRNA vaccine on semen quality, in terms of volume, concertation, motility, and total motile sperm count, in Israeli males pre/post vaccination [29]. Interestingly, our results showed a slight decrease in motility and normal forms following vaccination, while the motile sperm counts were similar, and all semen parameters were still in a normal range. The alternations in semen parameters may be attributed to a long interval between pre-post semen analyses in our study [30], which ranged from 41 to 2,302 days. Moreover, some other factors affecting sperm parameters may occur in such a long time, including andrological diseases such as prostatitis. Dynamic follow-up of their fertility and an enlarged sample size in prospective vaccination studies are needed to clarify these alterations. Additionally, the results of sperm analysis might be influenced by various factors, including but not limited to environment, lifestyle, and mental state [31], and it should be utilized together with other clinical or biochemical parameters to allow for a comprehensive male fertility evaluation.

Due to the variability and susceptibility of semen analysis, we further analyzed the IVF outcomes of the participants, which provided direct evidence for the impact of CoronaVac on gamete viability and embryonic developmental competency. Our results suggested that there were no significant differences in terms of laboratory and clinical outcomes of IVF, revealing that CoronaVac vaccination had no detrimental effect on the fertilization ability of gametes, embryonic development, or embryo implantation potential. Similarly, another observational study conducted in Israel included 36 couples undergoing IVF treatment after receiving BNT162b2 vaccines, and the ovarian stimulation and embryological variables before and after vaccination were comparable [29]. The results of these clinical studies were in accordance with our study, in which no adverse effect of SARS-CoV-2 vaccination on fertility was exhibited, although the types of vaccines used and the gender of participants were different. Based on the current studies, no clear evidence supported that CoronaVac impacted gamete and embryonic development, while semen quality fluctuated within the normal range observed in our study. Therefore, a closer long-term follow-up is required in the future.

However, there were still several limitations. This was a cohort study with small sample size, and the men enrolled suffered from infertility, which limited the generalizability of the conclusions. A study with a larger sample size, which includes broader healthy populations is required to support and validate our results in the future. Moreover, we did not evaluate the serum total testosterone and FSH levels of the participants, which were not routine laboratory examinations in our IVF center. They were another evaluation index for male fertility. In addition, the endpoint of the current study is a confirmation of clinical pregnancy, and a study with a longer period of follow-up is urgently needed.

CONCLUSIONS

In conclusion, our findings provide evidence that inactivated CoronaVac vaccinations in males may not have adverse effects on patient performance or the gamete and embryonic development potential during ART treatments. Larger studies among a wider population with longer follow-up in the future are required to support and validate our observations.

Conflict of Interest

The authors have nothing to disclose.

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Author contribution

Conceptualization: LZ, LJ. Data curation: LZ, QY, WM. Formal analysis: MW, QY. Funding acquisition: MW, LZ, LJ. Supervision: LZ, LJ. Writing – original draft: MW, QY. Writing – review & editing: LZ, LJ.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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