Long-term evaluation of sperm parameters after coronavirus disease 2019 messenger ribonucleic acid vaccination

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Objective: To determine whether the COVID-19 mRNA vaccines can negatively impact the semen parameters of young healthy men in the long-term.

Design: We conducted semen analyses on 12 men before, 3 and 9 months after achieving fully vaccinated status. Individuals who admitted a history of infertility or previous azoospermia were excluded from study participation.

Subjects: Healthy male volunteers between the ages of 18-50 years old were recruited between September 2021 - March 2022.

Main Outcome Measures: Semen analyses were performed and evaluated volume, sperm concentration, total motility, and total motile sperm count (TMSC). The primary outcome was median change in the TMSC at baseline, 3 months, and at least 9 months following vaccination.

Results: A total of 12 men voluntered in our study (median age 26 [25 - 30] years). Subjects provided follow-up semen samples at a median of 10 months following the second vaccine dose. There were no significant changes in any semen parameters between baseline, 3 months, and 10 months following vaccination. Baseline samples demonstrated median sperm concentrations and TMSC of 29.5 million/cc [9.3 – 49] and 31 million [4-51.3], respectively. At 9-month follow-up, sperm concentration and TMSC were 43 [20.5 – 63.5] (P= .351) and 37.5 [8.5 – 117.8] (P= .519), respectively. Of note, there were no significant changes in semen volume nor total motility (%) for participants at follow-up.

Conclusion: COVID-19 mRNA vaccines and the booster dose does not appear to negatively impact the semen parameters of healthy males up to 10 months following vaccination. (Fertil Steril Rep® 2022;3:211–3. © 2022 by American Society for Reproductive Medicine.)

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Severe acute respiratory syndrome coronavirus 2 can significantly affect the human reproductive system, with data suggesting that infection temporarily decreases sperm production thereby negatively impacting male fertility (1, 2). Despite the proven safety of vaccination against coronavirus disease 2019 (COVID-19), vaccine hesitancy remains prevalent for both males and females, with some studies citing fear of future impact to reproductive health as a major reason (3). Previously, we have reported that messenger ribonucleic acid (mRNA) COVID-19 vaccination did not negatively impact semen parameters after 3 months (2). Nevertheless, fertility status remains a concern among the vaccine-hesitant, with many citing a lack of long-term data (3). Therefore, we conducted a follow-up of our initial investigation, evaluating the long-term impact of COVID-19 vaccination on male fertility potential at least 9 months after vaccination. We hypothesized that long-term COVID-19 vaccination would not negatively impact semen parameters.

MATERIALS AND METHODS

Study Design
We conducted a follow-up of our single-center prospective study at the

Received May 22, 2022; revised July 18, 2022; accepted July 19, 2022.
P.D. reports funding from the Miami Andrology Research Scholar (MARS) Program for the submitted work. R.R. reports funding from the Miami Andrology Research Scholar (MARS) Program and National Institutes of Health, United States Grant R01 DK130991 for the submitted work. A.D. has nothing to disclose. M.P. has nothing to disclose. R.B.-B. has nothing to disclose. R.R. has nothing to disclose. K.K. has nothing to disclose. E.I. has nothing to disclose. J.B. has nothing to disclose. Reprint requests: Ranjith Ramasamy, M.D., Desai Sethi Urology Institute, Miller School of Medicine, University of Miami, 1120 NW 14th Street, Suite 1563, Miami, Florida 33136 (E-mail: Ramasamy@miami.edu).
University of Miami investigating the long-term impact of COVID-19 vaccination on sperm parameters. This study was approved by the Institutional Review Board of the University of Miami (No. 20201451). All 45 of the healthy male volunteers who participated in our previous survey between the ages of 18 and 50 years were contacted between September 2021 and March 2022 and asked to participate in this follow-up study. On enrollment, participants provided information regarding their COVID-19 infection history, previous COVID-19 vaccinations, and fertility history.

The inclusion criteria were as follows:

- Men aged 18–50 years
- Men who received at least 2 COVID-19 mRNA vaccines within the last 9 months
- Men with a history of COVID-19 infection or positive test (polymerase chain reaction, nucleic acid amplification test, or antigen testing) result within the last 3 months
- Men with a history of azoospermia
- Men with a genetic or other medical condition known to be associated with decreased semen parameters (i.e., Klinefelter syndrome, Y chromosome microdeletion, and postchemotherapy treatment)

### TABLE 1

| Semen parameters of subjects at baseline, 3-months, and 9-months following COVID-19 mRNA vaccination. | Baseline (n = 12) | 3-month follow-up (n = 12) | 9-month follow-up (n = 12) | P value |
|---|---|---|---|---|
| Semen volume (mL) | 1.5 (1.2–2.6) | 2 (1.6–3.3) | 1.9 (1–2.8) | .452 |
| Sperm concentration (million/mL) | 29.5 (9.3–49) | 27 (14.8–35.8) | 43 (20.5–63.5) | .351 |
| Total motility (%) | 56.5 (45.3–64.8) | 64.5 (52–70) | 67.5 (51.8–75.3) | .224 |
| TMSC (million) | 31 (4–51.3) | 33 (13.5–84) | 37.5 (8.5–117.8) | .519 |

Note: Data are presented as median (interquartile range, 25th–75th). TMSC = total motile sperm count.

Diaz. COVID-19 vaccination impact on semen. Fertil Steril Rep 2022.

