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Impact of COVID-19 on Male Infertility

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1. Abstract

Background: The impact of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-Cov-2) on male fertility is unclear.

Objective: To clarify the effects of COVID-19 on male gonadal function.

Methods: PubMed search up to March 4, 2021. Search terms included COVID-19, testicles, testosterone, spermatogenesis, hypogonadism. Case reports, retrospective, prospective, cross-sectional and autopsy studies are included.

Results: Orchitis and/or epididymitis were demonstrated by scrotal ultrasound (US) in approximately 22-42% of men with COVID-19 admitted to the hospital and can be frequently asymptomatic. Circulating testosterone levels are reduced in men admitted with severe COVID-19 with concomitant elevation of luteinizing hormone (LH) consistent with testicular dysfunction. Men recovering from severe COVID-19 exhibit abnormal semen parameters. Few studies detected SARS-CoV-2 in semen during active COVID-19 infection and after recovery. Autopsy investigations showed extensive damage of testicular tissues and evidence of inflammation and presence of SARS-CoV-2 in testicles of men who died from severe COVID-19.

Conclusion: COVID-19, particularly in its severe presentation, may compromise male gonadal function and fertility. Evaluation of semen analysis after recovery from COVID-19 is necessary to rule out any residual effects on sperm quality.

2. Keywords: COVID-19; Fertility, Male; Semen; Spermatogenesis; Testosterone; Testes; Cryopreservation.

3. Introduction

Increasing evidence suggests that the testicles may be one of the targets of SARS-CoV-2. Many viruses such as mumps, human immunodeficiency virus (HIV), Zika virus, and others can invade the testicles [1] In fact, several studies reported the presence of testicular pain in patients hospitalized with COVID-19 [2-5]. SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as receptor and the transmembrane protease serine 2 (TMPRSS2) as co-receptor for host cell binding and penetration [6]. Conflicting data exist regarding expression of these

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receptors in testicular tissues. Thus, some workers found that ACE2 receptors were expressed in testicular germ cells, Leydig cells, and Sertoli cells [7,8]. In addition, ACE2 receptors and TMPRSS2 are expressed in prostate [9]. However, Pan et al [5] found that ACE2 and TMPRSS2 are expressed sparsely in the human testes and Stanley et al [10] failed to detect co-expression of ACE2 and TMPRSS2 in testicular cells. Nevertheless, emerging data provide convincing evidence that several men affected with COVID-19 exhibit significant gonadal dysfunction. The purpose of this review is to present the most recent evidence of testicular involvement by COVID-19, and its implications on male fertility.

3.1. Testicular imaging in patients with COVID-19

The first case of testicular inflammation associated with COVID-19 was reported in the pediatric population by Gagliardi et al [11] who reported a 14-year-old boy presenting with scrotal swelling and fever. Scrotal US showed orchitis and epididymitis [11]. Bridwell et al [12] described a 37-year-old man with mild asymptomatic COVID-19 pneumonia presenting with bilateral testicular pain, mild fever, and myalgia approximately 10 days after testing positive with nasopharyngeal polymerase chain reaction (NP-PCR) for COVID-19. Orchitis was confirmed by US without evidence of epididymitis [12]. In a retrospective study from Wuhan, China, Chen et al [13] performed testicular US in 142 hospitalized patients with confirmed COVID-19 and median age 58.3 years (range 24-93). They found that 32 of 142 (22.5%) of patients had evidence of acute orchitis (n=10), epididymitis (n=7), or epididymo-orchitis (n=15) [13]. The risk of scrotal infection increased with age and severity of COVID-19 [13]. Thus, prevalence reached 53% in men older than 80 years [13}. Moreover, acute scrotal infection was more likely to occur in the group with severe COVID-19 compared to the group with non-severe disease, 35.6% and 13.5%, respectively (P=0.002) [13]. Interestingly, only 10 of the 32 (31.3%) patients with abnormal scrotal US presented with acute scrotal symptoms. Conversely, 3 of the 110 patients (2.7%) who had negative scrotal US had acute scrotal symptoms [13]. These observations suggest that orchitis associated with COVID-19 may be asymptomatic. The latter notion might be also true with respect to epididymitis. In fact, in a small retrospective study from Brazil, Carneiro et al [14] performed testicular US in 26 young men (age range 21-42 years) hospitalized for mild to moderate COVID-19. None of patients had scrotal symptoms [14]. Using similar diagnostic criteria to study of Chen et al [13], they found that 11 patients (42.3%) had US signs of epididymitis, and no patient had signs of orchitis [14].

