

The effect of COVID-19 infection on seminal fluid parameters

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Abstract

With the worldwide threat of SARS-CoV-2 as well as the growing number of infectious agents, little is recognized about how such a virus impacts the reproductive-system of males. This new coronavirus illness (COVID-19) outbreak puts men at a greater risk than females. So far, research on the andrological effects of coronavirus has been limited. The purpose of this study was to see how COVID-19 affected sperm characteristics in infertile males. Such study includes 30 males in total. In the prospective cohort study, different demographic as well as semen parameters have been assessed. The demographic factors including age, BMI, diabetes, and hypertension have somehow little or no effect on the patients after the COVID-19 diagnosis. Furthermore, the semen characteristics include sperm count and concentration, total motility, semen volume, and progressive motility. The COVID-19 infection has a significant impact on all these parameters. We present significant experimental proof that the COVID-19 outbreak can harm and target male fertility. The long-term outcomes of coronavirus on the reproductive systems of males have yet to be determined. Infection with SARS-CoV-2 can impair men's reproductive function. Standard treatment plans must be made timely to protect infected patients' fertility. Fertility evaluations and competent fertility assistance should be offered concurrently for recovered individuals with fertility needs.

Keywords: viruses; infection; seminal fluid

Introduction

People from around the world have developed health issues related to COVID-19. It causes multi-organ dysfunction, predominantly in the respiratory system. Since its first infection in 2019 (December), the new coronavirus pandemic has spread rapidly, resulting in an unusual worldwide health crisis that harms individuals in several facets of life. According to WHO, more than 143 million people around the world have been detected to have COVID-19. WHO has identified the coronavirus held to account for this pandemic as severe-acute respiratory-syndrome-coronavirus, i.e., SARS-CoV-2 (1).

Despite the fact that several states are fighting the coronavirus ailment 2019, over 150 million individuals have been diagnosed with SARS-CoV-2 and more than 120 million individuals have recovered. Since the eradication of such viral diseases in the coming years is unsure, humanity would have to continue living with coronavirus for at least some years. Even though COVID-19 infection is primarily a respiratory illness, the high rate of infection caused by such a virus has forced us to concentrate on its negative impacts on some other organs. COVID-19 reaches host cells through binding to ACE2 (angiotensin-converting-enzyme 2) and TMPRSS2 (transmembrane-serine protease-2) receptors on the cell surface (2).

Initial clinical studies throughout China found that males are more probable to contract the COVID-19 infection and experience more serious conditions. Punjani has made similar findings (3). At least within the respiratory system, males have higher ACE2 levels than

women (4). Men may have elevated amounts of ACE2 or TMPRSS2 expressed throughout various organs, which could describe their sex-based specificity. This has been established that TMPRSS2 and ACE2 are strongly expressed not just in kidney, lungs, heart, and intestine tissues (5,6), yet also in the individual's testes' Sertoli and Leydig cells, spermatogonia, along with other men's reproductive organs such as the seminal vesicles, bulbourethral glands, and prostate gland (7), which add seminal fluid/vesicles to that sperm, signifying that coronavirus can harm men's reproductive organs, putting male reproduction system at risk. In this respect, coronavirus patients have been already found to have deficient spermatogenesis as well as decreased sperm quality attributes (8).

Previous research has found that COVID-19 can pass the blood-brain boundary and infect glial cells and neurons via ACE-2 receptors, activating inflammatory reactions within neural tissues such as the pituitary gland and hypothalamus. However, the potential impact of coronavirus illness on that hypothalamic-pituitary-adrenal axis was already presumed, and the processes by which coronavirus interrupts this hypothalamic-pituitary-gonadal-axis are unknown (9). Furthermore, a growing body of literature suggests that coronavirus infection might impact the men's genital tract and testes, interrupting gonadal processes. The disease's damaging effects might be the consequence of either significant cytopathic impacts of coronavirus on target tissues or implicit damage caused by the inflammatory reaction to the virus (10). SARS-CoV-2 cell entry is dependent on highly contagious spike (S)-proteins binding to receptor molecules as well as S-protein stimulation by host tissue proteases.

