Effect of COVID-19 infection on Semen Parameters

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Objective

To investigate the possible effects of coronavirus disease 2019 (COVID-19) infection on semen parameters in recovering men.

Patients and methods

In this prospective study, we investigated the impact of COVID-19 infection on semen parameters in a cohort of 44 reproductive-aged men who had recently recovered from COVID-19. Two sperm samples were collected from these participants at 3 and 6 months after infection and were compared with the patients' pre-COVID-19 semen parameters.

Results

The mean age of the participants was 35±5 years. The mean duration of fever was 3 days. Most of our studied patients 32 (73%) were not hospitalized, and none were admitted to an intensive care unit. Thirty-two cases (73%) had a normal baseline semen analysis.

There was no statistically significant change in semen volume after 3 or 6 months or between 3 and 6 months. Meanwhile, the sperm concentration, total sperm count, progressive sperm motility, and normal morphology significantly declined after 3 and 6 months compared with baseline. These parameters partially recovered after 6 months, compared with 3 months.

In contrast to patients with normal baseline semen analysis, patients with abnormal baseline semen analysis had a significant increase in semen volume, a decrease in sperm concentration, and progressive motility at 3 and 6 months.

Patients who had high-grade fever had a statistically significant change in total count at 3 and 6 months and normal morphology at 3 months compared with patients with low-grade fever.

Conclusion

This study demonstrated that most semen parameters were negatively impacted after COVID-19 infection. The changes were partially reversible 6 months after the infection.

Keywords:

coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, semen, sperm count, sperm motility, sperm parameters

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Introduction

December 2019 was the birth of a new 'era' with the first detected case of coronavirus disease 2019 (COVID-19) infection in China and hence the start of the pandemic of coronavirus disease [1]. The virus shows a male prevalence (male to female ratio of 2.7 : 1), and during active viremia, the male reproductive tract is a potential target [2]. Nevertheless, some studies detected a pattern following COVID-19 infection showing a reversible negative effect on sperm parameters, including sperm concentration and motility, during the forthcoming cycle of spermatogenesis (72–90 days) [3].

Many hypotheses have been suggested to justify sperm affection by COVID-19 infection, including a) direct threat to spermatogenesis by febrile attack and b) hypothalamic-pituitary-gonadal axis compromise, as demonstrated by some gonadotropin level imbalances [3]. The testosterone to luteinizing hormone (LH) ratio, which reflects Leydig cell function, was significantly decreased in COVID-19 patients [4], c) orchitis, whether autoimmune or not, d) Leydig cell and germinal epithelial influence by oxidative stress, e) blood testicular barrier fragility by high body temperatures permitting leakage of macromolecular substances to the testes [5], and f) disease medication with steroids during the acute phase [3].

Seventy percent of COVID-19 patients suffer from fever. Testicular function is highly sensitive to the rise in temperature (proportional to degree and duration),

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which reflects sperm parameters, including sperm concentration, motility, morphology, and DNA fragmentation [6].

Acute fever at ~40°C for 1–4 days may also alter the metabolism of germ cells, consequently influencing the synthesis of DNA, RNA, and protein. Nevertheless, vascular changes to the testis have also been hypothesized [3]. In addition, fever ignites an inflammatory cascade with immune cell activation resulting in copious inflammatory mediators, including interferons and cytokines, that can result in testicular compromise [7].

Aim

The aim of this study is to investigate the possible effects of COVID-19 infection on semen parameters in recovering men.

Patients and methods

In our prospective observational study, we evaluated 50 reproductive-aged male patients who had recovered from COVID-19 within the last 3 months. The eligibility criteria for enrollment of patients included (a) age between 18 and 50 years, (b) positive for COVID-19 RNA polymerase chain reaction (PCR) in nasopharyngeal swab test within the last 3 months, and (c) semen analysis within 6 months prior to infection.

The following subjects were excluded from our study: (a) if the patient received steroidal drug treatment as part of the anti-COVID-19 regimen, (b) if the patient received drug treatment for infertility, (c) if there was a history of diseases that may influence spermatogenesis (diabetes mellitus, undescended testis, varicocele, testicular torsion, mumps, genital tract infection, exposure to pelvic radiotherapy or environmental chemicals, etc.), and (d) if the patient experienced a non-COVID-19 febrile illness in the last 3 months.

