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RESEARCH ARTICLE

Vaccination with either mRNA or Vector-Based COVID-19 Vaccine has no Detectable Effect on Sperm Parameters

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ABSTRACT

Background: With the introduction of COVID-19 vaccines in 2021, concerns arose regarding their impact on male fertility. Therefore, this study investigated the effect of mRNA- and vector-based COVID-19 vaccination on male fertility by analyzing sperm parameters in subjects with unrestricted and restricted fertility.

Methods: In this prospective self before-after control study at a single University-based Infertility Center in Duesseldorf, Germany, a total of 25 male subjects were recruited, who were scheduled to receive their first vaccination against COVID-19 between January and August 2021. Semen samples were obtained before and after the first COVID-19 vaccination to perform an analysis of semen quality according to the 2010 World Health Organization guideline. Main outcome measures were ejaculate volume, sperm concentration, total sperm number, percentage of sperm motility and sperm morphology.

Results: There were no significant changes in sperm parameters before and after the vaccination.

Conclusion: Both, mRNA and vector-based COVID-19 vaccination had no short-term effect on sperm parameters. Therefore, an influence of COVID-19 vaccination on male fertility appears to be very unlikely.

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Abbrevations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; WHO: World Health Organization; HPV: Human Papillomavirus; COVID-19: Coronavirus Disease 2019; ART: Assisted Reproductive Technology; BAU: Binding Antibody Units

Introduction

Triggered by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), a pandemic started in Wuhan (Hubei Province, Republic of China) in December 2019, with more than 6 million deaths worldwide until 2022 [1]. Since then, the primary goal to combat the pandemic has been to develop a vaccine against the single-stranded RNA virus of the coronavirus family.

As of mid-2022, various types of vaccines became available with different molecular formulations. While Vaxzevria® (AstraZeneca) is based on viral vectors,

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others use inactivated virus and protein subunits. The mRNA vaccines Comirnaty® (BioNTech/Pfizer, Mainz, Germany) and Spikevax™ (Moderna, Cambridge Massachusetts, USA) however, are a novel development with regards to the vaccine formulation and became the predominant vaccine type currently used in Europe.

While Coronavirus Disease 2019 (COVID-19) is believed to cause male fertility deterioration [2], no information on the effect of vaccination on male fertility existed at the time of emergency approval of the SARS-CoV-2 vaccines. This led to an uncertainty among the general public, as evidenced by an increase in google queries at the time of the emergency approval of the SARS-CoV-2 vaccines [3]. In clinical practice we still observe men who deliberately choose to not get vaccinated because they fear an abatement of their fertility. This concern is based on the erroneous theory that the RNA or DNA contained in the vaccines can cause damage to their own DNA. The vaccination skeptics were supported by the fact that women and men of reproductive age who participated in the pivotal trial were asked to use a safe method of contraception or maintain sexual abstinence [4,5].

It was not until after the emergency approval that a small number of studies were published that examined the relationship between SARS-CoV-2 vaccines and male fertility.

The studies demonstrated that mRNA vaccines have no effect on sperm parameters such as sperm concentration and sperm motility or on the outcome of Assisted Reproductive Technology (ART) [6-9]. Vector vaccines were also shown to have no effect on sperm parameters [8]. However, since the studies were either of small size or of retrospective design there is still little to no prospective and reliable evidence regarding the effect of different vaccines on sperm parameters and therewith male fertility.

Therefore, the present work investigated in a prospective study design the effect of mRNA- and vector vaccines against SARS-CoV-2 on male fertility by analyzing sperm parameters before and after vaccination. In addition, blood serum was tested for SARS-CoV-2 antibodies at the time points of ejaculation before and after vaccination.