In some other research, RNAs of SARS-CoV-2 were observed in the sperm of 4 patients in the severe stage and 2 patients in the recovery phase, though this outcome was attributed to contamination due to methodological problems. In one analysis, 6 of 34 subjects faced scrotal discomfort due to viral orchitis throughout the coronavirus infection (11). Only one of the twelve patients who did not survive had SARS-CoV-2 identified by RT-PCR (reverse-transcription-polymerase chain-reaction) in the reproductive organs (the virus observed likely came from plasma instead of seminiferous tubules), and none had it detected by microscopic examination. Despite this, substantial changes in scrotal histology were noticed, such as morphological variations in Sertoli-cells, tubular cell loss as well as sloughing within the lumen, and a decrease in the Leydig cells, plus minor lymphocytic inflammation, indicating testicular harm during the course of illness (12).

Several studies have looked into the sperm attributes of coronavirus patients (13). The findings of such research suggest that COVID-19 infection may have a negative impact on sperm parameters, although there is still debate about the impact of COVID-19 on sperm quality potential due to a lack of data. These impacts can be the outcome of COVID-19's severe infections as well as cytokine storms, or a profound impact of the infection on men's reproductive organs. Moreover, systemic interference with such a body, in conjunction with inflammation and fever, might also dysregulate hormonal balance by that HPG (hypothalamic-pituitary-gonadal) axis, potentially impairing sperm count. In addition, oxidative stress and inflammation interact reciprocally, thus one can induce the other (14). The negative impacts of such oxidative-stress on spermatogenesis have previously been addressed (15).

At least eleven viruses could sustain within the testicle and might also arise in the sperm, which might be due to the virus's stable structure, particular immune evasion, viral epitopes, and certain other factors (16). Numerous infections have been discovered to engage directly with semen, hinder sperm production, or interfere with spermatogenesis by inciting local inflammation. Multiple opinion articles have already been printed, suggesting the potential of the COVID-19 ailment to cause testicular damage. Some researchers think that full-grown sperm could attach to the pathogen and perhaps even copy it, raising the risk that sperm could function as a COVID-19 vector (17). The testis, on the other hand, is the part of the body that forms sperm. However, if SARS-CoV-2 invades it, this will impair spermatogenesis. Moreover, the prostate is another organ that has a high level of ACE2 expression (18). The prostate secretes prostatic fluid, or EPS, which is a light milky white viscous liquid that is an important element of sperm. As a result, it is fair to speculate that SARS-CoV-2 may affect the prostate.

Due to the limited amount of information, viral mRNA was already found in the sperm of patients

having COVID-19, with some proof of changed seminal characteristics. This new global epidemic has compelled us to recognize several significant problems that may have an impact on the testicles: Firstly, is there SARS-CoV-2 present within the seminal fluid? Secondly, how well does coronavirus affect sperm or male reproductive capacity, both indirectly or directly? We, therefore, provide a thorough understanding of the study of whether COVID-19 can affect the reproductive system of males or not in this analysis. The sub-topics which have been summarized throughout this paper include the presence of coronavirus in seminal fluid, damage of COVID-19 infection on men's reproductive organs, and what are the effects of the virus on male fertility. All this research would be beneficial for future studies.

Patients and Methods

The recent prospective research was performed in Salahdin-Province (Tikrit-and-Samarra) between April 2021 and April 2022. The research included a total of 30 men who had their sperm analyses performed after and before being diagnosed with coronavirus. Patients were called and scheduled consultations with such an assisted reproduction group to give sperm samples. After sexual abstinence for 3 months, the patient's sperm was examined. Patients have been excluded from this research in case they had urogenital processes during this time, had azoospermia, were taking pills that could impact sperm variables (antibiotics, supplements, testosterone, and so on), or had a record of any fractious illness other than coronavirus in the previous three months.

