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Research Article

Male Reproduction and Health after Recovery from COVID-19 Infection

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Objective. To study the reproductive hormones, semen quality, psychology, and sexual function of childbearing age men after recovery from Corona Virus Disease-2019 (COVID-19) infection. *Materials and Methods*. We recruited 387 men of childbearing age who recovered from COVID-19 infection and underwent prepregnancy health checks at the Reproductive Center of Shandong Maternal and Child Health Hospital from January to March 2023 as study subjects. Routine semen analysis and reproductive hormones were performed. The clinical symptoms, anxiety, depression, erectile function, and premature ejaculation questionnaire were investigated during the COVID-19 infection period. A control group of 226 men of childbearing age who were not infected with COVID-19 between August 2022 and October 2022 were selected based on questionnaire responses, reproductive hormones, and semen parameters. *Results*. The main clinical symptoms during COVID-19 infection of the 387 research subjects were fever (342/387, 88.37%), muscle pain (155/387, 40.05%), anosmia (124/387, 32.04%), cough (106/387, 27.39%), throat pain (53/387, 13.70%), nausea and vomiting (16/387, 4.13%), and testicular discomfort (5/387, 1.29%). The rates of anxiety and depression were 11.37% (44/387) and 32.82% (127/387), respectively; erectile dysfunction (ED) and premature ejaculation (PE) of the research subjects were accounted for 32.30% (125/387) and 6.98% (27/387). The IEF-5 score ($P < 0.001$) decreased significantly compared to the control group, while the PHQ-9 score ($P < 0.001$), the rate of increased ED ($P < 0.001$), and the rate of depression increased ($P < 0.001$). There were statistically significant differences in liquefaction time ($P < 0.05$), the progressive sperm motility ($P < 0.05$), total sperm motility ($P < 0.05$), the rates of progressive sperm motility <32% ($P < 0.05$), and total sperm motility <40% ($P < 0.05$) between the 1 month, the 2 months after recovery from COVID-19 and controls. Circular cell counts ($P < 0.05$) at 2 and 3 months were lower than in the controls. No changes in reproductive hormones before and after recovery from infection. *Conclusion*. COVID-19 infection exacerbates depression and ED. It has a sustained effect on sperm motility and liquefaction time in men. The effects of COVID-19 infection on semen persist for approximately 2 months, with recovery occurring in the third month. Reproductive hormone levels do not appear to be continuously affected after recovery from COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA virus belonging to the coronavirus subfamily [1]. Its envelope has spikes of 20 nm which is similar to coronaviruses under electron microscopy, hence the name coronavirus [2]. The first case of SARS-CoV-2 infection was reported in December 2019 and spread rapidly worldwide. In February 2020, the World Health Organization (WHO) designated it as COVID-19 [3]. By March 7, 2022, the number of confirmed cases of COVID-19 worldwide had exceeded 440 million, and the cumulative death rate has exceeded 6 million [4], which has caused serious impact on human life and health. As the pandemic continues to develop, the impact of COVID-19 on human reproduction has received increasing attention.

SARS CoV-2 has the largest genome among known RNA viruses [5]. Nucleoprotein surrounds the RNA genome to form a helical structure and is surrounded by the viral envelope [1]. The matrix protein is embedded in the viral envelope, and spike (S) proteins are anchored to the viral envelope [1]. During viral infection, the S protein is crucial for receptor recognition, cell attachment, and fusion [6]. The S protein binds to angiotensin-converting enzyme 2 (ACE2) in human tissues, allowing the virus to enter through cell membrane transfusion [7]. In addition to ACE2, COVID-19 also utilizes host cell transmembrane serine protease 2 (TMPRSS2) hydrolysis activation to promote the fusion of viruses with cells and enter into cells [8]. ACE2 can be expressed in the testes and seminal vesicles, TMPRSS2 can also be detected in the prostate, testes, and epididymis [9, 10], and they are all potential targets for SARS-CoV-2. It suggests that COVID-19 may have an impact on male fertility.

