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Effectiveness of inactivated and mRNA COVID-19 vaccines on sperm parameters

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Abstract

Objective: The mRNA SARS-CoV-2 vaccine has been shown to have no adverse effects on semen parameters. However, it is yet unknown whether the inactivated vaccinations have the same effect. Thus, our objective was to evaluate the parameters of sperm prior and following the administration of mRNA and inactivated COVID-19 vaccinations.

Methods: In this study, the sperm quality was evaluated both before and after receiving the COVID-19 mRNA and inactivated vaccines. Of the participants, 28 received two doses of CoronaVac vaccine and 152 received two doses of mRNA BNT162b2 mRNA vaccine (Pfizer-BioNTech). Semen analyses were repeated 72 (57-145) days after the same individuals had received their second dose of COVID-19 vaccination.

Results: No significant differences were found in the parameters of sperm before and after administration of two doses of BNT162b2 vaccine. Prior to and following administration of the two doses of the inactivated vaccine, there was no appreciable variation in the volume of semen, sperm concentration, progressive motility, total motility, immotility, or morphologically normal sperm features. Following CoronaVac vaccination before and after two doses, only the total sperm count was shown to statistically decrease (p=0.03).

Conclusion: As a result, while there was no significant difference in the sperm parameters of the mRNA vaccine, it was determined that there was a statistical decrease in the total sperm count before and after two doses of CoronaVac vaccine. Since the semen volume of all patients is within normal limits, the first issue to be used here as a number is sperm per ml, which is important in terms of infertility, is the number.

Key words: Inactivated vaccine, mRNA vaccine, male fertility, sperm parameters

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İnaktive ve mRNA COVID-19 aşılarının sperm parametreleri üzerine etkinliği

Öz

Amaç: mRNA SARS-CoV-2 aşısı olmanın semen parametreleri üzerinde herhangi bir olumsuz etkisinin olmadığı gösterilmiş olmasına rağmen, inaktive aşıların aynı etkiye sahip olup olmadığı henüz netlik kazanmamıştır. Bu nedenle bu çalışmadaki amacımız, mRNA ve inaktive COVID-19 aşılarının uygulama öncesi ve sonrası sperm parametrelerini karşılaştırmaktı.

Yöntemler: Bu çalışmada sperm kalitesi, COVID-19 mRNA ve inaktif aşıların hem öncesi hem de sonrasında değerlendirildi. Katılımcılardan 28'i iki doz CoronaVac aşısı ve 152'si iki doz mRNA BNT162b2 BNT162b2 mRNA (Pfizer-BioNTech) aşısı aldı. Aynı kişilere ikinci doz COVID-19 aşısı yapıldıktan 72 (57-145) gün sonra semen analizleri tekrarlandı.

Bulgular: BNT162b2 aşısının iki dozundan önce ve sonra sperm parametrelerinde anlamlı fark yoktu. İnaktif aşının iki dozunun uygulanmasından önce ve sonra, semen hacminde, sperm konsantrasyonunda, progresif motilite, toplam motilite, immotilite veya morfolojik olarak normal sperm özelliklerinde kayda değer bir değişiklik olmamıştır. CoronaVac aşılamasının ardından iki doz öncesi ve sonrasında sadece toplam sperm sayısında istatistiksel olarak azalma olduğu görüldü (p=0,03).

Sonuç: Sonuç olarak mRNA aşısının sperm parametrelerinde anlamlı bir fark bulunmazken, iki doz CoronaVac aşısı öncesi ve sonrasında toplam sperm sayısında istatistiksel olarak azalma olduğu belirlenmekle beraber tüm hastaların meni hacmi normal sınırlar içerisinde olduğundan burada sayı olarak kullanılacak ilk husus, kısırlık açısından önemli olan, ml başına sperm sayısıdır.

