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SARS-CoV-2 spike protein seropositivity from vaccination or infection does not cause sterility

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Several reports claim that the purported similarity between syncytin-1 and the SARS-CoV-2 spike protein may induce immune cross-reactivity resulting in female sterility. We used frozen embryo transfer as a model for comparing the implantation rates between SARS-CoV-2 vaccine seropositive, infection seropositive, and seronegative women. No difference was found in serum hCG documented implantation rates or sustained implantation rates between the three groups. Reports claiming that COVID-19 vaccines or illness cause female sterility are unfounded.

Key Words

SARS-CoV-2
COVID-19
COVID-19 vaccination
spike protein
synctin-1
implantation

Vaccine hesitancy in reproductive-aged women has been heightened as a result of the spread of misinformation on social media stating that COVID-19 vaccines will cause sterility in women (1). The proposed mechanism is the presumed similarity between the SARS-CoV-2 spike protein and syncytin-1 (2), a protein that is critical to the formation of the syncytiotrophoblast in a developing embryo (3). The hypothetical ensuing immune cross-reactivity would result in damage to the developing trophoblast, thereby preventing embryo implantation. If true, then this cross-reactivity would cause sterility not just from vaccination but also from natural illness and would be lifelong. Laboratory analysis has failed to demonstrate any such cross-reactivity, but no human clinical data are available (1).

We used in vitro fertilization frozen embryo transfer (FET) as a model for evaluating the impact of COVID-19 seropositivity on implantation. The detection of elevated maternal serum hCG levels after an embryo transfer provides the earliest confirmation of syncytiotrophoblast formation and embryo implantation.

Materials and methods

Before the initiation of treatment, serum samples obtained from patients undergoing FET were analyzed to quantitatively determine the level of anti-SARS-CoV-2 spike IgG (Roche, Elecsys, nonreactive <0.79 U/mL; specificity, 100% [99.7%–100%]). Reactive patients were asked to determine any history of vaccination or infection. The study ran from January 1, 2021, until May 7, 2021. During this period, three types of COVID-19 vaccines were available: BNT162b2 vaccine (BioNTech/Pfizer), mRNA-1273 vaccine (Moderna), and Ad26.COV2.S vaccine (Janssen, Johnson and Johnson). Due to local availability, only the Pfizer and Moderna vaccines were received by the patients in this study. Both of these vaccines are lipid nanoparticle–mRNA vaccines that encode a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein (4).

A total of 171 FETs were performed during the study period. Twenty-eight patients had more than one transfer. In these patients, only the first transfer was analyzed leaving 143 transfers for analysis. All patients underwent embryo transfer using a single expanded blastocyst in a hormone-prepared uterus. Approximately 37.8% of the patients were reactive. Of those, 64.8% were reactive from vaccination, while

35.2% were reactive from infection. Patients with COVID-19 had mild cases or were asymptomatic. None of the patients with COVID-19 were hospitalized. None of them reported exposure to infection and at the same time received the vaccination.
Before embryo transfer, all patients were confirmed to have normal uterine cavity via diagnostic hysteroscopy or hysterosonogram. The protocol for uterine preparation used micronized estradiol tablets, either orally, vaginally, or both, until the endometrial thickness measured on transvaginal ultrasound reached 6 mm or greater followed by a combination of vaginal progesterone (Endometrin, 100 mg three times a day or Crinone 8% two times a day) and intramuscular progesterone (50 mg once every three days). A single embryo transfer was performed under transabdominal ultrasound guidance.
Baseline characteristics were analyzed using analysis of variance. Chi-square test was used to compare the pregnancy rates among the three groups, and Bonferroni correction was applied to correct for multiple comparisons. Chi-square test and Bonferroni correction were performed using R version 4.0.2 (R Core Team, 2020). Results of the chi-square power calculation showed a 99% chance to detect a 50% decrease in the ongoing pregnancy rate in all patients (n = 143, sig level = 0.05) and a 79% chance in euploid patients (n = 67, sig level = 0.05).

Results

The baseline characteristics of the three groups are listed in Table 1. No statistically significant difference was observed in the mean age at the time of egg retrieval and cryopreservation (*P*=.3277). The mean number of days of estradiol supplementation (*P*=.703) and the mean endometrial thickness (*P*=.08) before the initiation of progesterone treatment were similar. However, the infection group had a higher mean body mass index than the vaccinated group and the nonreactive group (*P*=.005).