A comprehensive history of comorbidities and details of COVID-19 infection were taken to determine certain disease parameters that may explain any future influence on semen parameters. This included fever degree (low below 38.5°C and high above 38.5°C), fever duration, shortness of breath, hospital admission, ICU admission. We chose to stick to simple parameters that patients could recall easily since most patients in this age group were home medicated with no hospital records.

Two sperm samples were collected at 3 and 6 months after infection. Samples were obtained by masturbation after 2–5 days of sexual abstinence into noncytotoxic sterile containers. Samples were transported immediately to the laboratory and liquefied at 37°C for 30 min. Semen was analyzed within 1 h of ejaculation following the World Health Organization (WHO) guidelines for semen analysis [8]. The gravimetric method was used for semen volume measurement. The sperm concentration was assessed using an improved Neubauer chamber. The motility of each spermatozoon was measured manually and graded as progressively motile, nonprogressively motile, and immotile. The following parameters were measured in all samples: volume (ml), sperm concentration (10^6/ml), total number of spermatozoa per ejaculate, progressive motility, and morphology.

Statistical analysis: the collected data were revised, coded, tabulated, and analyzed using the Statistical package for Social Science (SPSS 25.0.1 for Windows; SPSS Inc., Chicago, IL, 2001). Shapiro Wilk's test was used to evaluate the normal distribution of continuous data. The mean, standard deviation (±SD), and range were used for parametric numerical data, while the median and interquartile range (IQR) were used for nonparametric numerical data. Qualitative variables were expressed as frequencies and percentages. The Mann–Whitney test was used to compare quantitative variables between two study groups. Changes in semen parameters within groups were analyzed with paired t tests. A P value less than 0.05 was considered statistically significant.

Results

Our study recruited 50 COVID-19 patients. Six patients were lost during follow-up, leaving a pool of 44 patients. The mean age was 35 years. The mean duration of fever was 3 days; 36 (81%) patients had low-grade fever, while 32 (73%) had shortness of breath. Most of our studied patients 32 (73%) were not hospitalized, and none were admitted to an intensive care unit (ICU). Thirty-two cases (73%) had a normal baseline semen analysis. Patient characteristics are summarized in Table 1.

Table 2 shows no statistically significant change in semen volume after 3 or 6 months or between 3 and 6 months. Meanwhile, the sperm concentration declined after 3 and 6 months compared with baseline by a median of 44 and 14%, respectively (P=0.001). Compared with baseline, the total sperm count decreased after 3 months, with a mean percent change of 27.8±100.8 and a median of 60. At 6

Table 1 Description of personal and medical history data among study cases

	Mean±SD
Age (Y)	34.91±5.27
Medical History	
DM	
No	44±100.0%
Hypertension	
No	40±90.9%
IHD	
No	44±100.0%
Hepatic	
No	44±100.0%
Relevant clinical data related to COVID-19 infection	
Fever duration (days)	3.18±0.95
Fever degree	
Low	36±81.8%
High	8±18.2%
SOB	
No	12±27.3%
Yes	32±72.7%
Hospitalization	
No	32±72.7%
Yes	12±27.3%
ICU	
No	44±100.0%
Yes	0±0.0%
Baseline semen analysis	
Normal	32±72.7%
Abnormal	12±27.3%

DM, Diabetes mellitus; ICU, Intensive care unit; IHD, Ischemic heart disease; SOB, Shortness of breath.

months, the mean decrease was 16.2±54.8%, with a median of 29.9% (*P*=0.001). Progressive sperm motility decreased after 3 months with a mean percent change of 32.1±18 and a median of 30.6 and at 6 months with a mean percent change of 14.25±15.8 and a median of 11.5 (*P*=0.001). Additionally, normal morphology decreased after 3 months with a mean percent change equal to 14.95±12.4 and a median of 11.3 and at 6 months with a mean percent change equal to 6.19±7.2 and a median of 4.2 (*P*=0.001).

There was a statistically significant improvement in sperm concentration, total count, motility, and morphology after 6 months compared with 3 months.