All subjects were identified with coronavirus infection around 3 months before and now they are recovering. However, all the semen characteristics (total motility, sperm concentration and count, semen volume, and progressive motility) pre, as well as post-coronavirus, were evaluated. All the patients' age was between twenty to forty-five years. In addition to that, seminal fluid assessment was as per WHO-2010 5th edition standards. Other parameters comprise age, hypertension, diabetes, BMI, and smoking.

Statistical Analysis

Data is demonstrated as a median due to the limited group of participants. Master tables were used for statistical analyses, and skeletal tables along with standard-deviation and mean were used for data presentation. The Wilcoxon-test or paired t-test was utilized to compare sperm parameters in patients after and before coronavirus infection. Statistical significance was assigned to values of $p < 0.05$. The proportion of participants (COVID+/COVID-) or perhaps the appropriate SD (standard-deviation) and mean difference were available for every seminal parameter, and such mean-differences and SDs have been measured using data available.

Results

Overall, 30 patients' data were analyzed for infertility. The spermogram findings reported after and before the detection of coronavirus were assessed in this data. The patients' ages were between 20 to 45 years. However, the demographic factors and clinical features of these patients are observed in (Table-1). The average age of all the subjects was 30 years. Also, the average BMI (body-mass index) for all such subjects was 26.8 kg/m², which is above the higher limit of the standard range. Moreover, 9 patients

have a history of smoking, 3 have hypertension and only one has a history of diabetes.

Table 1: Different parameters of the participants: n=30

Different Parameters n=30	
Age (years)	30.6 ± 8.9
Smoking	9 (30 %)
Hypertension	3(10%)
Diabetes	1 (3.33%)
BMI(kg/m ²)	26.8 ± 2.9

Table 2: Pre-and Post-COVID-19 seminal-fluid characteristics of the participants: n=30

Parameters	Pre-COVID-19	Post-COVID-19	P-value
Volume(ml)	4.2 ± 1.8	4.1 ± 1.6	0.62
Total motility(%)	49.2 ± 6.1	38.6 ± 9.2	0.005
Total motile sperm count (millions)	68.2 ± 56.2	54.6 ± 45.2	0.01
Sperm concentration (million/ml)	55.1 ± 16.2	52.2 ± 15.2	0.07
Progressive motility(%)	33.4 ± 1.1	30.8 ± 5.2	0.2

The values of semen characteristics were compared among the subjects before as well as after the COVID-19 diagnosis. The total motility percentage, semen volume, progressive motility percentage, and sperm concentration and count were observed as considerably reduced after coronavirus ($p = 0.62$, $p = 0.005$, $p = 0.2$, $p = 0.01$, and $p = 0.07$ respectively) (Table 2). The parameter of smoking has some effects on the patient's seminal fluid (19). In addition, factors like hypertension, diabetes, and BMI have little or no impact on the seminal fluid of COVID-19 patients. According to this research, the semen parameters are significantly decreased after the diagnosis of coronavirus. It shows that such parameters are strongly associated with COVID-19.

Analysis of Parameters

Our results demonstrated a noteworthy correlation between COVID-19 ailment and reduced semen-volume from 4.2 ± 1.8 to 4.1 ± 1.6 , showing a p-value of 0.62. The inclusive impact also presented that coronavirus infection was adversely associated with semen-volume within subjects. Also, the concentration of sperm in subjects after COVID-19 infection showed decreased sperm concentrations, however, it wasn't significant ($p=0.07$). COVID-19 cases had considerably declined sperm concentrations compared to before the coronavirus from 55.1 ± 16.2 to 52.2 ± 15.2 , showing a p-value of 0.07.