Currently, there is still debate on whether COVID-19 affects the parameters of male semen. Sacha et al. [11] concluded that COVID-19 has basically no effect on patient semen parameters. But the studies of Scroppo et al. [12] and Best et al. [13] showed that the sperm concentration, sperm count, and progressive sperm motility of patients with COVID-19 were finally decreased. However, the sample sizes of these studies are relatively small, and there have been relatively few reports on studies of semen in men recovering from COVID-19 infection.

In this study, we recruited 387 men of reproductive age who had recovered from COVID-19, analyzed their reproductive hormones, semen parameters, and conducted questionnaire testing to determine the impact of COVID-19 on the reproductive health of men after recovery.

2. Materials and Methods

2.1. Study Participants. This study was approved by the Ethics Committee of Shandong Maternal and Child Health Hospital on October 27, 2022 (No. 2022-034), and the study was conducted according to guidelines described in the Declaration of Helsinki. All participants provided written informed consent and signed.

We recruited 387 men of childbearing age who recovered from COVID-19 infection and underwent premarital health checks at the Reproductive Center of Shandong Maternal and Child Health Hospital between January and March 2023 as study subjects. The participants had previously been diagnosed as positive for COVID-19 through nucleic acid testing in December 2022. Their clinical symptoms persisted for about 2 weeks before they eased up. All of the participants tested negative for nucleic acids again. Participants ranged in age from 22 to 44 years.

A medical history was taken and all participants were given a male specialist physical, all of which showed normal testicular size. Routine semen analysis and reproductive hormones were performed. Conduct clinical symptoms, anxiety (GAD-7), depression (PHQ-9), erectile function (IIEF-5), and premature ejaculation (PEDT) questionnaire survey were investigated during COVID-19 infection in the quiet clinic room.

A control group of 226 men of childbearing age who tested negative for nucleic acid between August 2022 and October 2022 was selected based on questionnaire responses, reproductive hormones, and semen parameters.

2.2. Analysis of Semen Quality Parameters. All participants abstained from sex for 2–7 days. Semen samples obtained by masturbation were placed into noncytotoxic sterile containers provided to them by the study center and transported to the laboratory. All samples were analyzed following the 2010 guidelines of the World Health [14]. After complete liquefaction of semen at 37°C, measuring the following semen parameters: volume (mL), sperm concentration (10^6/ml), total number of spermatozoa per ejaculate, total motile count, pH, and presence of round cells (10^6/ml). Microscopic evaluations were performed using a phase-contrast microscope (IX51; Olympus, Tokyo, Japan) at 400× magnification. The computer-assisted semen analysis (CASA) of Sperm Class Analyzer® (SCA, Spain) was used.

2.3. Statistical Analysis. Excel 2020 was used for data collection and management, and SPSS statistical software version 26 was used for statistics. Quantitative variables are represented by mean ± standard deviation (SD), N (%) was used for categorical variables. While the independent sample t-test is used for intergroup comparisons of quantitative variables, the chi-squared test is used for intergroup comparisons of categorical variables. $P < 0.05$ was considered to indicate statistical significance.

3. Result

3.1. Clinical Symptoms. During COVID-19 infection, the main clinical symptoms were fever (342/387, 88.37%), muscle pain (155/387,40.05%), loss of smell and taste (124/387, 32.04%), dry cough (106/387, 27.39%), throat pain (53/387, 13.70%), nausea and vomiting (16/387, 4.13%), and testicular discomfort (5/387, 1.29%) (Figure 1). Most participants (84.50%) have 1–3 symptoms during the initial infection, 9.56% had more than three symptoms, and 5.94% had no symptoms.

