Original Article

Delayed impacts of COVID-19 infection on unexplained male infertility: 2-year follow-up of normal sperm parameters in unexplained male infertility in KSA

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Abstract

Purpose: The current study aimed to assess the long-term effect of COVID-19 infection on unexplained male infertility.

Materials and Methods: A retrospective comparative study of 134 men attending the infertility outpatient clinic of our institution before exposing to COVID-19 infection in KSA from January 2019 to July 2022. Medical recorded data of these patients who were investigated before COVID-19 infection were retrospectively collected using the hospital's electronic database, including semen analysis, sex hormonal, and ultrasound testicular size, and their data were compared prospectively to collected data after 2-year follow-up.

Results: One hundred and thirty-four infertile males who got COVID-19 infection in KSA (median age, 33 years) were assisted retrospectively preinfection and delayed 2 years postinfection (median of 23 months). Of the 134 men, 44 (32.83%) were asymptomatic positive COVID-19 (Group A), 68 (50.74%) had mild-to-moderate symptomatic positive COVID-19 (Group B), and 22 (16.41%) had severe symptomatic positive COVID-19 (Group C). There was no significant change between pre- and postinfections in sperm parameters, sex hormonal level, and testicular size. Subgroup analyses were performed for patients regarding the severity of infections. None of the evaluated parameters differed significantly after infections up to 2 years. Results of this study demonstrate that COVID-19 infection does not have significant changes in sperm parameters, sex hormonal level, and testicular size.

Conclusion: The long-term impact of COVID-19 infections has no significant effect on normal sperm parameters, sex hormones, and testicular size in male infertility in KSA.

Keywords: COVID-19, infertility, semen, testis, ultrasonography

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INTRODUCTION

Infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[1] Infertility is a common reproductive disorders affecting 13%–15% of couples, male factors is representing more than 50%

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of the couples who are asking to conceive.[2] Adult male subfertility is mostly due to congenital or acquired disorders such as anatomical urogenital anomalies, varicocele, genitourinary infections, hormonal disturbances, genetic disorders, immunologic problems, systemic diseases, and postexposure to gonadotoxic factors.[3] Coronavirus is theoretically considered one of these factors which affecting on male fertility.[4] The exact cause of male infertility in most cases may be difficult to determine but may include disturbance of sex hormones.

Male infertility condition of unknown origin is a fertility impairment that occurs due to an unidentified or unknown pathological cause, which accounts for 37%–58%. Unknown infertility includes two types: unexplained male infertility and idiopathic male infertility. The characteristic item between these categories is semen analysis, which is completely normal in unexplained infertility and abnormal in idiopathic infertility.[1,2] Their semen analysis plays an important role in the evaluation of infertile couples.[2,3]

COVID-19 worldwide spread induced several global multidisciplinary distress affecting millions of humans worldwide.[4] The direct impact of COVID-19 on the reproductive system was initially destructing and has been found recently by many studies.[4,5] However, most of these studies investigating the correlation between SARS CoV 2 and male reproductive functions were observational, undersized sample, incomplete data, unsatisfied reports and heterogeneous outcomes that doesn't provide definitive clear satisfying answers explaining accurate pathogeneses.

Furthermore, the male gonads may potentially be unprotected and exposed to COVID-19, and early studies found a significantly negative impact of COVID-19 infection on sperm parameters (4 and 5). This study was concerned to evaluate long-term impacts of COVID-19 infections on unexplained male infertility after 2 years postinfections in KSA.

Statistical analyses

Data were entered and analyzed using the IBM Statistical Package for the Social Sciences (SPSS) software version 25.0 (IBM Corp., Armonk, NY, USA). The change (pre/post) in outcomes such as sperm parameter, hormone level, and testicular volume was computed. As the change was negatively skewed and the observations were paired, the Wilcoxon signed-rank test was used. $P = 0.05$ was considered for statistical significance.

MATERIALS AND METHODS

Of 187 men who had a past history of underlying infertility issues and asking for investigations, only 134 met our inclusion criteria and were initially involved in our study. Patients, according to the severity of infections, were divided into three groups. Group A: asymptomatic positive COVID-19, Group B: mild-to-moderate symptomatic positive COVID-19, and Group C: sever symptomatic positive COVID-19. Data of all patients were collected and evaluated and followed up 2 years postinfections.