### FIGURE 1

Boxplot demonstrating differences in (A) total motile sperm count (TMSC), (B) semen volume, (C) sperm concentration, and (D) total motility among patients before and after coronavirus disease 2019 vaccination.

Diaz. COVID-19 vaccination impact on semen. Fertil Steril Rep 2022.
Men who have been receiving testosterone replacement therapy or anabolic steroids within the last year

Recruitment
Flyers were created and emailed to potential returning participants. Interested subjects emailed the research coordinator to begin the enrollment and prescreening process to ensure no exclusion criteria were met.

Semen Collection
Volunteers were advised to remain abstinent for 2–5 days before their sample collection appointment. Samples were produced via self-stimulation in the office with immediate analysis (under 45 minutes) performed by 2 trained andrologists per the World Health Organization guidelines (4).

Outcomes
Twenty of the 45 volunteers in the previous study were available to participate in this follow-up analysis. A semen analysis was performed at least 9 months after vaccination and evaluated volume, sperm concentration, total motility, and total motile sperm count (TMSC). The primary outcome was median change in the TMSC at baseline, 3 months, and at least 9 months after vaccination.

Statistical Methods
Statistical analysis was performed with SPSS v.28 (IBM). Continuous variables were presented as median and interquartile ranges (25th to 75th percentiles) in accordance with data distribution. The Kruskal-Wallis test was used to compare the 3 semen parameter intervals. A P value of <.05 was considered statistically significant.

RESULTS
A total of 12 men volunteered in our study (median age, 26 [25–30] years). The participants provided follow-up semen samples at 3 months and a minimum of 9 months after their second vaccine doses (Supplemental Table 1, available online). Samples were collected a median of 11 and 10 months after the first and second vaccine dose administrations, respectively. Half of the participants (n = 6) received booster doses (median of 2 months before analysis), and 33% of men had a history of COVID-19 infection with mild symptoms after vaccination. It was found that 58% (n = 7) of men completed their first series (2 doses) with Moderna vaccines, whereas the remaining 42% (n = 5) received Pfizer vaccines. At baseline, 3 months, and a minimum of 9 months after COVID-19 vaccination, semen analyses demonstrated median TMSCs of 31 (45.13), 33 (13.5–84), and 37.5 (8.5–117.8) million (P = .519), respectively (Table 1). Overall, there were no significant differences in any parameter between time measurements (Fig. 1A–1D). Three men had semen analyses demonstrating oligospermia at baseline. Of these 3 men, 2 were found to be normospermic at 3 and at least 9 months of follow-up, and the other remained oligospermic for all semen analyses.

DISCUSSION
In this follow-up study, we examined the long-term effects of COVID-19 vaccination on semen parameters and found no significant changes compared with those at baseline and 3 months after vaccination, which is consistent with the results of our previous study by Gonzalez et al. (2). The plausible explanations for this maintenance of semen parameters may be the mechanism of the mRNA vaccine, lack of live virus, and its inability to alter an individual's deoxyribonucleic acid (4, 5). In addition, the apparent absence of mRNA localization to the gonads is most likely in part due to the blood-testis barrier. Because research has demonstrated that female ovarian reserve in subsequent in vitro fertilization after mRNA vaccination is unaffected, the results of this study should serve as reassurance to vaccine-hesitant individuals concerned about future fertility (6).

This study has some limitations. Although semen analyses remain the gold standard male fertility test and 2 patients were proven fertile before study participation, they are imperfect with significant variability between samples for a given individual and no qualitative assessment (7). In addition, 4 participants experienced previous COVID-19 infection, and although those with infections within 3 months were excluded, the number of spermatogenic cycles required to return to baseline semen parameters remains unknown. Finally, the small number of men enrolled for this follow-up study was due to a variety of factors——such as moving out of state, deactivated E-mail addresses, and nonresponse. Nevertheless, this study remains one of the first to demonstrate the long-term reproductive safety of mRNA COVID-19 vaccines in men. Future studies should be performed to determine whether COVID-19 vaccines can affect the quality of sperm thereby impacting the live pregnancy rate.

REFERENCES
1. He Y, Wang J, Ren J, Zhao Y, Chen J, Chen X. Effect of COVID-19 on male reproductive system - a systematic review. Front Endocrinol (Lausanne) 2021;12:677701.
2. Gonzalez DC, Nassau DE, Khodamoradi K, Ibrahim E, Blachman-Braun R, Ory J, et al. Sperm parameters before and after COVID-19 mRNA vaccination. J Am Med Assoc 2021;326:273–4.
3. Diaz P, Zizzo J, Balaji NC, Reddy R, Khodamoradi K, Ory J, et al. Fear about adverse effect on fertility is a major cause of COVID-19 vaccine hesitancy in the United States. Andrologia 2022;54:e14361.
4. World Health Organization. WHO laboratory manual for the examination and processing of human semen. Available at: https://www.who.int/docs/default-source/reproductive-health/srhr-documents/infertility/examination-and-processing-of-human-semen-5ed-eng.pdf. Accessed May 20, 2022.
5. Centers for Disease Control and Prevention. Understanding mRNA COVID-19 vaccines. Available at: https://cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html. Accessed April 3, 2022.
6. Orvieto R, Noach-Hirsh M, Segov-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.
7. Keel BA. Within- and between-subject variation in semen parameters in infertile men and normal semen donors. Fertil Steril 2006;85:128–34.