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CLINICAL ARTICLE

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The impact of COVID-19 vaccine on sperm quality

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Abstract

Objective: To examine the effect of the BNT162b, mRNA, SARS-CoV-2 virus vaccine on sperm quality.

Methods: This was a prospective cohort study conducted on sperm donors at the sperm bank of a tertiary, university affiliated medical center. All sperm donors donated sperm repeatedly and the average sperm parameters of all available samples were compared before and after receiving the SARS-CoV-2 vaccine. Each donor served as his own control. For all participants, at-least one sperm sample was received 72 days after completing the second vaccine. Main outcome measures included total sperm count, total motile count and percent of motile sperm.

Results: A total of 898 sperm samples from 33 sperm donors that were vaccinated with the Pfizer BNT162b, mRNA, SARS-CoV-2 virus vaccine were analyzed, 425 samples were received before the vaccine, while 473 samples were received after vaccination. Total sperm count and total motile count increased after the second vaccine compared to samples before vaccination. Percent of motile sperm did not change after vaccine.

Conclusion: The Pfizer BNT162b, SARS-CoV-2 vaccine has no deleterious effect on sperm quality. Patients and physicians should be counseled accordingly.

KEYWORDS
COVID-19, sperm count, sperm quality vaccine

1 | INTRODUCTION

On March 11, 2020, the COVID-19 outbreak was declared a pandemic by the general director of the World Health Organization.[1] Since then, the outbreak has directly affected the lives of millions of people worldwide. As a result of the pandemic, an urgent call was made to develop a vaccine against the SARS-CoV-2 virus. After several commercial vaccines, including the Pfizer BNT162b, mRNA, SARS-CoV-2 virus vaccine were approved for public use, nationwide vaccination programs were initiated in many countries. Prior to the initiation of vaccination programs, the safety and efficacy of the vaccine was tested in phase 1 and 2 trials,[2] followed by a phase 3, prospective, randomized, placebo-controlled trial.[3] The Pfizer BNT162b, SARS-CoV-2 vaccine is given, in two, 30 μg, intramuscular injections, 21 days apart. Reported side effects of the vaccine included mainly local pain at the injection site. Most common systemic side effects included fatigue (59%) and headache (51%), specifically after the second vaccine dose. A total of 16% of the younger vaccine recipients reported fever ≥38°C.[3]

Concerns regarding the effect of coronavirus on male fertility have been raised. Impaired spermatogenesis was described among COVID-19 patients, a finding that could be explained by elevated immune response and cytokine storm in testis tissue or by autoimmune orchitis that was observed in pathological specimen of deceased

COVID-19 male patients.[4,5] A similar effect could theoretically be seen also after the SARS-CoV-2 vaccine that may elicit a similar immune response.

Studies addressing the COVID-19 pandemic have shown that about a quarter of the U.S. population has little or no interest in receiving the COVID-19 vaccine.[6] Among the many factors affecting the decision to receive the vaccine, conspiracy theories have been spreading during the pandemic,[7,8] some of which claim that the vaccine may cause irreversible damage to female and male fertility. The aim of our study was to describe the effect of the SARS-CoV-2 vaccine on sperm quality.

2 | MATERIALS AND METHODS

This was a prospective, observational cohort study conducted at the institute for the study of fertility at a tertiary, university-affiliated medical center. Participants were healthy, elective sperm donors that had the SARS-CoV-2 vaccine administered according to the local national vaccination program. All recruits received the Pfizer BNT162b, mRNA, SARS-CoV-2 virus vaccine in a two, 30 μg, intramuscular injections, 21 days apart. No intervention was made for the purpose of the study for any of the recruits.

Sperm donors were asked to participate in the study by completing a short questionnaire. The data collected included donor demographics, vaccinations date and side effects after each vaccine. Average sperm parameters including total sperm count, total motile count and percent of motile sperm were compared before and after vaccination. As all donors donate sperm repeatedly, for each donor, we included in the analysis all available sperm samples ever received both before and after vaccination. The average sperm parameters of all samples before and after vaccination was used for comparison. As the date of second vaccine was known, for each donor, at least one sample was received 72 days or more after the second vaccine. Each donor served as his own control. In a sub group of donors, sperm samples were available also between the first and second vaccine. For these cases, the average sperm parameters were compared at three time points, before the first vaccine, between the first and the second vaccine, and after the second vaccine.

2.1 | Semen analysis

All participants were instructed to abstain from sexual activity for 2–3 days before sample collection. The semen samples were collected by masturbation into a sterile plastic container. Each ejaculate was allowed to liquefy for at least 30 min at 37°C and was analyzed following the WHO manual guidelines for the examination and processing of human sperm.[9] Two-hundred spermatozoa from each aliquot were analyzed for sperm concentration and total motility (progressive and non-progressive). Sperm morphology was evaluated by Papanicolaou staining under ×1000 magnification and scored as being "normal" or "abnormal" according to the strict criteria of Kruger et al.[10] Semen parameter abnormalities were defined by 2010 WHO reference values.[11] The laboratory successfully participates in various quality control exercises (UK NEQAS, External Quality Assessment Schemes) for sperm concentration, motility, and morphology.