Anahtar kelimeler: İnaktive aşı, mRNA aşısı, erkek fertilitesi, sperm parametreleri

INTRODUCTION

The first case of coronavirus disease 2019 (Covid-19), which has now spread to other parts of the world, was reported in Wuhan, China, in December 2019. Covid-19, an infectious disease, has been caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. In March 2020, the World Health Organization (WHO) announced it to be a pandemic, and tens of millions of people have subsequently been impact worldwide[2]. There is debate right now about whether SARS-CoV-2 could affect male fertility by breaching the blood-testicular barrier[3]. Local expression of the proteins transmembrane protease serine 2 (TMPRSS2) and angiotensin converting enzyme 2 (ACE2) in Leydig cells increased the likelihood of virus presence in the testicles[4,5]. It was established that SARS-CoV-2 enters host cells through ACE2 receptors and that TMPRSS2 is also crucial for SARS-CoV-2 cell entrance[6]. Although everyone intends to gain from the vaccination's protection, some individuals are troubled, and there have been concerns regarding the adverse effects of the vaccine[7]. Concerns have been expressed about the coronavirus's effect on male fertility[8]. Among COVID-19 patients, impaired spermatogenesis was reported; this finding may be explained by an augmented immune response and cytokine storm in testis tissue or by autoimmune orchitis, which was monitored in pathological samples from the male COVID-19 patients who had deceased[9,10]. The SARS-CoV-2 vaccine, which could result in a similar immunological response, might, in theory, have a similar impact[8].According to several research, some semen parameters, for instance total sperm count, the concentration of semen, and total motile count, can be significantly decreased by COVID-19 infection or its adverse impacts, for example fever[11-13]. Even though there has been

still a lack of knowledge on how the COVID-19 vaccines affect the male fertility, these findings make it understandable that couples and donors have reservations about their decision.

The COVID19 vaccination campaign in Turkey began on January[14], 2021. In the world, several COVID19 vaccines are being developed at various stages. The inactivated virus vaccine Sinovac, the mRNA-based COVID19 vaccine

developed by Pfizer-BioNTech, the adenovirus viral vector vaccine Sputnik V, and the inactivated virus vaccination TurkoVac are all now being used in Turkey[14]. In Diyarbakr, vaccinations made by Pfizer-BioNTech and CoronaVac are now being given. Understanding how the COVID-19 vaccine impacts the quality of men's sperm is crucial for medical study as well as decision-making by donors and couples. There was no discernible variation in any semen parameter values between the pre- and post-vaccination levels, according to a recent study on the mRNA COVID-19 vaccine[15]. Yet, there is limited information on how the inactivated COVID-19 vaccine impacts semen quality[7]. In this study, we evaluated the semen's quality both before and after those who received the inactivated COVID-19 vaccination and the mRNA vaccine. The results of this study may serve as a guide for future suggestions regarding fertility, which may aid donors and recipients of assisted reproductive technology (ART) in making wiser choices.