Patient selection

After getting ethical approval from our institutional ethical committee, male partners of the infertile couples attending the infertility unit of the Al-Jedaani group of hospitals from January 2019 to July 2022 were included in the study. This study included electronic hospital-based data from patient from our computerized medical records system for any infertile couples in whom male infertility was suspected and evaluated by semen analysis, hormonal assay, and color scrotal Doppler ultrasounds.

Data collected regarding age, infertility type (primary or secondary), hormonal tests (serum testosterone, follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), semen analysis (sperm count, motility, and morphology), and reports of color Doppler ultrasound (US) examinations were extracted from medical records.

Inclusion criteria

Infected adult male (18–50 years old) with a history of unexplained infertility and has normal spermogram, normal hormonal assay, and color Doppler US examinations.

Exclusion criteria

Recurrent COVID 19 infection, patients with organic cause for infertility (varicocele, hormonal, anatomical causes), pre-infected abnormal spermogram, patients with genital infections (orchitis and prostatitis), and serious medical conditions (hospital admission, and genital trauma) in the past 2 years post-infections.

All patients meeting our criteria were contacted and informed about the study, written informed consent was taken. All participants provided two semen tests, 1st before exposing to infections, 2nd semen analysis approximately 24 ± 3 after the date exposing to infection.

Semen analysis

Retrospective collected data from two semen analyses were done two times and have normal criteria. All semen samples were obtained in privacy by masturbation into a sterile plastic container after a standard abstinence time of 3–5 days. Specimens were delivered to the laboratory

within 15 min and examined within 30–60 min. All semen parameters including semen volume, total sperm count, progressive motility, vitality, and normal morphology spermatozoa were analyzed. The mean characteristic seminal parameters of each patient were compared to the WHO 2010 normal reference values.[6] Data of all patients were collected and evaluated and followed up 2 years postinfections.

Color Doppler ultrasound examinations

Color Doppler US examinations of the scrotum were performed mandatory for all patients as a local assessment for infertility patients at the time of initial assessment, which is considered pre-COVID-19 infectious if done within 1 month before the attack. Follow-up US was done after 6 months and 2 years post-COVID-19 infection to detect any pathological changes at long-term follow-up period. The scrotal US examinations focused on acute and chronic testicular disorders imaging manifestations, such as orchitis, epididymis, varicocele, hydrocele, spermatocele, and testicular mass. Any patients who had pathological findings at initial examinations were excluded from the study.

RESULTS

A total of 187 unexplained infertile patients were exposed to COVID-19 infection in KSA, 53 patients were excluded for different issues. The final analysis included 134 patients (mean age, 34.1 ± 8.6 years; age range, 21–47 years), and other clinical data of the study population are given in Table 1. The majority of participants (103 cases, 76.86%) was healthy and had no chronic medical conditions. Special habits (smoking) were recorded in 58.2% of reported smoking. Out of the 134 men, 44 (32.83%) were asymptomatic positive COVID-19 (Group A), 68 (50.74%) had mild-to-moderate symptomatic positive COVID-19 (Group B), and 22 (16.41%) had severe symptomatic positive COVID-19 (Group C). The basic clinical characteristics and spermogram parameters before infections are shown in Table 1.

Demographic data comparing pre- and long-term postinfections (2 years) semen parameters in our patients are shown in Table 2. We found no significant changes in semen parameters between pre covid and long term post covid infection, regarding semen volume, sperm concentration, progressive motility, sperm vitality, and morphology ($P > 0.05$).

Regarding to androgen secretion, data comparing pre-infectious and delayed post-infections COVID 19 showed insignificant decrease in total testosterone and elevated LH levels in severe cases of COVID 19 (Group C) [Table 3]. Data comparing pre and delayed postinfections scrotal imaging for symptomatic patients to address the effect of adverse events on testicular size are shown in Table 3.