2.2 | Sperm freezing

Each specimen was washed with human tubal fluid medium (Irvine Scientific) supplemented with 1% human serum albumin (Kamapharm Human Albumin; Kamada, Kibbutz Beit Kama, Israel) and carefully diluted by the addition of an equal volume of freezing medium test yolk buffer (Irvine Scientific). After dilution, the mixture was equilibrated for 15 min at room temperature, sealed in 0.5 ml straws, and cooled in a semi-programmable freezer (Nicool LM-10; Air Liquid). The specimens were cooled gradually and then transferred directly to liquid nitrogen (−196°C).

All samples were assessed for post-thaw semen quality. Frozen sperm samples were thawed on a hotplate at 37°C for 5 min and then transferred to 1.5 ml tubes and thoroughly mixed to ensure a homogeneous mixture. Sperm parameters were analyzed as above.

Statistical analysis was done using SPSS software (IBM, SPSS statistics, Version 25,2018. IBM® corp., Armonk, NY, USA) Distribution of continuous variables was evaluated using histograms and Kolmogorov-Smirnov test. Sperm parameters before vaccination and after the second vaccine were compared using paired samples *t*-test (for normally distributed continuous variables) or by using Wilcoxon rank test (for non-normally distributed variables). For the sub-group of sperm donors for whom sperm samples were available also between the first and second vaccine, sperm parameters were compared between three time points, using repeated measures ANOVA or Friedman test, according to distribution of variables. All statistical analyses were two-sided and $P < 0.05$ was considered significant.

2.3 | IRB

The study was approved by the local institutional review board. No intervention was made for any of the subjects.

3 | RESULTS

A total of 898 sperm samples from 33 sperm donors that were vaccinated with the Pfizer BNT162b, mRNA, SARS-CoV-2 virus vaccine were analyzed, 425 samples (47%) were received before, and 473 samples (53%) were received after vaccine. Mean donor age was 27 years. All sperm donors were healthy with no significant comorbidities. All were vaccinated between December 2020 to March 2021. Side effects were generally more common after the second vaccine. The most commonly reported side effect was pain at injection site occurring in 79% of cases after the first vaccine, and in 88%

of cases after the second vaccine. Lethargy was the second most common side effect occurring in 9%, and 48% of cases after the first and second vaccine, respectively. There was one case of fever reported after the second vaccine. The average number of sperm samples available for analysis was 27.2 per donor. Average sperm parameters before vaccination and after the second vaccine are shown in Table 1. The Pfizer BNT162b, SARS-CoV-2 vaccine had no negative affect on any of the fresh sperm quality parameters. In fact, total sperm count and total motile count significantly increased after the second vaccine. The percent of motile sperm was similar between groups. As in the fresh samples, the BNT162b, SARS-CoV-2 vaccine did not negatively affect frozen, thawed sperm quality. The motility percentage of thawed sperm was similar before and after vaccination, while the total progressive motile count was significantly higher after the second vaccine, resulting in a higher number of frozen samples yielded per ejaculate that meet our standard of care.

Out of the 33 donors, 21 gave sperm along the course of their vaccination, in the 3 weeks between the first and the second vaccine. For this subgroup of donors, we compared sperm quality at three time points, 326 samples before vaccination, 80 samples between the first and second vaccine and 260 samples after the second vaccine. Results are shown in Table 2. In this subgroup of patients, the Pfizer BNT162b, SARS-CoV-2 vaccine did not negatively affect any of the fresh sperm quality parameters. Similar to the whole cohort, the total sperm count and the total motile count significantly increased after the first vaccine, with no change in the percent movement. Moreover, the BNT162b, SARS-CoV-2 vaccine did not negatively affect sperm quality after freezing. The number of samples available for freezing was higher after vaccination, as well as the percent of motile sperm after freezing.

4 | DISCUSSION

Due to the urgent need for a COVID-19 vaccine to be approved for public use, many concerns regarding its safety were raised.[12] While some of the concerns had medical rationale, others were raised outside of the medical community, by the public,[8] among them were the concerns for the effect of the vaccine on fertility, both female and male.

Our data shows that the Pfizer, BNT162b, SARS-CoV-2 vaccine had no deleterious effect on sperm quality on any of the sperm parameters for both fresh and frozen, thawed samples. In-fact, sperm quality improved after the second vaccine, as compared to sperm samples given in the months prior to vaccination. Sperm samples that were obtained after the first vaccine dose also did not show any negative effect on sperm quality, which was found to be improved compared to samples before vaccination.

TABLE 1 Sperm parameters 0f 898 sperm samples before and after receiving the COVID-19 vaccine (33 donors)

	Normal ranges	Before vaccine ($n = 425$)	After second vaccine ($n = 473$)	P value
Fresh sperm				
Total sperm count (10^6)	>39	152 ± 43	174 ± 53	0.005*
Total motile count (10^6)	>9	96 ± 31	112 ± 37	0.004*
Motility percentage (%)	>40	63 ± 9	63 ± 4	0.760
Thawed sperm				
Motility percentage (%)		43 ± 9	43 ± 7	0.436
Total progressive motile sperm count (10^6)		7.8 ± 3	8.7 ± 3	0.048*
Number of frozen samples yielded per ejaculate		1.8 (0.8)	2.1 (1)	0.012*

Note: Results are expressed as (mean ± standard deviation). *$P < 0.05$.