In contrast to patients with normal baseline semen analysis, patients with abnormal baseline semen analysis had a significant increase in semen volume and a decrease in sperm concentration and progressive motility at 3 and 6 months. (Table 3).

In contrast to patients with low-grade fever, patients who had high-grade fever had a statistically significant change in total count at 3 and 6 months and normal morphology at 3 months. (Table 4).

Discussion

COVID-19 infection, similar to other viruses, exhibits a picture highly suggestive of autoimmune orchitis and explains the decline in semen parameters [9]. Several studies have demonstrated elevated levels of LH and prolactin and decreased testosterone to LH ratios, which could indicate disruption in sex hormone secretion. Furthermore, the severity of the disease was proportionate to the degree of hormonal disturbance [10,11]. Oxidative stress is alleged, albeit insufficiently, of Leydig cell and germinal epithelial

Table 2 Comparison between semen parameters at baseline, after 3 and 6 months of coronavirus disease 2019 infection

	Baseline	3 months	6 months	Percent of Change at 3 months versus baseline	Percent of Change at 6 months versus baseline	Percent of Change at 6 months versus 3 months
Volume (ml)						
Mean (SD)	3.00 (±1.24)	3.01 (±1.51)	3.27 (±1.28)	12.39% (±53.23) (*P*= 1.0)	23.69% (±60.43) (*P*=0.116)	(*P*=0.083)
Median (IQR)	3.0 (1.5, 4)	2.5 (2, 3)	3 (2, 4)	0.0 (−33.3, 33.3)	0.00 (−60, 14.29)	
Concentration (Millions/ml)						
Mean (SD)	44.85 (23.93)	22.30 (11.68)	32.83 (17.34)	−31.67 (42.5) **(*P*=0.001)**	−10.06 (44.8) **(*P*=0.001)**	**(*P*=0.001)**
Median (IQR)	54.0 (18–62)	18.0 (12–35)	30 (15.5–48)	−43.5 (22.2–67.1)	−13.9 (6.6–33)	
Total Count (Millions/ejaculate)						
Mean (SD)	186.26 (103.41)	69.92 (28.17)	122.65 (62.16)	−27.89 (100.89) **(*P*=0.001)**	−16.21 (54.82) **(*P*=0.001)**	**(*P*=0.001)**
Median (IQR)	182.0 (94.2–270)	78 (36–97.5)	138 (64.5–180)	60 (49.02–67.14)	29.92 (15.47–40.37)	
Progressive motility (%)						
Mean (SD)	47.09 (7.6)	31.64 (9.25)	40 (8.76)	32.12 (18.01) **(*P*=0.001)**	14.25 (15.81) **(*P*=0.001)**	**(*P*=0.001)**
Median (IQR)	49.0 (45–52)	31.0 (23–39)	38 (36–48)	30.6 (23.3–44.4)	11.5 (2.0–22.4)	
Normal Morphology (%)						
Mean (SD)	74.91 (5.29)	63.45 (8.58)	70.18 (6.35)	14.95 (12.42) **(*P*=0.001)**	6.19 (7.20) **(*P*=0.001)**	**(*P*=0.001)**
Median (IQR)	75.0 (72–79)	66 (59–69)	72 (67–74)	11.3 (4.2–20.3)	4.2 (2.5–7.8)	

Paired *t* test, IQR= interquartile range.

Table 3 Comparison between cases with normal and abnormal semen analysis as regard percent of change in semen parameters 3 and 6 months after coronavirus disease infection