3.2. Testosterone levels in patients with COVID-19

Testosterone is produced in testicles by Leydig cells and is essential in maintaining normal spermatogenesis and male fertility [15]. There is general agreement that circulating testosterone levels may be reduced in patients with COVID-19 admitted to the hospital [16-18]. Cayan et al [16] have shown that total testosterone levels significantly decreased in a subgroup of 24 Turkish men from 458 ± 198 ng/dl prior to COVID-19 infection to 315 ± 120 ng/dl on the first day of hospital admission (P=0.003). Furthermore, available data suggest that the degree of hypogonadism increases in parallel to the severity of COVID-19. Thus, in one prospective study from Turkey of young patients (mean age ± standard deviation 35.5 ± 9.8 years), Okcelik [17] showed that patients with COVID-19 pneumonia had significantly lower testosterone levels than COVID-19 patients without pneumonia, 260.3 and 435.1 ng/dl, respectively (P=0.01). In one Chinese

retrospective study, Ma et al [18] compared serum levels of testosterone in 119 young men (age range 20-49 years) hospitalized for COVID-19 (84% of them had moderate disease) with 273 age-matched control subjects. They found a non-significant trend of testosterone levels to be lower in COVID-19 patients compared with control subjects, median [interquartile range, (IQR)] being 397 (314-574) and 464 (351-638) ng/dl, respectively (P=0.18) [18]. Meanwhile, luteinizing hormone (LH) values were significantly higher in patients compared with control individuals; median (IQR) 6.36 (4.63-8.38) and 3.38 (2.48-4.52) mIU/L, respectively, P < 0.0001) [18]. Thus, testosterone/LH ratio, a marker of testicular function, was significantly lower in patients with COVID-19 compared with healthy subjects [18]. Limited data suggest that sex hormone abnormalities associated with COVID-19 may normalize after recovery. Thus, Xu et al [19] showed that serum testosterone and gonadotropin levels were within normal range in 39 men after recovery from COVID-19. Taken together, the above studies suggest that men hospitalized with COVID-19 may have testicular dysfunction as reflected by low serum testosterone and elevated LH concentrations. However, it is unclear whether the decreased testosterone levels are directly caused by COVID-19 or simply a marker of severe illness or both.

3.3. Impairment of semen characteristics in men with COVID-19

Multiple abnormalities in semen parameters, summarized in table 1, were described in men recovering from COVID-19 [20-24]. During acute illness with COVUID-19, semen samples could not be obtained clearly due to severe underlying illness. In an Italian prospective study, Gacci et al [20] examined semen parameters in 43 patients who recovered from COVID-19 after 2 consecutive negative nasopharyngeal swabs for SARS-CoV-2 RNA (median time from the first positive to second consecutive negative test was 31 days, range 3-65 days). They found that 8 patients (18.6%) had azoospermia, and 3 (7.0%) patients had oligospermia (< 2 million sperms/ml). Interestingly, semen impairment was significantly related to COVID-19 severity [20]. Thus, azoospermia was present in 4 of 5 patients admitted to the intensive care unit, in 3 of 26 patients hospitalized on Medicine wards, and in only one patient among the 12 non-hospitalized patients (P<0.001) [20]. All patients with azoospermia had normal fertility history and had biological children [20]. Ruan et al [21] described significant reduction in sperm count and motility in 70 patients who recovered from COVID-19 compared to age matched control men. In a small prospective study from Germany, Holtmann et al [22] showed that patients (n=2) recovering from moderate COVID-19 had significant impairment of sperm quality including sperm concentration, total number of sperms of ejaculate, and motility compared with patients who recovered from mild COVID-19 (n=18) and control men (n=14). In addition, they found that patients who had fever exhibited reduced semen volume and sperm motility compared to patients without history of fever [22]. Indeed, Temiz et al [23] reported that the reduced proportions of sperms with normal morphology could be due to occurrence of fever which ranged from 38.5 to 39.2 C few days before collection of semen. Conversely, the study of Guo et al [24] was the only investigation that showed normal sperm parameters in men recovering from COVID-19, likely because of its mild severity. In addition to fever, medications (e.g. corticosteroids), and previous severe illness may play a role in sperm abnormalities [25,26]. However, this does not exclude that SARS-CoV-2 infection could be a factor implicated in defective spermatogenesis. Unfortunately, repeat semen analysis at regular intervals after recovery was not performed to assess

the course and pattern of sperm impairment [20-24].