Material and Methods

The present work is a self before-after control study conducted at the Heinrich-Heine-University Hospital Interdisciplinary Fertility Center Duesseldorf UniKiD from May 2020 to November 2021. Since the aim of the study was to investigate the short-term effect of COVID-19 vaccination based on mRNA or vector vaccine on male fertility an ejaculate analysis was performed before as well as approximately 120 days after the first vaccination. In addition, examination of anti-SARS-CoV-2 antibodies before as well as after vaccination were performed. Written informed consent was obtained from each participating subject. Inclusion criteria were age ≥ 18 years and planned vaccination against COVID-19 (two doses) with an mRNA or vector vaccine. Exclusion criteria were prior immunization against COVID-19, history of PCR-confirmed COVID-19 or a PCR-confirmed COVID-19 infection at the time of study participation. An approval of the local ethics committee (2020-938) was issued.

Recruitment was performed in the infertility clinic, by word of mouth and among the medical staff at the University Hospital Duesseldorf.

Sperm analysis

Ejaculate was collected by masturbation into a sterile cup at the investigation site UniKiD. Participants were asked to maintain an abstinence of 2-7 days. The ejaculate was liquefied at room temperature for approximately 30-60 minutes before examination. Examination was performed using the 2010 World Health Organization (WHO) guideline laboratory manual for the examination and processing of human semen [10] consecutively by two highly experienced embryologists to control for consistency. The report includes ejaculate volume (ml), sperm concentration (number/ml), total sperm number, sperm motility (%), and sperm morphology (%). Sperm motility was reported as progressive motile sperm and as total motile sperm.

The evaluation of sperm concentration and motility was performed using a MAKLER® counting chamber by counting 10 squares twice. Evaluation of sperm morphology was conducted using TESTSIMPLETS® prestained slides by applying 10 µl of semen following liquefaction. The evaluation was performed at a magnification of 400 × counting 200 cells. Determining the sperm morphology with TESTSIMPLETS® is a common method in ART laboratories but does not belong to the methods recommended by the WHO [11]. In case of normal forms < 4%, it was not differed between head, neck or tail deformation in more detail. Normozoospermia was defined according to the fifth edition of the WHO manual for the examination and processing of human semen and subjects: total sperm number >39 Mio, progressive motility > 32% and normal forms > 4%.

Commercial Anti-SARS-CoV-2 IgG assay

Blood samples were tested for anti-SARS-CoV-2 antibodies using the commercially available Anti-SARS-CoV-2-ELISA IgG (sampling 1) and Anti-SARS-CoV-2 QuantiVac-ELISA IgG (sampling 2) test system from EUROIMMUN that was run on the EUROIMMUN ANALYZER I-2P according to the manufacturer's instructions. Anti-SARS-CoV-2-ELISA IgG (sampling 1) results < 0.8 were considered negative, between 0.8 and 1.1 were considered indeterminate and > 1.1 were considered positive. The anti-SARS-CoV-2 QuantiVac-ELISA IgG (sampling 2) assay includes a 6-point calibration curve and reports IgG antibody concentration as standardized units (binding antibody units per milliliter [BAU/mL]). Results < 25.6 BAU/mL were considered negative, between ≥ 25.6 BAU/mL and ≤ 35.2 BAU/mL were considered indeterminate, and > 35.2 BAU/mL were considered positive. The lower detection limit was < 3.2 BAU/mL, and the upper detection limit was > 384 BAU/mL.

In-house SARS-CoV-2 neutralization test

A serial dilution endpoint neutralization test was performed with an infectious SARS-CoV-2 B.1. Wuhan-Hu1 isolate (EPI_ISL_425126) to determine the SARS-CoV-2 neutralization capacity of the serum samples as previously described [12]. In brief, serial dilutions of heat-inactivated (56°C, 30 minutes) serum samples were pre-incubated in cell-free plates with 100 tissue culture infectious dose 50 (TCID50) units of SARS-CoV-2 for 1 hour at 37°C. After pre-incubation, 100 µL of cell suspension containing 7 × 10^4/mL Vero cells (ATTC-CCL-81) were added. Plates were incubated at 37°C, 5% CO_2 for 4 days before microscopic inspection for virus-induced cytopathic effect. The neutralization titer was determined as the highest serum dilution without virus induced cytopathic effect. Tests were performed as independent duplicates for each sample. Positive, negative, virus only, and cell growth controls were run during each assay.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 27. Sperm parameters before and after vaccination were compared using Wilcoxon matched pairs test. McNemar test was used for paired categorical data. As an effect size measures for the Wilcoxon test the Pearson correlation coefficient and for the McNemar test the odds ratio are reported. Regarding the Pearson correlation coefficient absolute values ranging from 0.01-0.09, 0.10-0.29, 0.30-0.49 and ≥ 0.50 represent a negligible, small, moderate, and strong effects. All statistical analyses were two-sided and p-values ≤ 0.05 were considered statistically significant.