3.2. Questionaire Score. The participants' mean score of Generalized Anxiety Disorder-7 (GAD-7) was 1.37 ± 2.79. Anxiety population (score 5–21) accounted for 11.37%, 81.82% was mild (score 5–9), and 18.18% was moderate or above (score 10–21). Their mean score of Patient Health Questionnaire-9 (PHQ-9) was 3.48 ± 3.72. Depression population (score 5–21) accounted for 32.82%. The mild (score 5–9) and moderate or above (score 10–21) were 80.31% and 19.69%. The mean score of International Index of Erectile Function-5 (IIEF-5) was 22.26 ± 2.89. Erectile dysfunction (score 0–21) accounted for 32.30%, most participants (97.60%) were mild, 2.40% were the moderate or above. The mean score of premature ejaculation diagnostic tool (PEDT) was 3.42 ± 3.12. Premature ejaculation (score 11–20) accounted for 2.84% (Table 1). There were no statistically significant differences in age, height, weight, and body mass index, GAD-7, PEDT, GAD-7 > 4, PEDT > 8 between research subjects and control group. Compared with the control group, the IIEF-5 score was significantly decreased, while the PHQ-9 score, the rate of increased ED and depression were increased (Table 2).

3.3. Treatment Situation. Three hundred and forty-two subjects self-administered ibuprofen or acetaminophen and Lianhua Qingwen Granules during COVID-19 infection. There was no statistically significant difference in semen parameters between the two groups (Table 3).

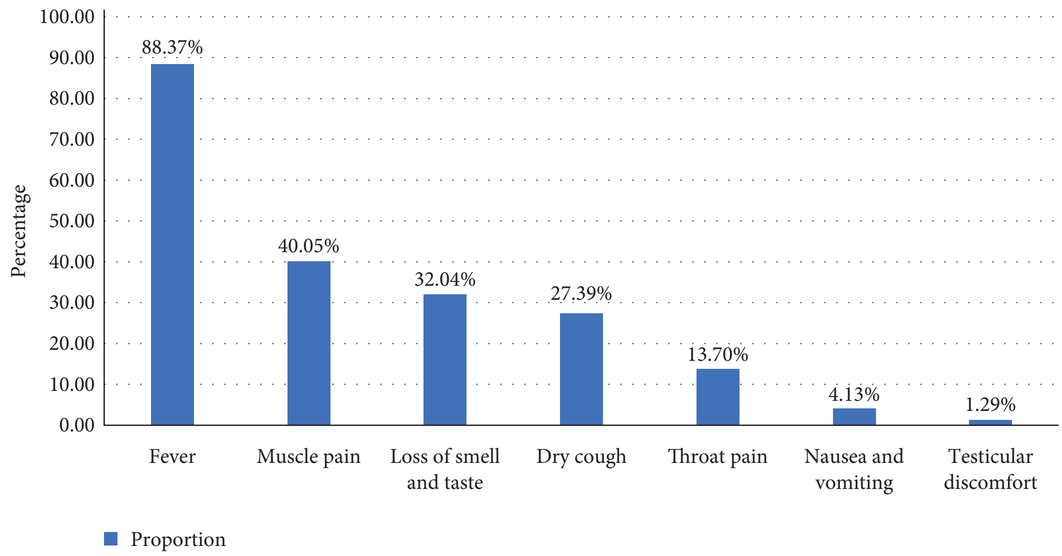

Figure 1: Clinical symptoms proportion.

Table 1: Questionnaire score distribution ratio.