METHODS

Male individuals who had semen analysis for suspected infertility at the University of Health Sciences Gazi Yaşargil Training and Research Hospital Gynecology Clinics Andrology Laboratory were included in this research. Vaccine application information was determined with the AŞILA mobile application developed by the Ministry of Health (Turkey), whether 1648 people who had semen analysis performed in the Andrology laboratory between September 2020 and March 2022 were inactive or mRNA COVID-19 vaccine. In terms of the treatment protocol, semen analyzes are routinely requested from the spouses of female patients who receive long-term ovulation induction treatment for infertility treatment in the Infertility Polyclinic of our hospital. The study was initiated with 188 people aged 18 to 54 years old, whose sperm analyses were recorded in the hospital information management system (HIMS) prior to and following two doses of COVID-19 vaccine. However, 8 people were not included in the study because they were diagnosed with azoospermia as a result of semen analysis. In addition, those who did not complete at least 2 doses of the same vaccine and those who had positive Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test in the hospital information management system were excluded from the study. The study included the same people who had a semen analysis before the COVID-19 vaccine, then received at least two doses of the COVID-19 vaccine and had another semen analysis. The trial comprised 152 participants who received two doses of the mRNA BNT162b2 vaccination from Pfizer-BioNTech and 28 participants who received two doses of the CoronaVac (inactivated-Sinovac) vaccine. Before the participants in the research received their first dose of the COVID-19 vaccination, semen analyses were conducted on average 113 (28-307) days earlier. The same participants underwent a second round of semen testing on average 72 (57–145) days following the second COVID-19 vaccination dose. The sperm parameters of sperm samples collected both before and after the COVID-19 immunization were assessed in accordance with the WHO's instructions. After 2-7 days of sexual abstinence from individuals who applied to the andrology laboratory for semen analysis for suspected infertility, semen samples obtained by masturbation without using any lubricant were taken into sterile disposable plastic containers. The collected semen was incubated for 30-60 min in a CO_2 incubator at 37 °C after semen was liquefied, all semen parameters were evaluated macroscopically and microscopically in light microscopy (Olympus CX31) according to 2010 WHO guidelines by an experienced Histology-Embryology specialist with a Makler counting chamber. Sperm parameters such as semen volume, color, pH, viscosity, leukocyte count,

total sperm count, sperm concentration, motility, total motility and immotility were evaluated. Using a pipette, about 10 µl of semen was inserted into the Makler camera to be tested for number and motility. Sperm cells in 10 frames were counted in light microscope with X20 objective and the result was expressed as million (10^6). Sperm count, forward fast and slow motile sperm, respectively, then motile and immobile sperm cells in situ were counted and their percentages were calculated.

According to Kruger's exact morphology standards, the spermatozoon morphology was assessed using the Spermac staining method. One stain fixative and three stains (A, B, and C) are included in the kit of spermac staining (Ref. no. SPS050, Ferti Pro NV Industrie park Noord 32 8730 Beernem, Belgium). After loading the slide with 10 µl of sperm, it was allowed to sit at room temperature for 20 minutes before being cleaned in a container with distilled water for 8-10 times after the fixative solution was added, which took about 10-15 minutes. The slides were once more washed with distilled water 8–10 times after each staining procedure, and then, in the proper order, incubated with the A, B, and C stains for 1 minute each. The slides were air dried for at least 20 minutes before being subjected to morphological examination with an Olympus CX31 light microscope with immersion oil at x100 magnification. The percentage of spermatozoa with a normal morphology was calculated after counting 100 spermatozoa on each slide in the succeeding stage. There were at least five separate fields where the sperm count was done. Teratozoospermia has been described as the existence of fewer than five spermatozoa with a normal morphology.

SPSS 21 for Windows analysis (IBM SPSS Inc., Armonk, NY, USA) was used to conduct the statistical. Using the Shapiro Wilk tests, the normality of the data distribution was evaluated. For pairwise comparisons when the data did not fit the normal distribution, Wilcoxon tests were applied. The means of the two groups were compared to determine whether there was a statistically significant difference between before and after vaccination data. The significance threshold was set at p 0.05.

RESULTS

This study included male individuals who underwent semen analysis and 2 doses of COVID-19 vaccine for infertility research in the andrology laboratory. Of the men included in the study, 152 had received two doses of mRNA BNT162b2 vaccine and 28 had received two doses of CoronaVac vaccine. All individuals receiving infertility treatments had their semen analyzed both before and after the vaccine. Semen analyzes were performed on average 113 (28-307) days before the people included in the study received the first dose of COVID-19 vaccine. Semen analyzes were performed again on average 72 (57-145) days after the second dose of COVID-19 vaccine was given to the same individuals. Table 1 displays the age and vaccination information of the study participants.