Table 1. Baseline characteristics.

	Reactive Vaccine (n = 35)	Reactive infection (n = 20)	Nonreactive (n = 88)	*P* value
Age at cryo (y)	36.4	33.1	34.6	.33
BMI at transfer (kg/m^2)	29.0	32.1	28.8	.005[a]
Days of Estrace	11.4	11.6	11.8	.70

	Reactive Vaccine (n = 35)	Reactive infection (n = 20)	Nonreactive (n = 88)	*P* value
P4 level (ng/mL)	0.37	0.40	0.42	.4
Endometrial thickness (mm)	8.4	8.1	9.0	.08

a

Vaccine vs. infection: *P*=.04, vaccine vs. nonreactive: *P*=.99, infection vs. nonreactive: *P*=.01

Embryo implantation was determined by a serum hCG level of >5 mIU/mL obtained 8 days after embryo transfer followed by a rising level two to three days later. The implantation rate (positive hCG per transfer) was not significantly different between seronegative (73.9%), vaccine seropositive (80.0%), and infection seropositive (73.7%) patients (*P*=.99) (Table 2).

Table 2. Pregnancy rates.

	Reactive vaccine	Reactive infection	Nonreactive	*P* value	Bonferroni adjusted *P* value
All patients	n = 35	n = 20	n = 88		
Biochemical (%)	80.0	73.7	73.9	.19	1
Clinical (%)	65.7	52.6	62.5	.15	1
Ongoing (%)	65.7	47.4	52.3	.11	.99
Euploid only	n = 17	n = 10	n = 40		
Biochemical (%)	82.4	80	80	.97	1
Clinical (%)	70.6	70	70	.99	1
Ongoing (%)	70.6	70	60	.68	1

Since trophoblast damage might also be manifested by reduced viability after implantation, a series of transvaginal ultrasounds were performed in women with hCG levels of more than 2,000 mIU/mL. Visualization of a gestational sac, an indicator of continued trophoblast development, was similar between all three groups (nonreactive, 62.5%; vaccine reactive; 65.7%; and infection reactive, 52.6%; *P*=.63) (Table 2). The sustained implantation rate, defined as the presence of ultrasound visualized fetal heart tones at two time points at least one week apart, may reflect the possible delivery rate (5) The sustained implantation rates for seronegative, vaccine seropositive, and infection seropositive groups were similar (52.3%, 65.7%, and 47.4%, respectively; *P*=.99) (Table 2) and were consistent with the prepandemic rates in our center (data not shown).

A total of 67 transfers were performed using euploid blastocysts. No statistically significant differences were found in the implantation, clinical, and sustained pregnancy rates between the three groups (Table 2).

Discussion

On December 1, 2020, the former head of respiratory research of Pfizer filed an application to the European Medicine Agency calling for the immediate suspension of all SARS-CoV-2 vaccine studies (2). One of the concerns laid out in the application was "infertility of indefinite duration in vaccinated women." However, the theoretical danger was not because of the vaccine per se, but from the subsequent production of antibodies against the virus spike protein and their cross-reaction with syncytin-1. Why this would be different than the antibodies produced from natural infection was never explained.

On binding to its receptor, syncytin-1 promotes the fusion of cytotrophoblast into syncytiotrophoblast, an essential process in implantation. Interference with the formation of syncytiotrophoblast might indicate a failed implantation, an early pregnancy loss, or later problems related to abnormal placentation such as preeclampsia. However, the theory of infertility resulting from cross-reactivity seemed unlikely for several reasons.

First, this theory relies on syncytin-1 being similar in structure to the spike protein. Syncitin-1 is 538 amino acids long with a size of 73 kDa (6). The SARS-CoV-2 spike protein is 1,273 amino acids long with a size of 180–200 kDa (7). More importantly, the longest similar sequence of amino acids between the two proteins is four amino acids long.

Second, a team from the Yale University School of Medicine, led by immunologist Dr. Akiko Iwasaki, examined the reactivity of 3,000 different proteins in humans to the antibodies formed as a result of a natural SARS-CoV-2 infection or COVID-19 vaccination. Reactivity to syncytin-1 was not observed. (1)

In vitro fertilization with FET is an excellent method to study the impact of various factors on implantation since it bypasses many of the variables that normally impact a woman's ability to conceive such as ovulation, fertilization, and preimplantation embryo development. The current study failed to identify the difference in the

implantation or pregnancy rates between women with documented seropositivity to the spike protein and women without seropositivity.