Questionnaire	Score	Controls, *N* (%)	Research subjects, *N* (%)
GAD-7	0–4	205 (90.71)	343 (88.63)
	5–9	16 (7.08)	36 (9.30)
	10–13	3 (1.33)	3 (0.78)
	14–18	1 (0.44)	4 (1.03)
	19–21	1 (0.44)	1 (0.26)
PHQ-9	0–4	194 (85.84)	260 (67.18)
	5–9	26 (11.50)	102 (26.37)
	10–14	4 (1.77)	22 (5.68)
	15–19	2 (0.88)	1 (0.26)
	20–27	0 (0)	2 (0.52)
IIEF-5	0–7	0 (0)	1 (0.26)
	8–11	0 (0)	2 (0.52)
	12–21	37 (16.37)	122 (31.52)
	22–25	189 (83.63)	262 (67.70)
PEDT	0–8	212 (93.81)	360 (93.02)
	9–10	8 (3.54)	16 (4.13)
	11–20	6 (2.65)	11 (2.84)

4. Reproductive Hormone and Semen Parameter

Comparing reproductive function indicators, there were statistically significant differences in liquefaction time, the progressive sperm motility, total sperm motility, the rates of progressive sperm motility <32% and total sperm motility <40% between the 1 month, the 2 months after recovery from COVID-19 and controls. The round cells of the 2 months and 3 months were lower than controls (Table 4).

5. Discussion

The COVID-19 global pandemic, which started in 2020, has had a dramatic impact on human physical and mental health. At present, the comprehensive prevalence rates of depression and anxiety reported in literature are 45% and 47%, and its higher than nonepidemic periods [15]. The pandemic led to a 27.6% increase in severe depression cases and a 25.6% increase in anxiety disorder cases worldwide [16]. The psychological impact of COVID-19 on different populations is different. There was a survey on 333, 21 medical workers from nearly 100 countries found that the prevalence of depression was 21.7%, while the anxiety rate was 22.1% [17]. According to the random effects results in a meta-analysis, the overall prevalence of pregnant women was 18.7% for anxiety and 25.1% for depression [18]. Apart from that, the prevalence of anxiety and the depression symptoms among college students during the COVID-19 pandemic was 31% and 34%, compared with men, women had a higher incidence of comorbid depression symptoms [19].

Studies have shown that anxiety and depression scores were independent predictors of male sexual health [20]. In the study, we conducted psychological assessments of men of childbearing age and found that the rates of anxiety and depression after recovery from the COVID-19 pandemic were 11.37% and 32.82%, respectively, and most of these were mild. Depression rates were higher than in the study subjects, and there was no statistically significant difference in the incidence of anxiety compared to the control group. However, the rates of anxiety and depression were relatively lower than those reported during the 2020 COVID-19 pandemic. This may be due to the relatively low incidence and case fatality rate of COVID-19 as the virus evolves, the gradual liberalization of the foreign epidemic situation, and the adjustment of national control of COVID-19. All of this has led to a greater understanding of the virus, which has reduced the incidence of anxiety and depression.

The COVID-19 pandemic is also having an impact on men's sex lives. It can cause injury to endothelial cells resulting in endothelial dysfunction [21]. The widespread endothelial dysfunction may lead to ED [22]. Research has shown that

Table 2: Questionnaire score between research subjects and controls.

Variable	Controls ($n = 226$)	Research subjects ($n = 387$)	P-value
Age (year)	29.74 ± 3.79	30.06 ± 3.95	0.324
Height (cm)	177.47 ± 6.46	177.56 ± 5.37	0.859
Weight (kg)	82.68 ± 14.74	81.78 ± 14.88	0.466
Body mass index (kg/m^2)	26.21 ± 4.15	25.89 ± 4.21	0.352
GAD-7	1.26 ± 2.79	1.37 ± 2.79	0.613
PHQ-9	2.02 ± 2.92	3.48 ± 3.72	<0.001
IIEF-5	23.12 ± 1.89	22.26 ± 2.89	<0.001
PEDT	3.26 ± 3.01	3.42 ± 3.12	0.559
GAD-7 > 4	21 (9.29)	44 (11.37)	0.503
PHQ-9 > 4	32 (14.16)	127 (32.82)	<0.001
IIEF-5 < 22	37 (16.37)	125 (32.30)	<0.001
PEDT > 8	14 (6.19)	27 (6.98)	0.708

Table 3: Comparison of semen parameters between treatment and nontreatment.

