ORIGINAL RESEARCH

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Probable Effects of COVID-19 Vaccination on Semen Parameters: An Observational Cross-Sectional Study

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ABSTRACT Objective: Assessment of the long-term effect of inactivated Sinopharm coronavirus disease-2019 (COVID-19) vaccine on semen analysis. **Material and Methods:** It is an observational cross-sectional study at Al-Kasr Al-Ainy hospital. A sample size of 128 men was included. Semen samples were collected after at least 1 year of the 2nd dose of the vaccine from 64 men who had a previously normal semen analysis (prior to the vaccination) and 64 samples of unvaccinated men. **Results:** There was no difference between the 2 groups in semen liquefaction time, semen volume, total sperm motility, sperm immotility, sperm morphology, semen pH, and semen viscosity. There was a statistically significant higher mean value of sperm concentration, total sperm count, and percentage of progressively motile sperm in the unvaccinated group, as well as a statistically significant higher mean value of non-progressively motile sperm percentage in the vaccinated group, all of which are clinically insignificant as both groups results fall within normal World Health Organization values. **Conclusion:** The results suggest the relative safety of the inactivated COVID-19 vaccine by Sinopharm. The vaccine did not have a clinically significant effect among the vaccinated men. There was no residual effect on male fertility; thus, the concerns raised about the vaccine's impact on male fertility have no condemning evidence.

Keywords: COVID-19; semen; fertility

The declaration of the coronavirus disease-2019 (COVID-19) pandemic by the World Health Organization (WHO) on March 11th 2020 changed the lives of everyone. The rising numbers of the newly infected coupled with the daily fatality count were followed closely by millions.[1] To cope with the situation worldwide, vaccines were being developed. The testing stage for assuring the efficacy and safety of the developing vaccines was conducted in 3 phases.[2] Unfortunately, the sudden acute state of the events did not allow for a study of the delayed effects of the vaccines being developed.[3]

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A raising concern about the effect of coronavirus infection on male fertility was brought upon by the discovery of impaired spermatogenesis in some the COVID-19 patients. This observation was explained in 2 ways: elevation of the immune response and cytokine storm in the testis or autoimmune orchitis observed in the pathology specimens of deceased patients with COVID-19.[4]

The virus targets trans-membrane serine protease 2 and angiotensin-converting enzyme 2. Unfortunately, both are expressed in the spermatogonia of the testis and spermatogonial stem cells, making them a target of the virus. Theoretically, it is possible that a resembling effect can occur in those acquiring the vaccine because it may illicit a similar immune response.[3]

Infertility is an important issue as it creates an array of different problems and burdens on the individual and the governments. The most pronounced of these problems are economical, social, and psychological distress to the infertile couple.[5] Additionally, there is an economical burden on the health care system, making the concerns regarding the vaccine's effect on male fertility an imperative one.[6]

MATERIAL AND METHODS

The study was conducted in accordance with the Helsinki Declaration principles. An observational cross-sectional analytical study was conducted at Cairo University Hospitals among couples attending the Al-Kasr Al-Ainy infertility outpatient clinic. Considering the great difficulty of recruiting a healthy male participant to voluntarily participate in a semen analysis screening in our community and in order to achieve the study objective, male partners of female patients attending infertility outpatient clinic for female factor only infertility were interviewed for the recruitment. Approval of the ethical committee was obtained (date: May 23, 2023, no: MD-120-2023). Informed consent was obtained from each participant. A group of 128 healthy men who consented to be included in the study and matched the inclusion criteria were divided into 2 groups: 64 unvaccinated men and 64 men whom received 2 doses of the COVID-19 vaccine [Vero cell innactivated vaccine by Sinopharm (Sinopharm's Beijing institute of biological products, China)] the last dose at least 1 year before the inclusion into the study. The inclusion criteria included: men attending the *in vitro* fertilization clinic with female only factor infertility aging 18 to 45, for the vaccinated group previous 2 normal semen analyses before vaccination. Exclusion criteria included: men who were diagnosed with COVID-19 disease, chronic illnesses (uncontrolled diabetes, heart disease, hypertension, complicated liver disease), men on any long-term medication, men who started smoking within the last year, heavy smokers (more than 20 cigarettes/day), body mass index (BMI) more than 35, history of varicocele or presently diagnosed of varicocele grade II and III, recreational drug use, alcohol or any drug addiction.