Patients having COVID-19 infection specified significantly decreased sperm counts than before COVID-19. Such a decrease is from 68.2 ± 56.2 to 54.6 ± 45.2 , showing a p-value of 0.01. In addition, decreased overall sperm-motility was detected in patients with COVID-19. The data advocated that sperm-motility was considerably lesser in subjects with COVID-19 from 49.2 ± 6.1 to 38.6 ± 9.2 , showing a p-value of 0.005. Similarly, individuals with

coronavirus had significantly decreased progressive motility percentage from 33.4 ± 1.1 to 30.8 ± 5.2 , showing a p-value of 0.2.

Discussion

Our findings suggest that COVID-19 could cause major deficits in men's reproductive function by influencing various sperm parameters. The results of this study showed that COVID-19 had a negative impact on sperm concentration, sperm volume, sperm motility, and sperm count, resulting in a degradation of these factors in COVID-19 subjects. Then, Holtmann and coworkers in Germany conducted the first research to examine the implications of coronavirus on semen parameters (20). They found that a minor coronavirus does not appear to impair testis as well as epididymis activity, whereas a mild infection did show up to impair semen characteristics. Pazir obtained different outcomes. Their results indicated that in instances with a record of slight COVID-19, sperm count and sperm motility were greatly decreased (21). Similarly, Erby and coworkers reported in a study of 69 recovered subjects that COVID-19 has a short-term detrimental effect on sperm production (22).

Coronavirus was separated from the testicles in a medical examiner series performed by Bian as well as associates (10). Furthermore, they confirmed different levels of damage in the testis as well as a decline in the amount of spermatogenic-cells. In an autopsy conducted by Xu (23), SARS-CoV, the leading cause of SARS illness, was linked to the growth of orchitis. Histopathological examinations revealed inflammatory infiltrates, primarily in the Sertoli cells. The testes' most significant function is to make sperm, and coronavirus infections can impair sperm quality. We studied the impacts of COVID-19 on sperm parameters in this study by comparing

such sperm characteristics of patients after and before infection and found substantial variations in sperm morphology and count.

Yang looked at the testicles of twelve people who died from COVID-19. They found normal sperm production in three of the specimens, but defects in the remaining ones. In addition, the coronavirus, like the pathophysiology postulated in the respiratory system, can lead to serious harm to the testicles. Inflammatory cytokines that further elevate in reaction to the virus's immune response might induce degradation of such a blood-testicular boundary and testicular damage. Furthermore, among the most essential activities of the testicles is sperm production, and infections can impair sperm quality (24).

SAR-CoV-2 could also function through a variety of techniques, which can interrupt the reproductive functions of males and potentially harm offspring growth. COVID-19 induces OS (oxidative-stress) by stimulating oxidant-sensitive mechanisms through inflammatory responses. OS could prompt peroxidative harm to the testicular plasma membrane as well as compromise the DNA integrity within the nucleus of sperm. It reduces sperm count plus speeds up the rate of abortion (25). Besides that, COVID-19 stimulates systemic OS, production, and discharge of elevated amounts of NO (nitric oxide), impacting androgen production, hindering spermatogenesis, impeding sperm motility, and having adverse implications for offspring (26).

Our patients are assessed before and after diagnosis of COVID-19 to analyze whether the damage in semen factors that we detected was initiated by an initial temporary spermatogenesis deficiency or maybe by late spermatogenesis failure. As we identified that all the patient's semen parameters have deteriorated after the coronavirus diagnosis, it has been cleared from our study that COVID-19 is significantly associated with seminal fluid. Additional research on post-infection males is required in the future to demonstrate the endless impact of infection.

