

The Effect of COVID-19 on Laboratory Parameters

COVID-19'un Laboratuvar Parametreleri Üzerindeki Etkisi

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Abstract

Objective: This study aimed to investigate the long-term effects of coronavirus disease-2019 (COVID-19) on semen parameters and hormone levels by dividing the timeline into pre-pandemic, pandemic, and post-pandemic phases.

Method: Between May 2017 and April 2024, we conducted a retrospective study including 10,082 semen analyses from 6,517 patients at our hospital. Patients were divided into three groups according to the World Health Organization (WHO)-defined pandemic start and end dates: pre-COVID-19 (May 2017–March 2020; n=2378), COVID-19 period (March 2020–May 2023; n=5568), and post-COVID-19 (May 2023–April 2024; n=2136). Semen analyses and hormone parameters [total testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and prolactin] were examined. However, it was not possible to determine whether each patient had been infected with COVID-19. All semen analyses were performed in accordance with WHO 2010 guidelines.

Results: Sperm concentration, motility, and morphology significantly increased during and after the COVID-19 period compared with the pre-COVID-19 period ($p<0.01$). Semen volumes remained similar across all three periods ($p>0.05$). Testosterone levels also showed significant increases during and after the pandemic ($p<0.01$). In contrast, FSH and LH levels decreased significantly during and after COVID-19 ($p<0.001$). No significant changes were observed in estradiol levels, whereas prolactin levels increased during and after COVID-19 ($p<0.001$).

Conclusion: COVID-19 was associated with notable changes in male reproductive health indicators; however, no permanent negative impact on male fertility was identified. Further prospective studies are needed to validate these findings and to elucidate the underlying mechanisms.

Keywords: COVID-19, male fertility, pandemic, semen

Öz

Amaç: Bu çalışma, koronavirüs hastalığı-2019'un (COVID-19) semen parametreleri ve hormon düzeyleri üzerindeki uzun vadeli etkilerini araştırmayı, dönem pandemiden önce, pandemi sırasında ve pandemi sonrasında olmak üzere üç aşamaya ayırarak incelemeyi amaçlamaktadır.

Yöntem: Mayıs 2017 ile Nisan 2024 arasında, hastanemizde 6,517 hastadan 10,082 semen analizi içeren retrospektif bir çalışma gerçekleştirdik. Dünya Sağlık Örgütü'nün (DSÖ) pandemi başlangıcı ve bitiş tarihlerine göre üç gruba ayırdık. COVID-19 öncesi (Mayıs 2017-Mart 2020): 2,378 hasta; COVID-19 dönemi (Mart 2020-Mayıs 2023): 55,68 hasta ve COVID-19 sonrası (Mayıs 2023-Nisan 2024): 2,136 hasta. Semen analizleri ve hormon parametreleri [toplam testosteron, folikül uyarıcı hormon (FSH), luteinize edici hormon (LH), estradiol ve prolaktin] incelendi. Ancak her bir hastanın COVID-19 enfeksiyonundan etkilenip etkilenmediği belirlenemedi. Tüm semen analizlerini DSÖ 2010 kılavuzlarına uygun olarak gerçekleştirdik.

Bulğular: Sperm konsantrasyonu, motilite ve morfoloji, COVID-19 öncesi dönemde kıyasla COVID-19 dönemi ve sonrasında anlamlı bir şekilde arttı ($p<0,01$). COVID-19 öncesi dönem, pandemi dönemi ve post-pandemi döneminde semen hacmi, COVID-19 dönemlerinden bağımsız olarak benzer kaldı ($p>0,05$). Testosteron seviyeleri de pandemi döneminde ve sonrasında anlamlı bir artış gösterdi ($p<0,01$). Aksine, FSH ve LH seviyeleri COVID-19 dönemi ve sonrasında anlamlı bir şekilde azaldı ($p<0,001$). Estradiol seviyelerinde önemli bir değişiklik gözlenmezken, prolaktin seviyeleri COVID-19 dönemi ve sonrasında arttı ($p<0,001$).

Sonuç: COVID-19, erkek üreme sağlığı göstergelerinde belirgin değişikliklere neden olmuş olsa da erkek fertilitesi üzerinde kalıcı bir olumsuz etki tespit edilmemiştir. Bu bulguları doğrulamak ve alatta yatan mekanizmaları araştırmak için daha fazla проспектив的研究が必要です.