3.4. Presence of SARS-CoV-2 in the semen

Available data suggest SARS-CoV-2 RNA may be present in semen albeit with low frequency. Li et al [27] detected SAR-CoV-2 virus RNA in the semen of 4 out of 15 acutely ill and 2 out of 23 men recovering from COVID-19. Among 43 men who recovered from COVID-19, Gacci et al [20] detected SARS-CoV-2 in semen of only one patient in whom semen sample was collected 21 days after the second negative nasopharyngeal swab. Importantly, his partner did not test positive for SARS-CoV-2 [20]. Among 15 men with positive nasal swab for SARS-CoV-2 and having no or mild symptoms, Machado et al [28] detected viral RNA in semen from 1 of the 15 subjects (6.6%). Meanwhile, 14 studies (n=299), including 2 studies that described men with orchitis-like symptoms, failed to demonstrate SARS-CoV-2 in seminal fluid among patients affected with various severities of COVID-19 [29].

3.5. Autopsy studies

Postmortem examination of testicles of patients who died from COVID-19 represent the effects of the extreme form of COVID-19 on gonadal function [30-33]. Results of the autopsy studies are summarized in table 2. Most autopsy studies showed severe injury of seminiferous tubules, germ cells, Leydig cells, and variable degrees of apoptosis and interstitial cellular infiltration of inflammatory cells. Interestingly, while viral particles were not identified in most studies, Ma et al [30] have detected viral particles in all testicular autopsies examined (n=5). In a proteomic (i.e protein quantification) autopsy study including samples from 5 patients who died from COVID-19 pneumonia, Nie et al [34] found evidence of reduced Leydig cells and sperm motility factor. In addition, there was reduced testicular biosynthesis of cholesterol, the source of testosterone [31].

3.6. COVID-19 and sperm cryopreservation

There is great concern that cryopreserved semen gets contaminated by SARS-CoV-2, particularly that viruses stored in liquid nitrogen may retain their pathogenic properties [35]. Huang et al [36] analyzed 100 cryopreserved semen samples collected during and after the COVID-19 pandemic to rule out infection of semen by SARS-CoV-2. All samples were negative for SARS-CoV-2 RNA [36]. Likewise, De Paoli et al [37] did not detect any SARS-CoV-2 RNA in semen samples from 10 cancer patients referred to sperm bank for cryopreservation. These preliminary experiments are somewhat reassuring and should include sexually active men recovering with COVID-19.

4. Conclusions and Current Needs

Growing evidence suggests that the testicles may be an extra-pulmonary target of SARS-CoV-2. Indeed, COVID-19 may be associated with multiple abnormalities relevant to male gonadal function. These include the common occurrence of scrotal pain, evidence of orchitis and epididymitis, sex-hormone defects consistent with testicular failure (i.e., hypergonadotropic hypogonadism), and impairment of spermatogenesis. Furthermore, autopsy studies showing degeneration of germ cells, and inflammatory cell infiltration represent direct evidence of testicular involvement in patients who died from severe COVID-19. The detection of SARS-CoV-2 RNA in few semen specimens of COVID-19 patients, although uncommon, is a matter of concern. While there is no evidence so far that COVID-19 is sexually transmitted, further studies are needed to rule out this possibility with certainty. The demonstration of impaired spermatogenesis in men recovering from COVID-19 implies that semen analysis should be done few months after recovery form COVID-19 to rule out any persistent abnormalities that may compromise fertility. This evaluation is particularly important in patients in reproductive age who wish to have

biological children. In the meantime, all semen and sperm specimens subjected to cryopreservation or assisted reproduction techniques should be tested for SARS-CoV-2. In this respect, the methodology used by Huang et al [36] appears to be highly sensitive and convenient for testing large number of semen samples. Whether to generalize this viral semen testing to all men recovering from COVID-19 is unclear, but it may be wise to test at least sexually active men who recovered from moderate and severe forms of COVID-19.

Conflict of interest

The authors do not have conflicts of interest to declare.

Table 1: Abnormalities in semen characteristics in men recovering from COVID-19.

	Gacci et al [20]	Ruan et al [21]	Holtmann et al [22]	Temiz et al [23]	Guo et al [24]
Design	Cross-sectional	Cross-sectional, controlled	Pilot cohort study	Cross-sectional	Cross sectional
Patients	43 men aged 18 to 65 years who recovered from SARS-CoV-2	70 men aged 20 to 50 years who recovered from SARS-CoV-2 and 145 healthy controls	18 men who recovered from SARS-CoV-2 infection (mean age 42 years), 14 controls (mean age 33 years), and 2 men with acute SARS-CoV-2 infection.	20 men hospitalized with COVID-19, and 10 controls (mean age approximately 37 years)	21 men with COVID-19 (18 patients with mild disease), with mean age 41 years.
Sperm abnormalities	8 men with azoospermia, and 3 men with oligospermia	Significant reduction in sperm count and motility vs controls	Reduction in sperm concentration in patients who had moderate COVID-19 vs those with mild disease and controls. Decrease semen volume and motility in patients who had fever (n=10) vs those who did not have fever (n=8)	Reduced normal sperm morphology in patients with COVID-19 (1%) vs controls (3%)	Normal sperm concentration and motility
Semen abnormalities	33 of 43 men (76.7%) have pathological levels of IL-8 in semen. SARS-CoV-2 RNA detected in one semen sample	No SARS-Co-V2 RNA was detected in any semen sample	No SARS-Co V-2 RNA was detected in any semen specimen	No SARS-Co V-2 RNA was detected in any semen specimen	Semen characteristic were within normal limits. No SARS-Co V-2 RNA was detected in any semen specimen.
Comments	Azoospermia was related to the severity of COVID-19	-	Decrease semen volume and motility in men who had fever	Semen samples obtained immediately after finishing 5-day in-hospital treatment protocol for COVID-19	Median interval from diagnosis of COVID-19 to providing serum samples was 32 days.