Table I: Vaccination information of the people included in the study

Characteristics	Number (%) or median (min-max)
Number of cases	180
Age	33.03 ± 6.86
BNT162b2 (Pfizer-BioNTech)	152 (84.5%)
CoronaVac (Sinovac)	28 (15.5%)
Time between first COVID-19 vaccine dose and pre-vaccine semen analysis median (min-max), days	113 (28-307)
Time between second COVID-19 vaccine dose and post-vaccine semen analysis median (min-max), days	72 (57-145)

COVID-19, Coronavirus Disease 2019; Min-Max: Minimum-Maximum.

When the results of the semen analysis of the people included in the study were examined, 54 people were diagnosed with oligozoospermia before the COVID-19 vaccine and 58 people after the COVID-19 vaccine. Similarly, 28 people were diagnosed with asthenozoospermia before the COVID-19 vaccine, while 25 people after the COVID-19 vaccine. In the morphological evaluation made according to Kruger Strict criteria, 105 people were diagnosed with teratozoospermia before vaccination, and 112 people were diagnosed after vaccination. Comparisons of semen parameters of 152 individuals before and after 2 doses of BNT162b2 vaccine are given in Table 2. In our investigation, there was no difference between the pre- and post-administration of the BNT162b2 vaccine in terms of the concentration of sperm, semen volume, total sperm count, the motility of progressive, total motility, immotility, and morphologically normal sperm parameters (p>0.05). Table 3 also compares the sperm parameters of 28 people prior to and following two doses of the CoronaVac vaccine. In the evaluation of semen analysis before and after 2 doses of Corona Vac vaccine, there hasn't been observed significant difference in terms of the volume of semen, the concentration of sperm, progressive motility, total motility, ımmotility and morphologically normal forms sperm parameters (p>0.05). It was determined that only total sperm count decreased statistically after vaccination before and after 2 doses of CoronaVac vaccine (p=0.03 In the individuals included in the study, there was no serious deterioration in semen parameters after both types of vaccination. However, the number of people diagnosed with oligozoospermia, asthenozoospermia and teratozoospermia increased when compared before and after vaccination. The number of people diagnosed with azoospermia before and after vaccination did not change.

Table II: Correlation between parameters of sperm before and after mRNA COVID-19 vaccination (BNT162b2 - Pfizer-BioNTech)

Sperm parameters	**Pre-vaccination** (n:152)	**Post-vaccination** (n: 152)	**p Value**
Abstinence time (days)	3.27 ± 0.46(3-5)	3.54 ± 0.51 (2-5)	0.000
Semen Volume (ml)Mean ± SD; (Min- Max)	3.05 ± 1.62 (0.2-10.3)	3.07 ± 1.36 (0.2-7)	0.99
Sperm concentration ($x10^6$/ ml) Mean ± SD; (Min- Max)	29.41 ± 29.16 (0.02-112)	27.68 ± 32.50 (0.01-257)	0.07
Total sperm count ($x10^6$) Mean ± SD; (Min- Max)	85.43 ± 98.16 (0.06-525)	81.91 ± 111.12 (0.01-1028)	0.12
Progressive motility (%) Mean ± SD; (Min- Max)	45.62 ± 21.24 (0-90)	46.34 ± 18.69 (0-85)	0.70
Total motility (%) Mean ± SD; (Min- Max)	53.47 ± 21.35 (0-93)	54.77 ± 18.22 (0-90)	0.38
Immotility (%) Mean ± SD; (Min- Max)	46.13 ± 21.31 (7-100)	45.42 ±18.56 (10-100)	0.55
Morphologically normal forms (%); (Min- Max)	4.26 ± 2.58 (0-14)	4.19 ± 2.48 (0-12)	0.80

SD, Standart Deviation; Min-Max: Minimum-Maximum.

Table III: Correlation between parameters of sperm before and after inactivated COVID-19 vaccination (CoronaVac-Sinovac).