STUDY PROCEDURE

The participant's latest semen analysis was included. The semen analysis was acquired after 3-5 days of abstinence. The sample was obtained through masturbation and collected in a sterile jar for analysis. The assessment started after the liquefaction of the semen. The parameters to be studied include (semen volume, liquefaction time, pH, sperm concentration, sperm motility, and sperm morphology). Semen samples were analyzed manually strictly following the WHO 2021 manual guidelines for the examination and processing of human semen. The container was preserved at 37°C temperature. The assessment began by measuring the volume and noting the color of the ejaculate, then assessment of liquefaction after 30 minutes of obtaining the sample, the container was slowly swirled for 15-30 seconds before starting the macroscopic assessment of liquefaction, next step the measurement of the pH, then the assessment of microscopic appearance, morphology, and sperm motility, finally assessing the presence of leukocytes or any other cellular content.

The parameters for the 2 groups were collected and compared to reveal the long-term or delayed effect of the vaccine.

STATISTICAL ANALYSIS

The data were analyzed with the social sciences statistical package version 23.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data with normal distribution were represented as mean±standard deviation and ranges, while the non-parametric data were represented as median with interquartile range. Qualitative variables were reported as numbers and percentages. The normality of the data was assessed using Kolmogorov-Smirnov and Shapiro-Wilk test.

The independent-samples t-test was used for the comparison of 2 means, while the chi-square test was used for comparisons involving qualitative data, and Fisher's exact test was used as an alternative to the chi-square test when the expected count in any cell <5.

The confidence interval was set at 95%, with an accepted error margin of 5%.

p value was considered significant at <0.05.

RESULTS

There was no statistical difference between the study groups regarding age and BMI; both groups are comparable in basic demographical data as shown in Table 1. The mean age in the unvaccinated group was 32.42±5.61 years, and in the vaccinated group it was 34.19±5.27 years, while the mean of the BMI in the unvaccinated was 22.38±2.07, while in the vaccinated group it was 22.66±1.99.

The study revealed no statistically significant difference between the 2 groups with regard to: semen liquefaction time, semen volume, total sperm motility, immotile sperm, sperm morphology, pH, viscosity, and other non-sperm cell content as shown on Table 2.

The study also revealed that the unvaccinated group had a statistically significant higher mean value in each of the following: sperm concentration (unvaccinated group 45.63±17.45 mil/ml and vaccinated group 37.92±16.95 mil/ml), total sperm count (unvaccinated group 143.46±80.27 mil and vaccinated group 111.85±65.67 mil), and progressively motile sperm (unvaccinated group 45.69±11.17 and vaccinated group 41.81±10.92). The study also revealed that the vaccinated group had a statistically significant higher mean value of non-progressively motile sperm (unvaccinated group 19.38±7.68 and vaccinated group 22.58±8.45). All of which are clinically insignificant as both groups' results fall within normal WHO values.

DISCUSSION

Due to the COVID-19 vaccine being a newly developed vaccine, studies of the long-term effects of the vaccine on the human body were not practical with the state of the world during the pandemic. Concerns regarding the effects of the vaccine on the semen analysis were raised due to the documented effects of the COVID-19 infection on the testes.[7] Impaired spermatogenesis was observed among COVID-19 patients, which was explained by an elevated immune response and cytokine storm in the testicular tissue or by autoimmune orchitis that was observed in the pathological specimen of deceased COVID-19 male patients.[8]

Angiotensin-converting enzyme 2 and transmembrane serine protease 2 are the main targets for

TABLE 1: Comparison between the 2 study groups according to the demographic data.

	Unvaccinated men group (n=64)	Vaccinated men group (n=64)			
Demographic data	$\bar{X}$±SD	$\bar{X}$±SD	Test value	p value	Sig.
Age "years"	32.42±5.61	34.19±5.27	-1.836	0.069	NS
BMI [wt/(ht)^2]	22.38±2.07	22.66±1.99	-0.785	0.434	NS

SD: Standard deviation; BMI: Body mass index; NS: Non significant

TABLE 2: Comparison between the 2 study groups according to semen parameters.