Table 1: Patient characteristics and spermogram results before COVID-19 infections

	All patients (*n*=134)	Group A (*n*=44)	Group B (*n*=68)	Group C (*n*=22)	*P*
Age/years (mean±SD)	34.1±8.6	32.1±6.6	34.3±7.4	36.7±7.9	0.0670
Smoking					
Yes	78	24	40	14	0.0567
No	56	20	28	8	0.0589
Type of fertility					
Primary	86	29	43	14	0.0569
Secondary	48	15	25	8	0.0509
Spermogram (mean±SD)					
Semen volume (mL)	3.2±1.8	3.3±1.6	3.0±1.7	2.9±1.4	0.0843
Sperm concentration	25.7±11.3	27.3±11.7	23.1±10.4	26.4±13.1	0.0657
Total count (millions)	58.8±33.1	57.6±22.4	60.9±32.4	54.9±22.7	0.0703
Progressive motility (%)	39±3.4	38±4.9	41±7.3	35±2.3	0.0586
Vitality (%)	55.6±7.2	56.3±7.6	59.1±5.9	53.1±5.9	0.0721
Normal morphology (%)	11±7.1	14±6.4	11±3.6	12±5.1	0.0680
Chronic medical conditions					
None	103	29	63	11	0.0545
Hypertension	6	1	3	2	0.0654
Diabetes mellitus	13	3	7	3	0.0534
Others	12	3	6	3	0.0502
Scrotal US/mL (mean±SD)					
Right testis size	14.7±3.6	14.9±2.3	14.5±2.6	14.7±3.2	0.0809
Left testis size	14.4±3.4	14.7±2.3	14.3±2.3	14.4±2.4	0.0742
Hormonal test (median with range)					
Testosterone (ng/dL)	261 (114–785)	287 (118–785)	258 (114–765)	267 (128–749)	0.0677
FSH (mIU/mL)	6.8 (3.1–9.1)	6.7 (3.2–9.1)	6.8 (3.4–9.0)	6.9 (3.1–8.9)	0.0734
LH (mIU/mL)	9.1 (3.8–13.4)	7.6 (3.8–13.7)	9.3 (5.2–12.9)	7.9 (3.9–13.4)	0.0671

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, SD: Standard deviation

Table 2: Spermogram results before COVID-19 infections and after 2 years

	Preinfections	Post 2 years	*P*
All patients (*n*=134)			
Semen volume (mL)	3.2±1.8	3.1±1.7	0.0702
Sperm concentration	25.7±11.3	26.8±12.6	0.0642
Total count (millions)	58.8±33.1	51.4±24.1	0.0574
Progressive motility (%)	39±3.4	36±2.7	0.0708
Vitality (%)	55.6±7.2	52.1±6.4	0.0586
Normal morphology (%)	11±7.1	11±8.1	0.0985
Group A (*n*=44)			
Semen volume (mL)	3.3±1.6	4.1±1.2	0.0582
Sperm concentration	27.3±11.7	31.3±12.3	0.0602
Total count (millions)	57.6±22.4	54.7±26.1	0.0589
Progressive motility (%)	38±4.9	38±3.8	0.0502
Vitality (%)	56.3±7.6	57.9±6.68	0.0678
Normal morphology (%)	14±6.4	13±7.2	0.0750
Group B (*n*=68)			
Semen volume (mL)	3.0±1.7	3.2±1.2	0.0812
Sperm concentration	23.1±10.4	21.1±11.6	0.0743
Total count (millions)	60.9±32.4	56.2±22.4	0.0780
Progressive motility (%)	41±7.3	40±5.6	0.0593
Vitality (%)	59.1±5.9	54.9±4.7	0.0624
Normal morphology (%)	11±3.6	9±5.1	0.0588
Group C (*n*=22)			
Semen volume (mL)	2.9±1.4	3.2±1.1	0.0812
Sperm concentration/mL	26.4±13.1	29.3±15.2	0.0743
Total count (millions)	54.9±22.7	52.8±24.2	0.0780
Progressive motility (%)	35±2.3	39±3.3	0.0593
Vitality (%)	53.1±5.9	51.6±6.3	0.0624
Normal morphology (%)	12±5.1	11±1.1	0.0588

Scrotal color Doppler ultrasonographic abnormalities [Table 3] were detected in of 9 (6.7%) patients in 12 (4.47%) testes post-COVID-19 infections 2 years ago revealed in the form of three cases of hydrocele (1 from each group) and four cases have varicocele (two cases left side and two cases bilateral side), one case orchitis, and one case spermatocele which detected at 2 year after the initial diagnosis without significant between all groups.