Abbreviations

COVID-19: coronavirus disease 2019.

SARS-CoV-2: acute respiratory syndrome-coronavirus 2.

Table 2: Autopsy studies of testicles of deceased patients with COVID-19.

	Ma et al [30]	Li et al [31]	Achua et al [32]	Yang et al [33]
Characteristics of deceased subjects	5 deceased patients with COVID-19 (age range 51-83 years), and 3 control deceased subjects without COVID-19 (age range 71-80 years)	6 deceased patients with COVID-19, and 6 control (age range 51-83 years) deceased subjects without COVID-19 (age range 56-85 years)	6 deceased patients with COVID-19 (age range 20-87 years), and 3 control subjects (age range 28-77 years who died from non-COVID-19 causes	11 deceased patients with COVID-19 (age range 42-87 years), and 5 control deceased subjects (age range 49-75 years) were used for studies of Leydig cells
Histopathology	Degenerated germ cells in COVID-19 autopsies, Sertoli cells were spared and similar to control testicles	Thinning of seminiferous epithelium, shedding of spermatogonia, interstitial edema in testicles and epididymis of COVID-19 autopsies	3 of 6 COVID-19 testes had degenerated germ cells, with sparing of Sertoli cells, and early maturation arrest.	9 of 11 testicles showed various degrees of seminiferous tubules injury. Sertoli cells showed swelling, vacuolation, cytoplasmic rarefaction, and detachment from basement membrane. Mean number of Leydig cells was 2.2 vs 7.8 in COVID-19 and control testicles ($P<0.001$). Spermatogenesis was normal for age.
Apoptosis in COVID-19 testes	Number of apoptotic cells greater than control testicles.	Proportion of apoptotic cells in COVID-19 testicles was 2.9 fold higher than in control testes (95% CI, 1.26-6.90, P=0.018)	Not reported	Not reported
Immune cells in COVID-19 testes	Scattered infiltration of $CD3^+$ T lymphocytes, $CD20^+$ B lymphocytes, CD68+ macrophages, activated B cells and plasma cells. Such cell	Infiltration of $CD3^+$ T lymphocytes, CD68+ macrophages in all COVID-19 testicles. Precipitation of IgG in 4 of 6 COVID-19 patients' seminiferous	One of 6 COVID-19 testes showed lymphocyte and macrophage infiltration	Infiltration of $CD3^+$ T lymphocytes, CD68+ macrophages

	infiltration is rare in control testicles.	tubules, and no such precipitation in control testicles		
Detection of nucleic acid of SARS-CoV-2 by reverse transcription-polymerase chain reaction	2 of 5 COVID-19 testicles were positive	Not reported	Not reported	One COVID-19 testicle was positive
Immunohistochemistry studies	Testicular COVID-19 sections stained positive for the spike protein of SARS-Cov-2	ACE2 protein was highly expressed in Leydig cells in both COVID-19 and control autopsies	ACE2 protein expression was significantly increased in the 3 COVID-19 testicles with abnormal spermatogenesis compared with the 3 COVID-19 testicles with normal spermatogenesis	ACE2 protein was highly expressed in Leydig cells, and diffusely in Sertoli cells, not in spermatogonia
Demonstration of viral particles by electron microscopy	Coronavirus-like particles in interstitial compartment in the 5 COVID-19 testicles.	Not performed	Coronavirus-like particles in 1 of 6 autopsies of patients with COVID-19	Viral particles not identified in 3 testicular autopsies examined.
Comments	-	-	Viral particles were demonstrated in testicles of one patient who recovered from COVID-19	Fever and use of glucocorticoids were reported in 10 patients.

Abbreviations

COVID-19: coronavirus disease 2019.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

ACE2; angiotensin-converting enzyme.

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