Sperm parameters	**Pre-vaccination** (n: 28)	**Post-vaccination** (n: 28)	**p Value**
Abstinence time (days); (Min- Max)	3.21 ± 0.41(3-5)	3.46 ± 0.5 (3-4)	0.05
Semen volume (ml)Mean ± SD; (Min- Max)	2.62 ± 1.32(0.7-5.5)	2.33 ± 0.93 (1-4.8)	0.08
Sperm concentration ($x10^6$/ ml) Mean ± SD; (Min-Max)	36.69 ± 33.2 (0.05-100)	30.01 ± 25.07 (0.02-78)	0.12
Total sperm count ($x10^6$) Mean ± SD; (Min- Max)	86.20 ± 90.26 (0.18-385)	61.74 ± 59.54 (0.07-273)	**0.03**
Progressive motility (%) Mean ± SD; (Min- Max)	48.57 ± 22.86 (4-85)	46.17 ± 20.46 (3-80)	0.53
Total motility (%) Mean ± SD; (Min- Max)	54.5 ± 22.39 (5-90)	56.57 ± 20.36 (5-86)	0.52
Immotility (%) Mean ± SD; (Min- Max)	45.5 ± 22.39 (10-95)	43.42 ± 20.36 (14-95)	0.52
Morphologically normal forms (%); (Min- Max)	3.85 ± 1.79 (2-8)	4.14 ± 2.79(0-11)	0.68

SD, Standart Deviation; Min-Max: Minimum-Maximum. The results statistically significant was shown in bold.

DISCUSSION

Because a COVID-19 vaccine had to be rapidly approved for use in the general population, many safety concerns were raised[8]. While some of the worries had a medical basis, others were voiced by members of the public who were not connected to the medical community[16], among them were worries about how the vaccine would affect both male and female fertility[8]. In this investigation, sperm quality was evaluated prior to and after administration of the mRNA and inactivated COVID-19 vaccines. This included measuring sperm volume, concentration, progressive motility (PR), and total progressive motile count (TPMC).

Men's reproductive health is negatively impacted by COVID-19 infection, according to earlier research. Serum hormone levels revealed a direct correlation between the presence of secondary hypogonadism and SARS-CoV-2 infection, with lower testosterone levels indicating the worst possible clinical prognosis[17]. More than 50% of men who have survived Covid-19 have reported the presence of circulating testosterone levels suggestive of hypogonadism several months later, as well[6]. It is commonly acknowledged that SARS-CoV-2 penetrates the cells of host via ACE2 receptors, and that TMPRSS2 also significantly facilitates SARS-CoV-2 entry into the cell[18]. Given that spermatogonia, Sertoli and Leydig cells have been shown to express ACE2 and TMPRSS substantially, an infection of SARS-CoV-2 may harm the testis and could have an adverse effect on spermatogenesis[5]. In a previous study, Li et al.[10] reported that6 (15.8%) of 38 patients had SARS-CoV-2 PCR-positive semen. They also found that testicular samples from the six deceased patients of SARS-CoV-2 showed histological evidence of localized elevated immune response and the damage of germ cell. Although this is the case, the vast majority of studies that have been published to date have not discovered any viral evidence in the semen of either men who are still ill or those who have recovered. According to a recent assessment, the likelihood of discovering SARS-CoV-2 in the COVID-19 patients' semen is exceedingly low[11,19-22].

There is yet very little proof that the COVID-19 mRNA vaccination affects human fertility[23]. Thankfully, some studies have demonstrated that neither the BNT162b2 nor the mRNA-1273 vaccination affects sperm parameters, for instance the volume of sperm semen,