Anahtar kelimeler: COVID-19, erkek doğurganlığı, pandemi, semen



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Introduction

First identified in Wuhan, China, in December 2019, the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) caused approximately 7 million deaths by March 2024. Due to its extreme contagiousness, the World Health Organization (WHO) declared coronavirus disease-2019 (COVID-19) a pandemic in March 2020. However, as of May 2023, the WHO declared it no longer a global emergency (1). According to the data from the Ministry of Health of the Republic of Turkey, the number of confirmed COVID-19 cases is 17,042,722, and the total number of deaths is 101,492. According to the data, 93.38% (57,961,404) of individuals aged 18 and over have received the first dose of the vaccine, while 85.7% (53,195,125) have received the second dose (2). This disease not only affects the respiratory system but also causes histopathological changes in various non-respiratory organs such as the heart, brain, liver, kidneys, and testes (3). Also, studies have reported that men are at a higher risk of contracting COVID-19 compared to women (4). The testes are also easily damaged because sperm does not have much of a defense against oxidative agents. This can cause problems with both the endocrine and exocrine functions of the testes. Therefore, how COVID-19 affects fertility in men has become a subject of research (5).

The human male reproductive system is more susceptible to viral infections due to the blood-testis barrier's inability to completely block virus entry. Researchers have detected 27 different infectious viruses in human semen to date (6). Angiotensin-converting enzyme 2 (ACE-2) receptors let SARS-CoV-2 into the host cell, and it uses transmembrane serine protease-2 (TMPRSS-2), a cellular membrane protease, to help the two cells join together (7,8). It has been reported that ACE-2 and TMPRSS-2 are highly expressed in spermatogonia, as well as in Sertoli and Leydig cells, and this expression inversely correlates with age (4). Accordingly, patients aged 20-30 have the highest levels of ACE-2 expression, while patients aged 60 and above have the lowest levels of ACE-2 expression (9).

The literature reports that COVID-19 affects sperm concentration, motility, and morphology; however, most descriptions of these changes are short-term and temporary (10,11). The aim of this study is to examine semen parameters before and after the COVID-19 pandemic with a high patient volume without reducing the focus to a specific group.

Materials and Methods

Our hospital's clinical research ethics committee approved the study under approval code 2024/03/04/028. Our

research included patients who had semen analysis and hormone parameters [total testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and prolactin] examined before, during, and after the COVID-19 outbreak in our hospital. The study excluded patients with testicular trauma, undescended testicle, varicocele, tumor surgery, patients receiving hormone therapy with a diagnosis of hypogonadotropic hypogonadism, and included patients over the age of 18 who did not meet any of these criteria. All patients participating in the study gave their consent.

Accordingly, between May 2017 and April 2024, we included 10,082 sperm analyses from 6,517 different infertility patients who applied to our clinic. The patients were not evaluated separately for whether they were affected by a COVID-19 infection or had a vaccination history. Instead, the patients were categorized according to the periods defined by the World Health Organization. We divided them into three groups based on the WHO's pandemic start and end dates: May 2017-March 2020 (before COVID-19): 2,378 patients; March 2020-May 2023 (COVID-19 period): 5,568 patients; May 2023-April 2024 (post-COVID-19): 2,136 patients. We performed all semen analyses in accordance with WHO 2010 guidelines (12).

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. University of Health Sciences Turkey, İstanbul Bağcılar Training and Research and Hospital's Clinical Research Ethics Committee approved the study under approval code 2024/03/04/028.

Statistical Analysis

We used non-parametric statistics to analyze the numerical data examined according to the COVID-19 periods. The Kolmogorov-Smirnov test evaluated the normal distributions of the variables. We performed Kruskal-Wallis on parameters with non-normal distributions. The significance level in this study was set at 0.05. We calculated the Pearson correlation coefficient to ascertain the presence of a linear relationship between two variables. For the statistical analysis of the data, SPSS (Statistical Package for Social Sciences for Windows, Release ver. 29.0) was used.