Table 3: Hormonal and testicular size assessment before COVID-19 infections and after 2 years

	Preinfections	Post 2 years	*P*
Hormone level (median with range)			
All patients (*n*=134)			
Testosterone (ng/dL)	261 (114–785)	263 (111–712)	0.0670
FSH (mIU/mL)	6.8 (3.1–9.1)	8.1 (3.7–9.1)	0.0561
LH (mIU/mL)	9.1 (3.8–13.4)	8.9 (3.3–12.2)	0.0795
Group A (*n*=44)			
Testosterone (ng/dL)	287 (118–785)	263 (111–712)	0.0782
FSH (mIU/mL)	6.7 (3.2–9.1)	8.1 (2.8–8.7)	0.0764
LH (mIU/mL)	7.6 (3.8–13.7)	8.3 (3.3–11.8)	0.0691
Group B (*n*=68)			
Testosterone (ng/dL)	258 (114–765)	238 (106–725)	0.0612
FSH (mIU/mL)	6.8 (3.4–9.0)	4.7 (3.2–8.5)	0.0572
LH (mIU/mL)	9.3 (5.2–12.9)	7.9 (3.7–10.6)	0.0687
Group C (*n*=22)			
Testosterone (ng/dL)	267 (128–749)	221 (98–713)	0.0512
FSH (mIU/mL)	6.9 (3.1–8.9)	6.4 (2.4–7.9)	0.0584
LH (mIU/mL)	7.9 (3.9–13.4)	8.8 (3.0–11.2)	0.0616
Testicular size (volume/mL), mean±SD			
All patients (*n*=134)			
Right testis	14.8±2.6	14.9±2.9	0.0770
Left testis	14.5±2.7	15.9±2.4	0.0845
Group A (*n*=44)			
Right testis	14.9±2.3	14.8±2.9	0.0882
Left testis	14.7±2.3	15.3±2.2	0.0986
Group B (*n*=68)			
Right testis	14.5±2.6	14.6±2.7	0.0990
Left testis	14.3±2.3	14.3±2.1	0.0982
Group C (*n*=22)			
Right testis	14.7±3.2	14.2±3.1	0.0712
Left testis	14.4±2.4	14.2±2.3	0.0681

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, SD: Standard deviation

DISCUSSION

Disorders of production and maturation of sperm are commonly identified causes of male infertility. Abnormal sperm morphology (teratospermia), abnormal motility (asthenospermia), low sperm concentration (oligospermia), and complete absence of sperm (azoospermia) may be common causes in men due to the different pathological conditions and infections.[2,3] Theoretically, coronavirus may be one of them. Coronavirus is recently considered one of the infected viruses that affected the male reproductive system, which has become one of the critical history in infertile patients and must be considered by treating doctors.[5,6]

Because of restricted evidence on testis infection by COVID-19 in asymptomatic patients or during the incubation period, people are advised to protect themselves in their sexual contact.[4,7] However, variable management strategies and providing sperm donation programs were recommended during an endemic attack of COVID-19 disease course.[8,9] Furthermore, some protective measures, such as using antioxidants, were prescribed to reduce the oxidative stress-induced injuries in testicular cells in patients with high prolonged fever and multiorgan dysfunction associated with COVID-19 disease.[7,8] Further studies are still required to assess the fate impact of COVID-19 disease on the male reproductive health conditions and hypothalamic–pituitary–tests axis related to different pathological complications associated with positive individuals during and after complete recovery from COVID-19.

Many earlier researchers supposed coronavirus affect normal human fertility, but no strong evidence has been recorded and proven till now. Many researchers recommended that coronavirus patients should investigate their fertility as this virus may induce acute damage to testicles. However, no powerful study has proved that coronavirus reduces sexual activity and male fertility.[4,8,10]

However, many researchers also supposed that coronavirus infection may affect the production of sperm and the formation of male sex hormone.[6,8] Although some previous reports demonstrated an increased risk of sperm concentrations among patients with active COVID-19 and those fully recovered from it,[10,11] the present study aimed to investigate any evidence of delayed permanent impact on the male reproductive system, including semen parameters, sex hormones, and testicular volume following COVID-19 infections.