Results

The present work involved the examination of 50 ejaculates obtained from 25 male subjects at two consecutive time points. The subjects, aged 42.0 (± 11.3) years, had at least one child in 66% of the cases. 20% of the subjects had a successful infertility treatment in the history, and 12% of the subjects were undergoing infertility treatment at the time of the study. Further basic characteristics of the subjects are depicted in table 1.

The first ejaculate was obtained before the first vaccination against COVID-19. The second ejaculate was obtained on average 118.3 (± 23.1) days after the first vaccination and 72.9 (± 26.6) days after the second vaccination. The interval between the first and second ejaculate was 157.0 (± 74.3) days.

Table 1: Characteristics of the study population. Data are mean (standard deviation) or number (%).

Participants` Characteristics	Results (n = 25)
Age (years)	42.0 (± 11.3)
Body mass index (kg/m²)	25.6 (± 3.0)
Smoker	5 (20%)
Diabetes mellitus Type 2	0 (0%)
Hypertension in need of medical treatment	2 (8%)
Paternity	14 (66%)
Of which resulting from fertility treatment	5 (20%)
History of testicular cancer	1 (4%)
Current fertility treatment	3 (12%)
Period between first vaccination and second sample (days)	118.3 (± 23.1)
Period between second vaccination and second sample (days)	72.9 (± 26.6)
Period between both samples (days)	157.0 (± 74.3)

Vaccine administered

In 18 of 25 subjects, mRNA vaccine was administered twice, 21 or 28 days apart. Of these, Spikevax™ in 14 and Comirnaty® in 4 cases. One patient received Vaxzevria® (AstraZeneca) twice 12 weeks apart. In 6 subjects, heterologous vaccination was performed consisting of Vaxzevria® as the first vaccine and Spikevax® or Comirnaty® as the second vaccine, with the second one occurring 12 weeks after the first one.

Before-after comparison of ejaculate parameters

The first sperm analysis of all 25 subjects showed a median ejaculate volume of 2.4 ml (1.8-3.9) with a median total sperm number of 111.6 Mio/ejaculate (45.1-205.8) and a median progressive motility of 30.0% (20.0-50.0). Morphology analysis revealed that a total of 84% of the subjects had more than 4% normal forms. In the second sperm analysis, there were no significant differences with respect to all examined sperm parameters compared to the first examination (Table 2).

Before vaccination 15/25 and after vaccination 17/25 subjects met the criteria for normozoospermia (Table 3).

Out of the 15 participants with a normozoospermia before vaccination, 12 of them continued to show a normozoospermia after vaccination, whereas 3 subjects did not meet the criteria for a normozoospermia anymore after vaccination. Out of the 10 participants who did not fulfill the criteria for normozoospermia before vaccination 5 converted to normozoospermia and 5 continued to have no normozoospermia. Subjects, who merely received an mRNA vaccine twice (n = 18), did as well not show any significant changes in terms of sperm parameters in the before after comparison (Table 4).

Table 2: Sperm parameters before and after vaccine. Continuous data are presented as median (Q1-Q3, Q1 = 25th percentile, Q3 = 75th percentile) and categorical data as frequencies (%).