Semen parameters	Unvaccinated men group (n=64) $\bar{X}$±SD	Vaccinated men group (n=64) $\bar{X}$±SD	Test value	p value	Sig.
Liquifaction time	28.36±5.12	28.83±4.86	-0.531	0.596	NS
Semen volume (ml)	3.24±1.37	3.15±1.33	0.363	0.717	NS
Sperm concentration mil/ml	45.63±17.45	37.92±16.95	2.533	0.013	S
Total sperm count	143.46±80.27	111.85±65.67	2.438	0.016	S
Total sperm motility %	65.38±9.67	64.39±11.10	0.535	0.594	NS
Progressive motility %	45.69±11.17	41.81±10.92	1.984	0.049	S
Non-progressive %	19.38±7.68	22.58±8.45	-2.244	0.027	S
Immotile	34.63±9.67	36.08±11.90	-0.758	0.450	NS
Sperm morphology abnormal form %	89.38±10.64	91.45±11.26	-1.073	0.285	NS
pH	7.38±0.11	7.34±0.13	1.773	0.079	NS
Non-sperm cells					
Pus 1	1 (1.6%)	5 (7.8%)			
Pus 1-2	59 (92.2%)	54 (84.4%)			
Pus 2	3 (4.7%)	0 (0.0%)	8.888	0.114	NS
Pus 2-3	1 (1.6%)	3 (4.7%)			
Pus 3	0 (0.0%)	1 (1.6%)			
Pus 5-6	0 (0.0%)	1 (1.6%)			
Viscosity					
Normal	64 (100.0%)	64 (100.0%)	0.000	1.000	NS

t-Independent Sample t-test for mean±SD; χ^2: chi-square test for number (%) or Fisher's exact test, when appropriate; NS: Non significant; S: Significant; HS: Highly significant

the virus, both of which are co-expressed in spermatogonia and spermatogonial stem cells, thus becoming a target for the infection. Theoretically, a similar effect might be a possibility in patients receiving the vaccine due to the different vaccines structures, some being live attenuated, while others are protein subunit or even a nucleic acid vaccine, all of which can elicit a similar immune response to the infectious state.[9]

In our study, there was no statistically significant difference between the 2 groups regarding liquefaction time, where the unvaccinated group liquefaction time was 28.36±5.12, and the vaccinated group liquefaction time was 28.83±4.86. Supporting our findings, Dong et al. found no difference in liquefaction time in comparing men receiving single dose inactive vaccine with unvaccinated.[10] Also showing no difference Xia et al in studying inactivated vaccines Sinovac (Sinovac Biotech Ltd, China) and Sinopharm, and Elhabak et al studying AstraZeneca (AstraZeneca, United Kingdom) and Sinopharm.[11,12]

Our study showed no statistically significant difference in semen volume between the 2 groups, with 3.24±1.37 ml in the unvaccinated group and 3.15±1.33 ml in the vaccinated group. Agreeing with our findings and Abd et al with 3.5 ml pre-vaccination and 3.3 ml post-vaccine.[1]

Against our study, Leisegang et al. showed an increase in the seminal volume after Pfizer-BioNTech (BioNTech SE, Germany) and Moderna (MOderna, Inc. USA) vaccines, with the pre-vaccination volume being 3.0±1.2 ml and the post-vaccination volume being 2.8±1.7 ml. The author commented about this finding with "it is not likely to be directly due to vaccine exposure", Leisegang also reported no change with AstraZeneca and Johnson and Johnson vaccines.[13] While Zhu et al. reported a transient de-

crease in semen volume after the 1st dose of inactivated vaccine from 3.1±1.3 ml to 2.8±1.2 ml, then recovered back to 3.3±1.7 ml after the 2nd dose.[14]

The present study showed a statistically significant lower mean value of sperm concentration in the vaccinated group (37.92±16.95 mil/ml) than in the unvaccinated group (45.63±17.45 mil/ml), as well as a lower total sperm count in the vaccinated group (111.85±65.67 mil) than in the unvaccinated group (143.46±80.27 mil). Both outcomes fall within the normal WHO values. Since both results fall within normal values, it is possible that the cause is related to variations in the duration of abstinence before sample collection.