Variable	Nontreatment	Treatment	P-value
Number of participants	45	342	—
Age (year)	30.29 ± 3.43	30.03 ± 4.02	0.683
Height (cm)	177.00 ± 5.45	176.63 ± 5.36	0.460
Weight (kg)	84.81 ± 18.12	81.38 ± 14.38	0.146
Body mass index (kg/m^2)	26.92 ± 4.82	25.75 ± 4.12	0.081
Semen volume (ml)	3.50 ± 1.53	3.78 ± 1.56	0.268
Liquefaction time (min)	20.67 ± 10.75	19.44 ± 10.95	0.481
pH	7.20 ± 0.10	7.21 ± 0.10	0.739
Sexual abstinence (day)	4.27 ± 1.85	4.19 ± 1.92	0.793
Progressive sperm motility (%)	38.19 ± 16.58	36.34 ± 15.48	0.454
Non-progressive sperm motility (%)	18.71 ± 5.56	18.64 ± 6.18	0.937
Total sperm count (×10^6/ml)	216.58 ± 186.49	192.34 ± 164.73	0.362
Sperm concentration (×10^6/ml)	61.21 ± 39.82	51.74 ± 37.91	0.118
Round cell (×10^6/ml)	1.28 ± 1.40	1.17 ± 0.92	0.457

cardiovascular diseases caused by COVID-19 and its subsequent treatment may also lead to ED, and neurological symptoms caused by cerebrovascular disease or hemorrhage may affect sexual desire and erectile and ejaculatory functions [23]. Sansone et al. [24] compared men with and without COVID-19 infection history and found that the prevalence of ED in men with infection history increased significantly. Fang et al. [25] found that approximately 8.4% and 8.5% of participants reported deterioration in erectile function and ejaculatory control through self-assessment, while 31.9% and 17.9% of participants showed a decrease in IIEF-5 score or an increase in PEDT score. Through research, we found that approximately 32.30% of IIEF-5 scores decreased, a result consistent with Fang's study. The increase in PEDT scores among participants was relatively low at 6.98%. We consider that this may be related to increased anxiety and depression. In addition, a decrease in the frequency of sexual activity during this time period can contribute to the condition to a certain extent.

Normal testicular function and stable levels of reproductive hormones are essential for sperm production. The study by Rastelli et al. [26] described the relationship between T levels and clinical outcomes in COVID-19 infected individuals, suggesting that those with reduced testosterone levels have poorer prognosis. Ma et al. [27] compared the sex hormone levels of 119 male patients of reproductive age infected with SARS-CoV-2 with 273 healthy males and found that COVID-19 patients had higher serum LH levels and lower T/LH ratios, while there was no significant difference in serum testosterone levels between the two groups. There are also studies showing that serum testosterone levels in COVID-19 male patients during the illness period are significantly lower than those in the healthy control group [28]. As can be seen, the impact of COVID-19 infection on reproductive hormones is somewhat controversial and lacks long-term research. To investigate whether COVID-19 infection has a long-term effect on male reproductive hormone levels, we tested the reproductive hormone levels of patients recovering from COVID-19 infection. By comparison, we found no statistically significant difference in testosterone, luteinizing hormone, and follicle stimulating hormone levels between infected and noninfected individuals after recovery. From this, it can be seen that reproductive hormone levels

Table 4: Changes of reproductive hormone and semen parameters at 1, 2, and 3 months after recovery from COVID-19.