Results

In the pre-COVID-19 period, epidemic period, and post-epidemic period, semen volumes remained similar regardless of COVID-19 periods ($p>0.05$). When sperm concentration was examined, the average sperm concentration was 25.4 ± 21.9 ($10^6/mL$) in the pre-COVID-19

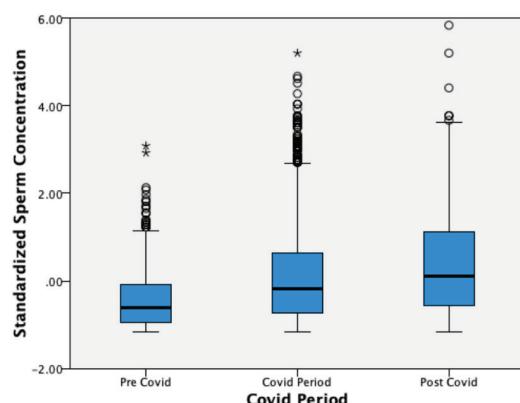
period, 46.5 ± 38.8 ($10^6/\text{mL}$) in the COVID-19 period, and 56.2 ± 41.3 ($10^6/\text{mL}$) in the post-COVID-19 period. This increase was found to be statistically significant ($p < 0.01$) (Graphic 1).

While the sperm motility rate was 40.5% in the pre-COVID-19 period, it was shown to be 42.54% in the pandemic period and 44.34% in the post-pandemic period, and these changes were shown to be statistically significant ($p < 0.01$). Analysis of the sperm morphology change revealed that the average level was 0.97% in the pre-COVID-19 period, 1.39% in the pandemic period, and 1.85% in the post-pandemic period. This change was shown to be statistically significant ($p < 0.01$). Table 1 and Figure 1 summarize these findings regarding semen analysis.

Testosterone levels were 3.81 ± 1.67 in the pre-COVID-19 period, increased to 4.24 ± 1.85 during the COVID-19 period, and then showed a slight decrease to 4.15 ± 1.72 after the pandemic. The increases in both periods are statistically significant compared to the pre-COVID-19 period ($p < 0.01$). When examining FSH (mIU/mL) and LH (mIU/mL)

hormone levels, it was found that the average levels in the pre-COVID-19 period were 11.60 ± 15.21 mIU/mL and 6.75 ± 5.52 mIU/mL, respectively. During the COVID-19 period, these levels were 7.96 ± 8.38 mIU/mL and 7.08 ± 4.91 mIU/mL, respectively. In the post-COVID-19 period, the levels were 6.93 ± 8.36 mIU/mL and 6.81 ± 4.14 mIU/mL, respectively. The decreases in both hormone levels were statistically significant ($p < 0.001$).

While estradiol levels were 29.12 ± 13.40 in the pre-COVID-19 period, they were 31.32 ± 15.04 in the COVID-19 period and 28.46 ± 13.05 in the post-COVID-19 period. There was no statistically significant difference between these levels ($p > 0.05$). Prolactin levels were 11.60 ± 5.84 in the pre-COVID-19 period, 12.72 ± 6.71 during the COVID-19 period, and 11.94 ± 4.50 in the post-COVID-19 period. The levels during and after the COVID-19 period were statistically significantly higher compared to the pre-COVID-19 period ($p < 0.001$). Table 2 and Figure 2 summarize these findings from the hormone analysis.



Graphic 1. Sperm concentrations of individuals according to COVID-19 periods

COVID-19: Coronavirus disease-2019

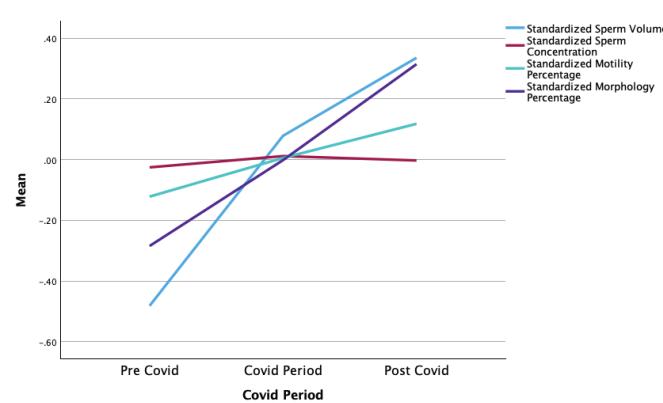


Figure 1. Sperm parameters of individuals according to COVID-19 periods

COVID-19: Coronavirus disease-2019

Table 1. Sperm parameters of individuals according to COVID-19 periods

Parameters	Pre-COVID-19 $\bar{x} \pm SD$ (n=2378)	Pandemic period $\bar{x} \pm SD$ (n=5568)	Post-COVID-19 $\bar{x} \pm SD$ (n=2136)	p-value
Age	30.14 ± 6.75	30.91 ± 7.32	30.72 ± 7.17	-
Sperm volume (mL)	2.78 ± 1.36	2.83 ± 1.38	2.81 ± 1.45	0.174
Sperm concentration ($10^6/\text{mL}$)	25.4 ± 21.9	46.5 ± 38.8	56.2 ± 41.3	0.001*
Motility (%)	40.5 ± 14.21	42.54 ± 16.08	44.34 ± 17.45	0.001*
Morphology (%)	0.97 ± 1.20	1.39 ± 1.42	1.85 ± 1.39	0.001*

Values are presented as mean \pm SD. Differences between groups were assessed using the Kruskal-Wallis test. Post-hoc pairwise comparisons were performed where applicable. A p-value < 0.05 was considered statistically significant.