Conclusion

The impact of coronavirus on the reproductive system of men is a new research area. After COVID-19 diagnosis, we found a substantial decline in average sperm count, progressive motility, sperm concentration, semen volume, and total motility. Clinicians must be cognizant that coronavirus may cause additional degradation of semen characteristics, which might be critical in the assessment of infertile males. Researchers from various countries need to pay more attention to the impact of COVID-19 on male reproductive-function. We propose studying the long and short-term impacts of COVID-19 on men's reproduction in various areas. The consequences of coronavirus infection on sperm quality potential in subjects of various ages, disease severity, and stages would greatly help researchers in further unveiling the

function of this viral disease in male fertility. However, more research is needed to determine the long-term impacts of COVID-19 on semen characteristics and fertility.

References

- Zhu N, Zhang D, Wang W, Li X, Yang B, et al. (2019). A novel coronavirus from patients with pneumonia in China. *N Engl J Med* 2020; 382: 727–33.
- Hoffmann, M., Kleine-Weber, H., Krüger, N., Müller, M., Drosten, C., & Pöhlmann, S. (2020). The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *BioRxiv*, 2020.01.31.929042. <https://doi.org/10.1101/2020.01.31.929042>
- Punjani, N., Ha, A., Caputo, J., Wang, V., Wiechmann, L., Chiasson, M. A., Li, P., Hotaling, J., Walsh, T., & Alukal, J. (2020). Outcome disparities among men and women with COVID-19: An analysis of the New York City Population Cohort. *Journal of Drugs in Dermatology*, 19(10), 960–967. <https://doi.org/10.36849/JDD.2020.5590>
- Li, H., Xiao, X., Zhang, J., Zafar, M. I., Wu, C., Long, Y., Lu, W., Pan, F., Meng, T., Zhao, K., Zhou, L., Shen, S., Liu, L., Liu, Q., & Xiong, C. (2020). Impaired spermatogenesis in COVID-19 patients. *EClinicalMedicine*, 28, Article 100604. <https://doi.org/10.1016/j.eclinm.2020.100604>
- Gkogkou E, Barnasas G, Vougas K & Trougakos IP. (2020). Expression profiling meta-analysis of ACE2 and TMPRSS2, the putative anti-inflammatory receptor and priming protease of SARS-CoV-2 in human cells, and identification of putative modulators. *Redox Biology* 36 101615. (<https://doi.org/10.1016/j.redox.2020.101615>)
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579 270–273. (<https://doi.org/10.1038/s41586-020-2012-7>)
- Zupin L, Pascolo L, Zito G, Ricci G & Crovella S. (2020). SARS-CoV-2 and the next generations: which impact on reproductive tissues? *Journal of Assisted Reproduction and Genetics* 37 2399–2403. (<https://doi.org/10.1007/s10815-020-01917-0>)
- Ruan Y, Hu B, Liu Z, Liu K, Jiang H, Li H, Li R, Luan Y, Liu X & Yu G. (2020). No detection of SARS-CoV-2 from urine expressed prostatic secretions, and semen in 74 recovered COVID-19 male patients: a perspective and urogenital evaluation. *Andrology*
- Selvaraj K, Ravichandran S, Krishnan S, Radhakrishnan RK, Manickam N, Kandasamy M. (2021). Testicular atrophy and hypothalamic pathology in COVID-19: possibility of the incidence of male infertility and HPG axis abnormalities. *Reprod Sci.* 1–8.
- Bian, X. W. (2020). Autopsy of COVID-19 patients in China. *National Science Review*, 7(9), 1414-1418.