Semen Parameters (*n* = 25)	Before Vaccine	After Vaccine	*p*-value	Effect Size
Volume (ml)	2.4 (1.8-3.9)	2.5 (1.8-3.3)	0.445[a]	-0.15[c]
Sperm concentration (10^6/ml)	46.0 (24.5-96.0)	48.0 (32.0-63.5)	0.607[a]	-0.10[c]
Total sperm number (10^6/ejaculate)	117.6 (45.1-205.8)	100.8 (72.0-193.8)	0.798[a]	-0.05[c]
Progressive motility (%)	30.0 (20.0-50.0)	30.0 (25.0-45.0)	0.356[a]	-0.18[c]
Complete motility (%)	40.0 (27.5-57.5)	40 (30.0-60.0)	0.210[a]	-0.25[c]
Normal morphology (n)	21/25 (84%)	22/25 (88%)	> 0.999[b]	0/1[d]
Normozoospermia (n)	15/25 (60%)	17/25 (68%)	0.727[b]	3/5[d]

Note: [a]: Wilcoxon matched pairs test; [b]: McNemar test; [c]: Pearson correlation coefficient; [d]: Odds Ratio (cases with changes before/after).

Table 3: Change of number of subjects with and without normozoospermia before and after COVID-19 vaccination (*p* = 0.727, McNemar test).

Normozoospermia		After Vaccine		
		Yes	No	Total
Before Vaccine	Yes	12	3	15
	No	5	5	10
	Total	17	8	25

Table 4: Sperm parameters before and after vaccine. Continuous data are presented as median (Q1-Q3, Q1 = 25th percentile, Q3 = 75th percentile) and categorical data as frequencies (%).

Semen Parameters (*n* = 18)	Before Vaccine	After Vaccine	*p*-value	Effect Size
Volume (ml)	2.2 (1.4-3.4)	2.4 (1.8-2.8)	0.959[a]	-0.01[c]
Sperm concentration (10^6/ml)	57.0 (33.5-98.0)	56.0 (38.0-75.0)	0.744[a]	-0.08[c]
Total sperm number (10^6/ejaculate)	121.3 (72.0-247.4)	121.8 (75.0-200.5)	0.811[a]	-0.06[c]
Progressive motility (%)	36.0 (25.0-51.3)	35.0 (28.8-45.6)	0.484[a]	-0.16[c]
Complete motility (%)	42.0 (29.3-61.3)	50.6 (38.9-61.3)	0.204[a]	-0.30[c]
Normal morphology (n)	17/18 (94%)	17/18 (94%)	> 0.999[b]	0/0[d]
Normozoospermia (n)	12/18 (67%)	15/18 (83%)	0.453[b]	2/5[d]

Note: [a]: Wilcoxon matched pairs test; [b]: McNemar test; [c]: Pearson correlation coefficient; [d]: Odds Ratio (cases with changes before/after).

Anti-SARS-CoV-2 IgG

Anti-SARS-CoV-2 antibodies were measured before (*n* = 21) the first vaccination and after (*n* = 20) the second vaccination. In particular, total anti-SARS-CoV-2-spike IgG as well as SARS-CoV-2 neutralizing antibodies were measured. Two of the 25 subjects showed positive results for SARS-CoV-2 specific antibodies even before vaccination, which is considered to indicate that they had undergone a COVID-19 infection before. However, because the subjects were unaware of the infection, the time point of infection is unclear. Interestingly, these were both subjects with sperm parameters below the 5th percentile according to WHO manual 2010. All subjects showed evidence of anti-SARS-CoV-2 antibodies after vaccination with total anti-SARS-CoV-2-spike IgG levels close to or above the upper detection limit of > 384.0 BAU/ml. Neutralizing antibody titers ranged from 1:40 to 1:1280 with a median titer of 1:160.