Supporting our results, Gat et al. showed a significant decrease in sperm concentration 75 to 125 days after receiving 2 doses of Pfizer-BioNTech vaccine [Confidence Interval (CI)-25.5%-3.9%]; however, the decrease in the concentration was not statistically significant when measured again over 145 days of the date of vaccination.[15] In addition, Zhu et al. showed similar changes after receiving the inactivated vaccine, with the sperm concentration increasing after the 1st dose from 55.6±21.7 mil/ml to 61.9±23.3 mil/ml and then decreasing again after the 2nd injection to 55.9±18.5 mil/ml with a net overall result of no significant change.[14]

Against our study, Leisegang et al. showed an increase in sperm concentration more than 3 months after Pfizer-BioNTech or Moderna vaccination, from 36.9±35.9 mil/ml pre-vacination to 41.1±40.3 mil/ml post-vaccination; which was explained by the author as not likely to be directly due to vaccine exposure.[13] Also against our study with no significant change are: Gonzalez et al. studying Pfizer-BioNTech and Moderna vaccines, and Adamyan et al. studying Pfizer-BioNTech and Moderna vaccines.[16,17]

The present study showed no statistically significant difference with regard to total sperm motility between the 2 groups (64.39±11.10 % in the vaccinated group and 65.38±9.67% in the unvaccinated group).

Supporting our study: Gat et al in studying Pfizer-BioNTech vaccine showed a transient decrease in the total motility count (22.1% reduction CI -35% to -6.6%) followed by recovery back to normal caused by the previously mentioned transient sperm concentration decrease in the same study.[15] Also, Gonzalez et al. and Olana et al. in studying Pfizer-BioNTech showed no significant difference.[16,18]

Against our study, Leisegang et al. showed an increase in total sperm motility more than 3 months after Pfizer-BioNTech and Moderna vaccination (from 57.0±67.5 mil pre-vaccination to 53.6±67.0 mil post-vaccination), no changes were observed on receiving AstraZeneca and Johnson and Johnson (Janssen Vaccines, Netherlands and Janssen pharmaceuticals, Belgian). The author explained that the findings regarding the Pfizer-BioNTech and Moderna vaccines are probably not due to the vaccine.[13]

In the present study, it was found that the vaccinated group had a statistically significant decrease in progressive motility (from 45.69±11.17% in the unvaccinated group to 41.81±10.92%). However, the difference is clinically insignificant as both groups fall within normal WHO values.

Supporting our study: Abd et al. studied the Pfizer-BioNTech vaccine and showed a significant decrease in progressive motility (from a median of 60% (19.3) pre-vaccination to 59 (16.5) post vaccination). However, the difference is clinically insignificant as both groups fall within normal WHO values. The author explained this result as being a natural variation between 2 semen samples of the same individual.[1]

In the current study, there was a statistically significant higher mean value of non-progressively motile sperm percentage in the vaccinated group than in the unvaccinated group (from 19.38±7.68% pre-vaccination to 22.58±8.45% post vaccination), yet it was clinically insignificant due to both groups being within normal WHO values. With both values falling within the normal range, the change between the groups could be attributed to lifestyle differences. Against our results, Xia et al. in studying inactivated

vaccines Sinovac and Sinopharm found no difference between the 2 groups.[11]

In the current study, there was no statistically significant difference between the 2 groups regarding the following: immotile sperm percentage (34.63±9.67% pre-vaccination and 36.08±11.90 % post-vaccination), sperm morphology (89.38±10.64 % pre-vaccination and 91.45±11.26% post-vaccination), pH (7.38±0.11 pre-vaccination and 7.34± 0.13 post-vaccination), non-sperm cell content (shown in Table 2), and viscosity.

Supporting our study in showing no statistically significant difference are: Huang et al in a systematic review and meta analysis, and Zhu et al studying inactivated vaccine.[14,19]

LIMITATION

Our study faces some limitations, including the following: all the volunteers were recruited from a single hospital, and the study groups came from a specific population not a random 1, which limits the diversity and may introduce sample selection bias. As well as the exclusion of men with oligozoospermia that are the most likely individuals to be susceptible to worsening parameters. As this is an observational study, the number of samples available for analysis for each volunteer was limited to 1, while including a mean value of multiple samples for each participant would provide more accurate data.

CONCLUSION

The results suggest the relative safety of the inactivated COVID-19 vaccine by Sinopharm. The vaccine did not have a clinically significant effect among the vaccinated men. There was no residual effect on male fertility; thus, the concerns raised about the vaccine's impact on male fertility have no condemning evidence.

Based on the findings in this study, it is recommended that male individuals with known fertility problems should consult their doctor before receiving the vaccine.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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