concentration, the volume of sperm, the motility of sperm, and the total amount of motile sperm[15,24]. In another related study, 75 fertile men's sperm samples were collected 1-2 months after they received the second dose of Pfizer's COVID-19 vaccination, and the semen parameters were compared with the WHO reference ranges[3]. Remarkably, only one patient (1.3%) was reported to display sperm parameters consistent with oligozoospermia and asthenozoospermia. Another study evaluating the efficacy of the mRNA SARS-CoV-2 vaccine compared pre- and post-vaccination data in 36 ART treated couples and found no differences in the quantity of mature oocytes collected, the rate of fertilization, or the pregnancy rate (30% per transfer). Additionally, it was reported that the male partner's sperm parameters were unchanged following vaccination[25]. Reschini et al. 18 concluded that mRNA or viral vector vaccinations should be regarded as safe for men's reproductive health because they had no effect on the quality of sperm and fertilization capacity. These earlier findings are supported by our study. In the current study, which evaluated the sperm parameters in this small cohort of healthy males prior to and after receiving two doses of the COVID-19 mRNA vaccine, none of the sperm parameters revealed a significant decrease. The mRNA vaccine is unlikely to have an impact on sperm parameters because it only contains mRNA and not live virus.

In the current study, we did not detect any significant differences between the pre- and post-administration of two doses of the inactivated vaccinations in terms of the concentration of sperm, the volume of semen, total motility, progressive motility, immobility, and morphologically normal sperm features ($p>0.05$). Only the total sperm count was found to statistically change following CoronaVac vaccine before and after two doses ($p=0.03$). In our study, the only value with a statistical difference was total sperm count, but this value is not as important as the number per ml for infertility. The semen volume of all patients is within normal limits, so the first consideration to use as a number here, which is important for infertility, is the number of sperm per ml.

The SARS-CoV-2 vaccines are effective in preventing infection[26]. CoronaVac is the one of the most commonly used vaccine in Turkey[14]. It contains live virus antigens and has demonstrated good immunogenicity in animal studies[27]. and phase 3 clinical trials[28,29] by inducing significant systemic inflammation and the development of SARS-CoV-2 neutralizing antibodies. CoronaVac-induced immune reactions, however, may be comparable to those caused by live viruses given the features of inactivated vaccines, which may damage human fertility[26]. In recent study, Wang et al.[26] assessed the effects of CoronaVac on male fertility. They reported a slight increase in semen volume and sperm concentration was detected following vaccination, and the total sperm count was similar when compared between cohorts ($p<0.001$). Additionally, they noted that although progressive and total motility declined following vaccination, there was no discernible difference in the number of progressive and total motile sperm. Similar to our study, they also reported that before vaccination, there were more sperm with normal morphology both in terms of percentage and total number. In another study, Xia et al.[30] reported that the groups that received the inactivated vaccination and the unvaccinated groups had similar sperm parameters

This study had some limitations. First, long-term semen analysis results have not yet been reported, as the participants were followed for 3-4 months after the second dose of the vaccine. Second, the sex-related hormone levels (FSH, LH, Testosterone, and Estradiol) were not looked at before and after the COVID-19

vaccine. Third, since male individuals included in this study were routinely asked for semen analyzes in terms of treatment protocol from the spouses of female patients who received ovulation induction treatment in the infertility outpatient clinic, the results obtained may not include individuals from the entire population. Finally, information about the side effects of the SARS-CoV-2 mRNA BNT162b2 and CoronaVac vaccines they used could not be obtained from the participants.

CONCLUSION

In conclusion, there hasn't been found significant difference in sperm parameters before and after 2 doses of BNT162b2-Pfizer vaccine. Since the mRNA vaccine contains only mRNA and no live virus, it is unlikely that this vaccine will have an effect on sperm parameters. According to the study's findings, only the total sperm count was found to statistically decrease following CoronaVac vaccination before and after two doses (p=0.03). However, the semen volume of all patients was found to be within normal limits. For clinicians, sperm count per ml is seen as a more valuable parameter than total sperm count in the evaluation of male infertility.

Ethics Committee Approval: Ethics committee approval for the study was obtained from University of Health Sciences Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee with the date of 03.12.2021 and number 941. This study was conducted in accordance with the current Declaration of Helsinki. All participants provided written informed consent for participation

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