11. Corona G, Baldi E, Isidori AM, Paoli D, Pallotti F, et al. (2020). SARS-CoV-2 infection, male fertility and sperm cryopreservation: a position statement of the Italian Society of Andrology and Sexual Medicine (SIAMS) (Società Italiana di Andrologia e Medicina della Sessualità). *J Endocrinol Invest*; 43: 1153–7
12. Yang M, Chen S, Huang B, Zhong JM, Su H, et al. (2020). Pathological findings in the testes of COVID-19 patients: clinical implications. *Eur Urol Focus*; 6: 1124–9.
13. Kayaaslan, B., Korukluoglu, G., Hasanoglu, I., Kalem, A. K., Eser, F., Akinci, E., and Guner, R. (2020). Investigation of SARS-CoV-2 in Semen of Patients in the Acute Stage of COVID-19 Infection. *Urol. Int.* 104, 678–683. doi:10.1159/000510531
14. BaSalamah, M. A., Abdelghany, A. H., El-Boshy, M., Ahmad, J., Idris, S., and Refaat, B. (2018). Vitamin D alleviates lead-induced renal and testicular injuries by immunomodulatory and antioxidant mechanisms in rats. *Sci. Rep.* 8, 4853. doi:10.1038/S41598-018-23258-W
15. Agarwal, A., Saleh, R. A., and Bedaiwy, M. A. (2003). Role of reactive oxygen species in the pathophysiology of human reproduction. *Fertil. Steril.* 79, 829–843. doi:10.1016/S0015-0282(02)04948-8
16. Salam AP, Horby PW. (2017). The Breadth of Viruses in Human Semen. *Emerg Infect Dis* 23(11):1922–4. DOI: 10.3201/eid2311.171049
17. Mao Q, Wu W, Liao Z, Li J, Jia D, Zhang X, et al. (2019). Viral Pathogens Hitchhike With Insect Sperm for Paternal Transmission. *Nat Commun* 10(1):955. DOI: 10.1038/s41467-019-08860-4
18. Yokoyama M, Hiwada K, Kokubu T, Takahaa M, Takeuchia M. (1980). angiotensin-converting Enzyme in Human Prostate. *Clinica Chimica Acta.* 100 (3):253–8. DOI: 10.1016/0009-8981(80)90274-0
19. Meri, Z. B., Irshid, I. B., Migdadi, M., Irshid, A. B., & Mhanna, S. A. (2013). Does cigarette smoking affect seminal fluid parameters? A comparative study. *Oman medical journal*, 28(1), 12–15. <https://doi.org/10.5001/omj.2013.03>
20. Holtmann, N., Edimiris, P., Andree, M., Doehmen, C., Baston-Buest, D., Adams, O., ... & Bielfeld, A. P. (2020). Assessment of SARS-CoV-2 in human semen—a cohort study. *Fertility and sterility*, 114(2), 233-238.
21. Pazir, Y., Eroglu, T., Kose, A., Bulut, T. B., Genc, C., & Kadihasanoglu, M. (2021). Impaired semen parameters in patients with confirmed SARS-CoV-2 infection: A prospective cohort study. *Andrologia*, 53(9), e14157.
22. Erbay, G., Sanli, A., Turel, H., Yavuz, U., Erdogan, A., Karabakan, M., ... & Gultekin, M. H. (2021). Short-term effects of COVID-19 on semen parameters: A multicenter study of 69 cases. *Andrology*, 9(4), 1060-1065.
23. Xu, J., Qi, L., Chi, X., Yang, J., Wei, X., Gong, E., ... & Gu, J. (2006). Orchitis: a complication of the severe acute respiratory syndrome (SARS). *Biology of reproduction*, 74(2), 410-416.
24. Yang, M., Chen, S., Huang, B. O., Zhong, J. M., Su, H., Chen, Y. J., ... & Nie, X. (2020). Pathological findings in the testes of COVID-19 patients: clinical implications. *European urology focus*, 6(5), 1124-1129.
25. Smith R, Kaune H, Parodi D, Madariaga M, Morales I, Rios R, et al. (2007). The extent of Sperm DNA Damage in Spermatozoa From Men Examined for Infertility. *Relationship Oxid Stress Rev Med Chil.* 135(3):279–86. DOI: 10.4067/s0034-98872007000300001
26. Amiri I, Sheikh N, Najafi R. (2007). Nitric Oxide Level in Seminal Plasma and its Relation With Sperm DNA Damages. *Iran BioMed J.* 11(4):259–64.