Variable	Controls	1 month	2 months	3 months
Number of participants	226	56	176	155
Age (year)	29.74 ± 3.79	30.61 ± 4.26	29.62 ± 3.99	30.37 ± 3.76
Height (cm)	177.47 ± 6.46	176.66 ± 5.37	177.48 ± 5.43	177.96 ± 5.29
Weight (kg)	82.68 ± 14.74	83.46 ± 16.28	80.54 ± 13.65	82.58 ± 15.65
Body mass index (kg/m^2)	26.21 ± 4.15	26.69 ± 4.72	25.52 ± 3.84	26.02 ± 4.40
Follicle stimulating hormone (mIU/ml)	4.62 ± 2.19	4.57 ± 2.16	4.74 ± 2.27	4.53 ± 2.20
Luteinizing hormone (mIU/ml)	4.60 ± 2.18	4.42 ± 1.92	4.54 ± 2.06	4.50 ± 2.10
Testosterone (nmol/l)	13.96 ± 5.01	13.95 ± 5.42	13.90 ± 5.10	13.95 ± 4.85
Semen volume (ml)	3.68 ± 2.36	3.40 ± 1.51	3.69 ± 1.41	3.93 ± 1.72
Liquefaction time (min)	17.32 ± 7.63	$20.27 \pm 11.85^*$	$20.97 \pm 12.29^*$	17.77 ± 8.45
pH	7.22 ± 0.12	7.22 ± 0.10	7.2 ± 0.12	7.21 ± 0.07
Sexual abstinence (day)	4.38 ± 2.04	4.11 ± 1.77	4.18 ± 1.88	4.25 ± 2.01
Progressive sperm motility (%)	42.77 ± 13.88	$29.43 \pm 15.39^*$	$35.01 \pm 15.60^*$	40.87 ± 14.45
Nonprogressive sperm motility (%)	18.86 ± 5.61	18.03 ± 5.62	19.18 ± 6.30	18.27 ± 6.03
Total sperm motility (%)	61.63 ± 15.14	$47.46 \pm 17.49^*$	$54.19 \pm 17.42^*$	59.14 ± 16.31
Total sperm count ($\times 10^6$/ml)	201.55 ± 177.99	157.67 ± 139.49	187.52 ± 166.32	217.38 ± 175.26
Sperm concentration ($\times 10^6$/ml)	56.25 ± 36.92	48.69 ± 35.75	50.47 ± 35.16	57.04 ± 42.04
Round cell ($\times 10^6$/ml)	1.53 ± 1.91	1.24 ± 1.04	$1.25 \pm 0.97^*$	$1.08 \pm 0.98^*$
Semen volume <1.5 ml (n)	19 (8.41)	6 (10.71)	6 (3.41)	8 (5.16)
Liquefaction time >60 min (n)	5 (2.21)	3 (5.36)	10 (5.68)	4 (2.58)
pH <7.2 (n)	17 (7.52)	0 (0.00)	5 (2.84)	3 (1.94)
Progressive sperm motility $<32\%$ (n)	53 (23.45)	35 (62.50)*	73 (41.48)*	45 (29.03)
Total sperm motility $<40\%$ (n)	24 (10.62)	20 (35.71)*	37 (21.02)*	27 (17.42)
Total sperm count $<39 \times 10^6$/ml (n)	24 (10.62)	6 (10.71)	13 (7.39)	10 (6.45)
Sperm concentration $<15 \times 10^6$/ml (n)	21 (9.29)	6 (10.71)	17 (9.66)	16 (10.32)
Round cell $>1 \times 10^6$/ml (n)	112 (49.56)	28 (50.00)	98 (55.68)	65 (41.94)

Note: *Representing that there is statistical difference, $P<0.05$.

are normal after COVID-19 recovery and do not appear to be continuously affected.

Currently, ACE2 has been shown to be the primary receptor mediating the entry of SARS-Cov-2 into human cells. Fan et al. [29] found that ACE2 is highly expressed in Sertoli cells, Leydig cells, and testicular germ cells. The COVID-19 virus binds to the ACE2 receptor, and the TMPRSS2 found on the surface of the host cell guides the S protein and other cell proteases to cleave the S protein into S1 and S2 subunits [8]. The virus enters the host cell, directly damaging testicular tissue and thereby affecting spermatogenic function. Yang et al. [30] found through autopsy of the testes of COVID-19 patients that the testes exhibited significant damage to the seminiferous renal tubules, decreased Leydig cells, and mild lymphocytic inflammation. So COVID-19 infection can also affect semen quality through secondary orchitis.