SD: Standard deviation, COVID-19: Coronavirus disease-2019, *: $p < 0.05$

Table 2. Hormonal parameters of individuals according to COVID-19 periods

Parameters	Pre-COVID-19 $\bar{x} \pm SD$ (n=2378)	During COVID-19 $\bar{x} \pm SD$ (n=5568)	Post-COVID-19 $\bar{x} \pm SD$ (n=2136)	p-value
Testosterone	3.81±1.67	4.24±1.85	4.15±1.72	0.001*
FSH	11.60±15.21	7.96±8.38	6.93±8.36	0.001*
LH	6.75±5.52	7.08±4.91	6.81±4.14	0.001*
Estradiol	29.12±13.40	31.32±15.04	28.46±13.05	0.126
Prolactin	11.60±5.84	12.72±6.71	11.94±4.50	0.001*

Values are presented as mean \pm SD. Group comparisons were conducted using the Kruskal-Wallis test. Correlations were examined with the Pearson correlation coefficient (r). A p-value <0.05 was considered statistically significant.

SD: Standard deviation, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, COVID-19: Coronavirus disease-2019, *: p<0.05

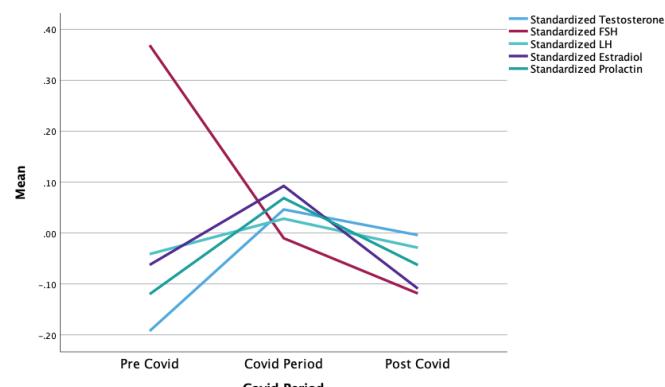


Figure 2. Hormonal parameters of individuals according to COVID-19 periods

COVID-19: Coronavirus disease-2019, FSH: Follicle stimulating hormone, LH: Luteinizing hormone

Discussion

In our study, we examined 10,082 semen analyses from 6,517 different patients, each given at different periods. This is because urology guidelines recommend examining at least two sperm analyses performed at different times to diagnose male infertility.

We predict that during the pandemic period, the restrictions leading to decreased air pollution, reduced water resource pollution, and lowered exposure to free oxygen radicals may result in positive changes in sperm parameters and hormone levels.

The data we obtained show significant changes in individuals' hormone levels during and after the COVID-19 pandemic. Specifically, the decrease in FSH and LH levels may indicate changes in hormonal balance during the pandemic. This situation appears to correlate with the increase in sperm levels and the positive changes in testosterone levels. Fluctuations in estradiol and prolactin levels indicate that stress, health status, and lifestyle changes during the pandemic may impact hormonal health.

In a meta-analysis conducted by Cannarella et al. (13), it was found that there was a significant decrease in sperm concentration and motility in COVID-19 patients compared to healthy individuals. Additionally, a decrease in total testosterone and FSH levels was observed, while increases in LH, prolactin, and estradiol levels were noted. However, sex hormone-binding globulin levels showed no changes (13). One of the differences of this study is that it was conducted only on COVID-19 patients rather than the general population. Another difference is that, due to its short duration, it cannot show long-term results.

In a study conducted by Kadihasanoglu et al. (14) on 265 COVID-19 patients, it was shown that testosterone levels were lower and serum LH levels were higher compared to control groups. It is necessary to demonstrate the long-term changes in these patients after COVID-19. Our study's advantage is that it examined the general population rather than an isolated patient group and demonstrated the long-term changes in this population.