Conclusion

We have documented, for the first time in women, that seropositivity to the SARS-CoV-2 spike protein, whether from vaccination or infection, does not prevent embryo implantation or early pregnancy development. Physicians and public health personnel can counsel women of reproductive age that neither previous illness with COVID-19 nor antibodies produced from vaccination to COVID-19 will cause sterility.

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Research Letter

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Sperm Parameters Before and After COVID-19 mRNA Vaccination

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COVID-19 Resource Center

Two mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), received Emergency Use Authorization from the US Food and Drug Administration. Despite high efficacy and few adverse events found in clinical trials, only 56% of individuals in the US reported wanting to receive the vaccine.[1] One of the reasons for vaccine hesitancy is the potential negative effect on fertility.[2] Because reproductive toxicity was not evaluated in the clinical trials and SARS-CoV-2 has been associated with decreases in sperm parameters,[3] we assessed sperm parameters before and after mRNA vaccine administration.

Methods

This single-center prospective study at the University of Miami recruited healthy volunteers aged 18 to 50 years scheduled for mRNA COVID-19 vaccine through flyers posted throughout the university hospital and internal listserve emails. The University of Miami institutional review board approved the study and written informed consent was obtained from all participants.

Men were prescreened to ensure they had no underlying fertility issues. Those with COVID-19 symptoms or a positive test result within 90 days were excluded. Participants provided a semen sample after 2 to 7 days of abstinence, prior to receiving the first vaccine dose and approximately 70 days after the second. Semen analyses were performed by trained andrologists per World Health Organization guidelines and included semen volume, sperm concentration, sperm motility, and total motile sperm count (TMSC).[4] Individuals with oligospermia (sperm concentration <15 million/mL) were included. After calculating data distribution on normality test, medians and interquartile ranges (IQRs) were reported for all variables. Wilcoxon rank sum test was used to compare pre- and postvaccination semen parameters. Change in TMSC is presented graphically. Statistical analysis was performed with SPSS version 24 (IBM). A 2-tailed *P* value less than .05 was considered statistically significant.

Results

Between December 17, 2020, and January 12, 2021, 45 men volunteered (median age, 28 years [IQR, 25-31]); follow-up samples were obtained at a median of 75 days (IQR, 70-86) after the second dose. The study ended on April 24, 2021. Baseline samples were obtained after a median abstinence period of 2.8 days (IQR, 2-3) and follow-up samples after a median of 3 days (IQR, 3-4). Of the 45 men, 21 (46.7%) received BNT162b2 and 24 (53.3%) received mRNA-1273. Baseline sperm concentration and TMSC were 26 million/mL (IQR, 19.5-34) and 36 million (IQR, 18-51), respectively. After the second vaccine dose, the median sperm concentration significantly increased to 30 million/mL (IQR, 21.5-40.5; $P=.02$) and the median TMSC to 44 million (IQR, 27.5-98; $P=.001$). Semen volume and sperm motility also significantly increased (Table).

Eight of the 45 men were oligospermic before the vaccine (median concentration, 8.5 million/mL [IQR, 5.1-12]). Of these 8, 7 men had increased sperm concentration to normozoospermic range at follow-up (median concentration, 22 million/mL [IQR, 17-25.5]), and 1 man remained oligospermic. No man became azoospermic after the vaccine.

The waterfall plot shows the within-participant change in TMSC from baseline (range, –22 million to 93 million) for each man (Figure).

Discussion

In this study of sperm parameters before and after 2 doses of a COVID-19 mRNA vaccine, there were no significant decreases in any sperm parameter among this small cohort of healthy men. Because the vaccines contain mRNA and not the live virus, it is unlikely that the vaccine would affect sperm parameters. While these results showed statistically significant increases in all sperm parameters, the magnitude of change is within normal individual variation and may be influenced by regression to the mean.[5] Additionally, the increase may be due to the increased abstinence time before the second sample. Men with oligospermia did not experience further decline.

The limitations of the study include the small number of men enrolled; limited generalizability beyond young, healthy men; short follow-up; and lack of a control group. In addition, while semen analysis is the foundation of male fertility evaluation, it is an imperfect predictor of fertility potential. Despite this, the study's time frame encompasses the full life cycle of sperm.

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