Holtmann et al. [31] first reported the impact of COVID-19 infection on semen parameters, and they found that the mild infection did not impair testicular and epididymal function, while moderate infection could decrease sperm concentration, total sperm count and sperm motility. On the contrary, the research of Guo et al. [32] had shown that COVID-19 infection had no impact on sperm concentration, motility, and morphology. Guo et al. [33] analyzed semen samples of patients after recovery from COVID-19 infection at the second and third month and found that in the first analysis, the total sperm count, sperm concentration, and sperm motility significantly decreased, but in the second sampling, all these parameters significantly increased. Their findings suggest that changes in sperm parameters after COVID-19 infection are temporary and semen quality may recover over time. Donders et al. [34] found that the recovery time for semen quality is approximately 3 months.

But the sample sizes in all these studies are relatively small. In this study, semen parameters of 387 men of reproductive age recovered from COVID-19 infection were analyzed. There were statistically significant differences in liquefaction time, the progressive sperm motility, total sperm motility, the rates of progressive sperm motility <32% and total sperm motility <40% between the 1 month, the 2 months after recovery from COVID-19 and controls. The circular cells at 2 and 3 months were lower than in the control. There were no changes in other semen parameters before or after infection. We found that COVID-19 infection mainly affects sperm motility, liquefaction time, and circular cell count, and semen quality is severely affected in the first month after recovery from COVID-19 infection and gradually improves in the second and third months, but semen quality fully recovers in the third month.

The patients of COVID-19 infection often experience clinical symptoms such as high fever, testicular and epididymal pain, and scrotal discomfort [35, 36]. There was a study had shown that high fever or testicular pain may reduce the quality of semen parameters, damage sperm DNA integrity, and affect fertility [37]. We also investigated symptoms during COVID-19 infection. Testicular discomfort accounted for 1.29%, and fever accounted for 91.99%. Among the participants with fever, approximately 66.85% were above 38.5°C and 33.15% were below 38.5°C.

The advantage of this study is that the sample size is relatively sufficient, the COVID-19 infection has clear evidence and timing, and the patient population is male of normal reproductive age. A limitation of our study is that we lack comparative sperm samples from participants prior to COVID-19 infection, nor can we include contemporary samples without COVID-19 because everyone in the country is infected. The only comparison samples we were able to handle were from males of normal reproductive age who were not infected with COVID-19 before the outbreak. In addition, no further follow-up was performed on the pregnancy outcomes of the study population. Therefore, by introducing a 1-year follow-up period as a revision to our study, we will be able to provide more specific and detailed information on the impact of COVID-19 on male reproductive health.

6. Conclusion

In this study, we recruited 387 men of reproductive age who recovered from COVID-19 infection and found that COVID-19 had some impact on the psychological and sexual lives of men of reproductive age. COVID-19 infection mainly affects sperm motility, liquefaction time, and circular cell count, and semen quality is severely affected in the first month after recovery from COVID-19 infection, gradually improves in the second and third months, and fully recovers in the third month.

Data Availability

If reasonably requested by the journal, the corresponding author will provide the data that support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Zhida Shi, Xiangyang Sun conceived, designed, and supervised the study. Zhida Shi, Xiangyang Sun, Jian Li, Lianbing Sheng, and Ganggang Wang recruited research subjects, conducted informed consent signing and questionnaire surveys. Lianbing Sheng and Song Liu carried out examinations. Xiangyang Sun, Jian Li and Lianbing Sheng collected, organized, analyzed data, and wrote the manuscript. Zhida Shi and Xiangyang Sun revised the manuscript. All authors approved the final manuscript to be published and agreed to be accountable for all aspects.

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