In a study by Zhang et al. (15) on the impact of COVID-19 on sperm quality, it was reported that the infection could lead to a decrease in sperm concentration, particularly after the infection. However, researchers reported that these effects on semen parameters were temporary and gradually recovered within 3-6 months post-recovery (16). These findings appear to be consistent with our study.

In a study conducted by Temiz et al. (17) on COVID-19 patients, a significant decrease in the percentage of normal sperm morphology was demonstrated, and it was suggested that this was due to fever (16). Indeed, other studies have also shown that fever, like inflammation and medications, has negative effects on sperm quality and is temporary (17).

Contrary to the aforementioned example studies, there are also studies in the literature indicating that COVID-19 may have adverse effects on sperm parameters and hormone levels. This discrepancy may have arisen in our study due

to the inability to obtain data on whether each patient was affected by a COVID-19 infection (18-20). However, studies in the literature reflect the short-term effects of COVID-19. In our study, unlike the literature, we evaluated the long-term results.

A meta-analysis reviewing 28 studies found that SARS-CoV-2 was not detected in semen and prostate fluid in 27 studies. A study that examined the semen of 300 patients found SARS-CoV-2 RNA in the semen of only 4 patients (21). The lack of sterile conditions during sample collection led to contamination from aerosols or other bodily fluids from the patients (22). Unlike viruses such as Zika, human immunodeficiency virus, Ebola, hepatitis B virus, and hepatitis C virus, which can cross the blood-testis barrier and affect semen parameters, it has been shown that SARS-CoV-2, which is 70-100 nm in size, cannot cross the blood-testis barrier and does not affect semen parameters (23,24). All these findings, consistent with the results of our study, indicate that COVID-19 does not have a long-term negative impact on semen parameters.

The COVID-19 pandemic prompted the granting of emergency use authorization for vaccines. This situation raised many concerns regarding the safety of the vaccines. Additionally, misinformation and anti-vaccine campaigns highlighted potential effects on fertility, causing ongoing concerns on social media and the internet. Researchers have examined the impact of mRNA (Pfizer-BioNTech, Mainz, Germany), inactivated virus (Sinopharm, Beijing, China), viral vector (AstraZeneca, Cambridge, UK), and Gam-COVID-Vac (Sputnik V, Gamaleya Institute, Russia) vaccines on semen and hormone parameters, and found no significant changes in these values (25-28). Given that 85% of our study population received at least two doses of the vaccines, long-term hormone and semen analyses reveal no adverse effects on semen parameters.

Study Limitations

According to data obtained from autopsies of individuals who died due to COVID-19 and those who died from various causes after recovering from COVID-19, it has been shown that SARS-CoV-2 infection causes changes in the male reproductive system in the early stages; however, it does not have a long-term impact on male fertility (29). In our study, whether the patients were affected by a COVID-19 infection and their vaccination history were not evaluated, which constitutes one of the limiting factors of the study. Our study's retrospective nature and the absence of semen analyses for all patients in all three periods are

other limiting factors. Despite this, our study is significant as it reflects a cross-section of the population.

Conclusion

Although there is sufficient evidence showing changes in the male reproductive system due to SARS-CoV-2 infection, no permanent, long-term effect on male fertility has been identified.

In our study, it was demonstrated that sperm concentration, motility, and morphology showed a significant increase during the COVID-19 period and post-COVID-19 period compared to the pre-COVID-19 period. We also observed significant changes in testosterone, FSH, LH, and prolactin levels. These findings may be attributed to reduced air pollution, decreased contamination of water sources, and lower exposure to free oxygen radicals due to pandemic restrictions.

Given that more than 85% of the population has received two doses of the vaccine, it appears that COVID-19 vaccines do not have harmful effects on male reproductive health. Given the retrospective nature of the study and the large number of patients, population data were adapted for the study. However, we need more randomized, prospective studies to confirm our findings.

Ethics

Ethics Committee Approval: The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. University of Health Sciences Turkey, İstanbul Bağcılar Training and Research and Hospital's Clinical Research Ethics Committee approved the study under approval code 2024/03/04/028.

Informed Consent: All patients participating in the study gave their consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Y., İ.O.C., İ.H., Concept: S.Y., G.Ç., İ.E.K., Design: S.Y., G.Ç., İ.E.K., Data Collection or Processing: S.Y., F.A., İ.O.C., İ.H., Analysis or Interpretation: S.Y., F.A., İ.O.C., İ.H., Literature Search: S.Y., F.A., İ.O.C., İ.H., Writing: S.Y., İ.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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