Coronavirus mainly targets the respiratory system and immunity system of the patient, so there is a possibility to altered men's ability to normal spermatogenesis. The corona virus infects human cells via binding of spike protein to the angiotensin-converting enzyme, inducing tissue damage.[12] Angiotensin-converting enzyme-2 is present in the lungs and abundant in men's testes. It can invade cells of male reproduction organs, including germ cells and Leydig cells.[12,13] The SARS outbreak in 2020 was associated with severe immunological damage, including testicular tissue of many infected male patients.[13] Many studies stated that many patients infected with SARS were found with inflammation in their sexual organs.[14,15]

COVID 19 looks quite similar to SARS, leading numerous researchers to express concern that it could lead to male infertility.[8] Hence, human infertility may be affected by coronavirus and can be diminished due to the depression and mood affection of the patient due to treatment or isolation management of the infected patient. Recently, all countries in the world have returned to normal precautions and successfully mitigate the spread of COVID-19; however, many researchers recommended to full resumption of full reproductive care in areas where COVID-19 has been well controlled.

Current long-term studies on COVID-19 impact on male reproductive function have been unavailable. However, frequent studies have addressed the impact of long-term viral infection on male reproductive function. Many viruses, such as human papillomaviruses, hepatitis B and C viruses, herpes viruses, cytomegaloviruses, and mumps viruses, have been proved to cause orchitis and influence male fertility.[16,17]

This long-term study on 134 patients post-COVID-19 infections found that 91.8% of all patients exhibited no seminal abnormalities and no significant changes compared to preCOVID-19 infections in seminographic data, 2 years after recovery. Only 3.73% (5 cases) of post-COVID-19 infections had many abnormal seminographic data after recovery 2 years without any orchitis manifestations, and most of them have a history of severe COVID-19 infections (five cases).

However, we did not have significant changes in two spermogram and only 6.7% (9 patients) have decreasing in one of the semen parameters, low sperm count (two cases), and progressive sperm motility (three cases), concentration (one case), and abnormal sperm morphology (four cases). Most cases with significant changes in sperm morphology with decreased sperm motility, viability, and concentration were observed in severe COVID-19 infections patients compared to asymptomatic and mild-to-moderate symptomatic COVID-19 infections.

Regarding long-term hormonal assessment, we have only 3 (2.2%) cases showed decreased total serum testosterone level, with slightly increased LH levels were recorded in two cases postsevere distressed COVID-19 infections and one case postmoderate severity of infections. These results are different from the results of another study that stated a significant decrease in testosterone levels in 113 (51.1%) patients with severe COVID-19, suggesting this parameter as a negative predictor of COVID-19 progression[18,19] which done during the attack of infection. Another study on 119 men with COVID-19 reported that the infected men had slightly decreasing testosterone levels, associated with increasing serum LH, and FSH, compared to 273 control healthy men.[20]

Testicular volume in general has been correlated with exocrine and endocrine testicular function, including spermatogenic, and hormone functions.[21] Detection of significant testicular atrophy using ultrasonography is essential as a fertility predictor because male infertility develops in 37%–87% of patients associated with testicular atrophy postmumps orchitis, which is seen in 40%–70% of affected cases.[22] In our study, Scrotal color Doppler ultrasonography showed no significant changes in testicular size occurring 2 years after infections. However, ultrasonographic abnormalities were found in 9 (6.7%) patients 2 years following COVID 19 infections; these abnormalities included 2 cases of hydrocele, 6 cases of varicocele, and 1 case of spermatocele. These abnormalities were most frequently observed in patients with severe infections and were likely the result of many factors, such as the aggressive treatment these patients received during the attack.

This study has several limitations as a small number of enrolled patients and limitations for a specific group of unexplained infertile men and lacking of a control group.

Cases were followed up only for 2 years after the infected episode (short follow-up). Long-term results have not yet been reported. Finally, a smaller percentage of the patients experienced postinfections systemic side effects and had multiple affecting factors cannot be controlled. In addition, study results need to be confirmed using all infected and vaccinated people. Despite this, the study's time frame encompasses a long period and acceptable time enough to ass many life cycles of sperm.

However, final diagnostic confirmation using sparing testicular biopsies is still pending, which remains the most accurate and the method of choice for assessment and detection of inflammation-associated finding in testicular tissue. Although clinical pathology and basic science medicine research have provided a valuable and lot of information about many important aspects; however, still need to be elucidated. This study will hopefully guide future clinical studies to better address the management of systemic viral infection-related infertility in men.

CONCLUSION

Long-term impact of COVID-19 infections has no significant effect on normal sperm parameters, sex hormones, and testicular size in male infertility in KSA.

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Conflicts of interest
There are no conflicts of interest.

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