Discussion

As of July 2022, 12-35% of the adult population in Germany was not vaccinated against SARS-CoV-2 [13]. One reason among many reasons was the fear of a negative impact on male fertility [3]. In this study we therefore analyzed sperm parameters prospectively before and after vaccination with an mRNA- and vector-based vaccine against COVID-19 in subjects with restricted and unrestricted fertility. Moreover, we analyzed SARS-CoV-2 antibodies at the time of ejaculation before and after vaccination.

We could not demonstrate any significant changes regarding sperm parameters like ejaculate volume, sperm concentration, sperm motility and sperm morphology in a comparison before and after vaccination with an mRNA or vector vaccine reinforcing previously published studies in which no effect of COVID-19 vaccination was observed either [7-9,14].

Surprisingly, there are only few studies that examined the influence of vaccination in general regarding ejaculate parameters and male fertility. While vaccine against influenza, anthrax and smallpox, for example, seem to have no effect on fertility [15-17], Human Papillomavirus (HPV) vaccination could even have a positive effect on ejaculate parameters and male fertility in HPV-positive subjects [18].

Likewise, Gonzalez, et al. [7] investigating the association between COVID-19 vaccination and sperm parameters were able to demonstrate significantly better sperm parameters after vaccination. Although no significant improvement in sperm parameters was observed in our study, it was illustrated that there was a 20% increase in subjects with normozoospermia after vaccination. However, as indicated by Gonzalez, et al. [7], this improvement in sperm parameters most likely emphasizes the intraindividual differences rather than indicating an influence of vaccination.

Current studies suggest that a SARS-CoV-2 infection, in contrast to the vaccination against SARS-CoV-2, may have a negative impact on sperm quality [19,20] possibly depending on the severity of the disease [2,21]. Since especially severe courses of COVID-19 are reduced significantly by vaccination against SARS-CoV-2 [22], a vaccination seems to be the best precaution to prevent a possible reduction in sperm parameters induced by a severe course of COVID-19. Although this hypothesis needs to be confirmed, it is particularly relevant for the group of men who refused the vaccination because of the fear that the vaccination leads to an impairment of the male fertility.

According to the fifth edition of the WHO manual for the examination and processing of human semen and subjects, normozoospermia is defined by the lower 5th centil. However, in our study population a total of 52% did not meet the criteria for normozoospermia, which can be partly explained by the fact that 32% of the subjects recruited were patients from our fertility clinic. This distinguishes the present work from other published studies such as the one from Lifshitz, et al. [14] in which only 2.7% of the subjects did not show a normozoospermia.

The antibody determination in our study revealed that 2 out of 25 subjects had a positive antibody titer, suggesting that most likely an infection with SARS-CoV-2 has taken place unnoticed and asymptomatic before. A systematic review and meta-analysis including 95 individual studies aimed to assess the global percentage of asymptomatic COVID-19 infections. They suggested the occurrence of asymptomatic infections in a COVID-confirmed population to be as high as 40.5% [23]. To further assess the number of convalescent patients, large scale cohort studies aide in the assessment of seroprevalence. However, seroprevalence is highly determined by the population examined (i.e. health care workers with a higher risk of exposure) as well as whether the region of sample collection generally had a high number of infection events (i.e. densely populated communities compared to rural areas) [24].

In our study, after vaccination, all subjects showed a high antibody titer as evidence of the successful vaccination. Titers were in line with previous study results that included individuals who received their full vaccination regimen [12].

Limitations of the study were the medium collective size, the lack of a control group and the short follow-up period. Furthermore, it must be added as a limitation that male fertility cannot be estimated with the analysis of ejaculate parameters alone. Among the strengths of the study is that the effect on ejaculate parameters was examined not only for mRNA and vector-based vaccines but also for heterologous vaccinations. Furthermore, in addition to the wide age range of the subjects, the patient population consists not only of healthy young men, but also of men undergoing fertility treatment due to reduced sperm quality.

Conclusion

In summary, the examination of ejaculate parameters before and after vaccination with vaccines licensed in the EU showed no significant short-term differences in healthy men as well as in males with impaired fertility. Thus, an influence of vaccination against COVID-19 on male fertility is unlikely.

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