CORRESPONDENCE

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

Randy S. Morris, M.D.

IVF1, 3 North Washington Street, Naperville, Illinois

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. (Fertil Steril Rep® 2021;■:■–■. ©2021 by American Society for Reproductive Medicine.)
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

Received March 26, 2021; revised May 24, 2021; accepted May 28, 2021.
R.S.M. nothing to disclose.
Reprint requests: Randy S. Morris, 3 North Washington Street, Naperville, Illinois 60540 (E-mail: rsm@ivf1.com).

Fertil Steril Rep® Vol. ■, No. ■, ■ 2021 2666-3341

https://doi.org/10.1016/j.xfre.2021.05.010

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
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

Morris. No impact of COVID antibodies on fertility. Fertil Steril Rep 2021.

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).

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).

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

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

Morris. No impact of COVID antibodies on fertility. Fertil Steril Rep 2021.

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.

REFERENCES

1. Lu-Culligan A, Iwasaki A. The false rumors about vaccines that are scaring women. The New York Times. Available at: https://www.nytimes.com/2021/01/26/opinion/covid-vaccine-rumors.html. Accessed January 26, 2021.
2. News, HaM. Head of Pfizer research: covid vaccine is female sterilization. Available at: https://archive.is/9EULk. Accessed January 6, 2020.
3. Frendo JL, Olivier D, Cheynet V, Blond JL, Bouton O, Vidaud M, et al. Direct involvement of HERV-W Env glycoprotein in human trophoblast cell fusion and differentiation. Mol Cell Biol 2003;23:3566–74.
4. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.
5. Forman EJ, Franasiak JM, Patounakis G, Scott RT. Why abandoning sustained implantation rate may be throwing the baby out with the bathwater. Hum Reprod 2016;31:1926–7.
6. Chang C, Chen PT, Chang GD, Huang CJ, Chen H. Functional characterization of the placental fusogenic membrane protein syncytin. Biol Reprod 2004;71:1956–62.
7. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin 2020;41:1141–9.

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

R. S. Morris
Naperville, Illinois