	Normal Semen				Abnormal Semen				
	Mean±SD	Median	IQR		Mean±SD	Median	IQR		*P* value
Change in volume at 3 months	7.96±31.63	21.4	−16.7	33.3	−66.6±61.95	−33.3	−50.0	−16.7	**0.000**
Change in volume at 6 months	−0.76±31.4	−5.6	−19.6	17.1	88.89±71.54	100.0	.0	166.7	**0.000**
Change in concentration at 3 months	52.9±18.5	55.5	36.5	68.6	−25.19±35.2	−44.4	−53.3	22.2	**0.000**
Change in concentration at 6 months	28.98±19.19	29.0	9.9	45.1	−40.4±54.6	−24.0	−111	13.9	**0.000**
Change in count at 3 months	61.05±9.02	62.42	53.78	66.90	−60.56±166.81	9.26	−283.3	75.78	0.265
Change in count at 6 months	33.18±17.22	30.67	20.61	44.63	−29.04±88.54	13.89	−148.0	40.37	0.063
Change in motility at 3 months	39.90±12.56	41.0	27.8	48.8	11.37±13.33	11.5	−4.3	26.9	**0.000**
Change in motility at 6 months	18.21±16.46	19.0	5.8	24.5	3.68±6.78	3.8	−4.3	11.5	**0.011**
Change in morphology at 3 months	13.48±7.90	11.5	7.6	18.4	18.89±20.09	7.8	2.9	45.9	0.397
Change in morphology at 6 months	5.62±3.68	5.2	2.6	7.4	7.70±12.68	3.1	−4.3	24.3	0.672

Mann Whitney test.

Table 4 Comparison between cases with low and high fever as regard percent of change in semen parameters 3 and 6 months after coronavirus disease infection

	Fever degree								
	Low				High				
	Mean±SD	Median	IQR		Mean±SD	Median	IQR		*P* value
Change in volume at 3 months	−15.15±56.43	0.00	−33.3	28.57	0.00±35.63	0.00	−33.3	33.3	0.623
Change in volume at 6 months	−15.99±38.33	0.00	−20.0	11.11	−58.3±115.81	−58.3	−166.6	50.0	1
Change in concentration at 3 months	38.39±38.51	43.55	25.00	67.14	1.41±49.02	1.4	−44.4	47.2	0.143
Change in concentration at 6 months	21.25±24.73	13.89	8.33	32.96	−40.3±75.69	−40.31	−111.1	30.4	0.143
Change in count at 3 months	18.46±109.52	55.94	46.43	66.90	70.31±5.85	70.31	64.84	75.78	**0.01**
Change in count at 6 months	8.08±57.29	24.18	13.89	35.90	52.81±13.29	52.81	40.37	65.24	**0.001**
Change in progressive motility at 3 months	33.21±18.32	30.61	25.00	44.44	27.2±16.74	27.2	11.5	42.8	0.328
Change in progressive motility at 6 months	14.04±16.66	11.54	1.96	22.45	15.1±12.13	15.1	3.8	26.5	0.327
Change in morphology at 3 months	11.92±8.29	11.11	4.17	16.46	28.6±18.55	28.6	11.2	45.9	**0.015**
Change in morphology at 6 months	4.72±4.58	4.17	2.67	6.94	12.7±12.33	12.79	1.25	24.3	0.625

Mann Whitney test.

damage, consequently hindering testosterone production and spermatogenesis, respectively [12].

Negative impact of COVID on semen

Our study showed a negative impact of COVID-19 infection on sperm concentration, motility and morphology that was regressive within 6 months. In agreement with our findings, Patel and his colleagues reported that sperm concentration, motility, and morphology were compromised for 74 days after COVID-19 infection [13]. Similarly, Maleki and colleagues examined 84 patients recovering from COVID-19 over 60 days. They reported a similar pattern in addition to a reduction in semen volume [14].

In another study, patients exhibited oligoasthenoteratospermia after COVID-19 infection. The impact of affection was highest on sperm morphology and lowest on sperm concentration ($P<0.0001$) [15]. Furthermore, 7 studies observing males recovering from COVID-19 were included in a systematic review. The overall mean difference [95% confidence interval (CI)] in semen volume was −0.2 (−0.5, 0.1) ml, sperm concentration was – 16.6 (– 34.8, 1.7) million/ml, total count was −45.4 (−84.6, −6.3) million/ejaculate, and progressive motility was −1.7 (−8.2, 4.8) [16].

In a controlled study examining 41 reproductive-aged male patients post COVID-19 infection, total sperm count, concentration, percentage of motile and progressively motile sperm were compromised 56 days after hospital discharge but recovered after a median time interval of 29 days from first sampling [17]. In contrast to our study, vitality and morphology were unaffected.

Li and colleagues [43] reported that 39% of patients recovering from COVID-19 were oligozoospermic [18].