TABLE 2 Sperm parameters of 666 sperm samples before COVID-19 vaccine, after the first vaccine and after second vaccine (21 donors)

	Normal range	Before vaccine ($n = 326$)	After first vaccine ($n = 80$)	After second vaccine ($n = 260$)	P value
Fresh sperm					
Total sperm count (10^6)	>39	158 ± 39	186 ± 70	181 ± 45	0.034*
Total motile count (10^6)	>9	101 ± 28	121 ± 48	116 ± 33	0.048*
Motility percentage (%)	>40	63 ± 4	65 ± 4	63 ± 4	0.188
Thawed sperm					
Motility percentage (%)		43 ± 7	47 ± 8	45 ± 7	0.023*
Total progressive motile sperm count (10^6)		8 ± 3	9 ± 3	9 ± 2	0.101
Number of frozen samples yielded per ejaculate		1.8 (0.9)	2.2 (1)	2.3 (1)	0.023*

Note: Results are expressed as (mean ± standard deviation). *$P < 0.05$.

Limited data showed that male COVID-19 patients may experience a severe cytokine storm with an acute immune response and autoimmune orchitis that could damage spermatogenesis.[4,5] Even though the vaccine may elicit a similar immune response and potentially harm the delicate process of spermatogenesis, our data shows otherwise, as no negative effect on sperm quality was seen following one or two vaccine doses. The autoimmune orchitis that was reported among male COVID-19 patients, was seen among deceased patients, in autopsy reports.[5] These specific patients may have experienced an extreme immune response, that may be related to their death, and among others, caused testicular tissue damage. This extreme response may not be representative of most COVID-19 patients or one that is seen during vaccination. Reported side effects of the COVID-19 vaccine are usually mild,[2,3] and accordingly, none of the sperm donors in our cohort experienced any severe side effects from the vaccine.

The nation-wide vaccination programs, that began as early as December 2020, resulted in a gradual ease in quarantines and social distancing. This may have led to decreased psychological distress that could explain the improvement in sperm quality observed in our cohort after vaccination.

Concerns regarding potential side effects of the vaccine, as well as proper physician counseling, are among the major determinants of vaccine uptake across many countries.[13–16] Our data may reassure both the public and counseling physicians about the safety of the vaccine with regard to male fertility, an important concern raised by many fertility-aged couples.

Our work has several limitations. As this was an observational cohort, the number of sperm samples available for analysis differed between subjects, according to the number of samples given during each period (before or after vaccination). Several commercial vaccines were approved for clinical use other than the Pfizer BNT162b, SARS-CoV-2 vaccine and even though side effects may be similar, generalization of our results to other commercial vaccinations should be made with caution.

The advantages of our work include the very large cohort of sperm samples, with confirmed quality sperm, that was available for analysis. While sperm samples before vaccination were retrospectively retrieved, further samples were prospectively collected. As sperm quality may differ significantly within subjects on different samples, we used the average data of all sperm samples given both before and after the vaccine rather than one sample. The average number of sperm samples available per donor was large (27 per donor). This enabled us to overcome possible outliers in any one random sperm count that are common. As spermatozoa mature along 72 days, all subjects had at least one sample given 72 days or more after the second vaccine. Another major advantage of our work was the large number of sperm samples that available for analysis during vaccination, confirming that the vaccine does not cause any negative affect on sperm quality both in the short term, during vaccination, and in the long term after completing the vaccine.

In conclusions, our data shows that the Pfizer BNT162b, SARS-CoV-2 vaccine has no deleterious effect on sperm samples, and can be administered safely. Patients and physicians should be counseled accordingly in-order to increase vaccine uptake.

AUTHORS CONTRIBUTION

Author contribution statement: All authors contributed substantially to planning and caring out this work. Nadav Michaan: main author, involved in: conceptualization, methodology, project administration, investigation, data analysis, supervision, writing - original draft, and writing - review and editing. Shimi Barda: involved in: methodology, project administration, data curation and analysis, supervision, reviewing original draft. Ofer Lehavi: involved in: methodology, project administration, data curation and analysis, supervision, reviewing original draft. Sandra Kleiman: data curation, investigation, supervision, and writing of original draft. Atalia Wenkert: data curation, investigation, supervision, and writing of original draft. Ido Laskov: Involved in: conceptualization, data curation, investigation, supervision, and writing of original draft. Ron Hauzer: Involved in: conceptualization, methodology, project administration, data curation, supervision, writing - original draft and reviewing. Foad Azem: Involved in: methodology, project administration, data curation and analysis, supervision, reviewing original draft. Dan Grisaru: Involved in: Conceptualization, methodology, project administration, investigation, data curation and analysis, supervision, writing - original draft and reviewing.

CONFLICTS OF INTEREST

The authors have no conflicts of interest

DATA AVAILABILITY STATEMENT

No. Research data are not shared.

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