In another study, oligospermia was encountered in 37% of men in the first month after COVID-19 infection, 29% of men between 1 and 2 months, and 6% of men after 2 months. The pattern of recovery is similar to our study, although on a shorter time frame. Furthermore, asthenospermia was encountered in 51% of men in the first month after COVID-19 infection, 26% of men between 1 and 2 months, and 21% of men after 2 months [15].

Sergerie and colleagues tested semen at 15, 37, 58, 79, and greater than 180 days after febrile insult. They concluded that fever, not COVID infection, compromised the DNA fragmentation index, caused oligospermia from 15 to 58 days post fever and recovered on day 79. The pattern of recovery here is approximate to the pattern we reported in our study. They also reported asthenospermia between days 15 and 37 post fever and recovered on day 58 [6].

Ma and colleagues examined sperm motility and sperm DNA fragmentation. They encountered asthenospermia in one-third of patients. Accordingly, only asthenospermic patients exhibited higher sperm DNA fragmentation [10].

Temiz *et al.* reported a decline in normal sperm morphology after COVID-19 infection [19]. This was similar to the pattern reported in our study.

Others observed that sperm concentration and total motility were influenced, but volume and progressive motility were spared [20]. In another study examining 23 recovering males from COVID-19, no change in sperm parameters was witnessed in all cases [21]. Furthermore, a small case-controlled cross-sectional study reported no change in semen parameters except sperm morphology, which was compromised in the pretreatment group compared with the control group but recovered posttreatment [19]. Similarly, 24 patients who were previously normal and recently recovered from mild COVID-19 were examined and showed negligible differences in semen parameters before and after infection with regard to volume, sperm concentration, and progressive motility. Only total motility was compromised significantly in this study [22]. Another study also contradicted our findings and reported that the time lapse after infection does not significantly affect sperm morphology [15].

Correlation between disease severity/fever and semen parameters

Our study exhibited a correlation between the grade of fever and the degree of compromise of semen parameters. Holtmann and colleagues observed similar findings, as they reported that moderate COVID-19 infection had a significantly larger impact than mild cases and the control group [23]. Likewise, in a multicenter study on 69 patients, motility and vitality alone were compromised with mild symptoms, while all semen parameters were affected with moderate symptoms.

In the same context, sperm concentration was observed to be inversely proportionate to disease severity and to long recovery times (>90 days) compared with less severe cases with shorter recovery periods [20]. Gacci and colleagues studied males recovered from COVID-19 and reported a 25% COVID-19 severity-proportionate oligoasthenoteratospermia [24]. Carlsen and colleagues reported a directly proportional relationship between the number of febrile days and compromise of sperm parameters [25].

In contrast, another study found no correlation between COVID-19 infection severity and sperm parameters [15].

Conclusion

This study demonstrated that most semen parameters were negatively impacted after COVID-19 infection. However, the changes were partially reversible 6 months after the infection.

Strengths and limitations

The strong points of this study are the unbiased group of patients, the proof of the presence and timing of COVID-19 infection, and the correlation of sperm quality parameters with disease severity. We had baseline sperm samples from the subjects before they contracted COVID-19 and 3-month interval re-evaluation samples at 3 and 6 months to detect the insult on spermatogenesis and demonstrate recovery of sperm quality over time.

A weakness of our study is the lack of samples from matched control men without COVID-19, although our patients themselves acted as a self-control owing to their preinfection semen records. Although we performed a subset analysis for cases with high grade fever, it remains difficult to determine whether the virus or the symptoms are the cause for the semen parameter affection since the disease coexists with viremia, fever, and other constitutional symptoms. This is particularly problematic because the disease is not chronic and the reversible nature of the affection of semen parameters left us with little time to confirm the theories produced by peer studies. This may be a study limitation, but it is still a limitation of the majority of other peer studies.

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Not applicable

Declarations

Ethical Approval and Consent to participate: the study has been approved by the institutional research ethics committee. Informed consent was obtained from all individual participants in this study.

Consent for publication: the authors have reviewed the manuscript and approved its publication in the journal.

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Conflicts of interest
Competing interests: the authors declare that they have no conflicts of interest.

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