Virol Curr Res
Volume 5:4, 2021

Virology: Current Research

Research Article

Open Access

# The Effect of COVID-19 on Spermatogenesis

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## Abstract

**Background:** The 2019 coronavirus disease (COVID-19) viral pandemic has become a significant public health emergency worldwide, evolving rapidly. Although the lungs are the main organ targeted in this disorder, other vital organs may be involved. Angiotensin converting enzyme 2 (ACE2), a major component of the renin-angiotensin-aldosterone system, is the principal host receptor for SARS-CoV-2 (RAAS). The ACE2 is important in testicular male regulation of steroidogenesis and spermatogenesis. A recent report published in JAMA network revealed that in an analysis 38 semen samples from COVID-19 patients pcr positive. Since SARS-CoV-2 is capable of infecting the testis via ACE2 and adversely affecting the male reproductive system. From this point the purpose of this study is how covid-19 affect spermatogenesis.

**Methods:** How covid-19 affect spermatogenesis.

**Design and setting of the study:** A 100 patients had been enrolled in the study by a criteria suggesting good semen analysis. two sets of semen analysis done, the first after 72days of first positive swab for covid-19 to show changes in semen analysis from normal values in the cycle of spermatogenesis during infection, the other sample after 72 days from the first sample to show if the changes regress to normal and to compare it with the first sample.

**Results:** A total number 100 patients first sample show 2% of patients oligospermia, 36% of patients teratospermia. The second sample show 4% of patients teratospermia by comparing the two samples there is a significant increase in sperm concentration with mean concentration in the first sample 96.49 m/ml, mean concentration in the second sample 104.67 m/ml, a significant increase in motility (A+B) with mean percentage of 44% in the first sample and 46% in the second sample, a highly significant increase in the normal forms of sperms with mean percentage of 23.4% in the first sample and 30.55% in the second sample.

**Conclusions:** Covid-19 affect spermatogenesis in the form of reversible teratospermia, reversable decrease sperm count but within normal level, reversable decrease in the sperm motility but also within normal level.

**Keywords:** COVID-19 • Semi analysis • Spermatogenesis

## Introduction

The 2019 coronavirus disease viral pandemic (COVID-19), created by a new, exponentially evolving, mutated severe acute respiratory syndrome coronavirus (SARS-CoV-2), has become a major public health emergency worldwide. Although the lungs are the key organ targeted in this disease, other vital organs may be involved, such as the heart and kidney [1]. The main host receptor of the SARS-CoV-2 is Angiotensin Converting Enzyme 2 (ACE2), a major component of the Renin-Angiotensin-aldosterone system (RAAS). The ACE2 is also important in testicular male regulation of steroidogenesis and spermatogenesis. Since SARS-CoV-2 is capable of infecting the testis via ACE2 and adversely affecting the male reproductive system [2-4]. A recent report published in JAMA Network Open revealed that in an analysis 38 semen samples from COVID-19 patients, 6 (four at the acute stage of infection and, alarmingly, two who were recovering) tested positive for the virus by RT-PCR. Importantly, at this point, If the real virus was viable and contagious, we have no idea. However, additional data indicating that active COVID-19 infection significantly reduced the testosterone-to-LH ratio indicated the possibility that this coronavirus may have a pathophysiological effect on the studies, suggesting a major impact on the responsiveness of Leydig cells to LH stimulation [5,6]. In several ways, these findings do not surprise us because, considering the large variety of pathogenic viruses (HIV, hepatitis, mumps, papilloma) that are known to be capable of destroying the testes and making the host infertile, the blood test barrier is known to offer little protection against viral invasion [7]. The angiotensin system plays a vital role in human spermatozoa's survival and functionality, but also creates a weakness to the attack of COVID-19. Angiotensin 1 is a biologically inactive decapeptide that in turn activates the AT1R and AG2R receptors, both of which are present in these cells, by cleaving ACE1 to generate angiotensin II. ACE2 is further processed by angiotensin II to produce angiotensin 1-7, which binds to the PI3K activating MAS receptor [8]. The latter then phosphorylates AKT, which, by phosphorylating essential sperm apoptosis regulators such as BADD, maintains cell viability. As long as BAD is phosphorylated, it is held in abeyance by a 14-3-3 keeper protein. However, BAD dephosphorylates are released from their interaction with 14-3-3 if the PI3/AKT pathway is disrupted, and transfer to the mitochondria where it inactivates anti-apoptotic factors and facilitates the intrinsic apoptotic cascade [9]. The spike protein on COVID-19 specifically targets ACE2 and in so doing removes an essintial stimulus for PI3K/AKT, thereby compromising sperm viability. Subsequent to COVID-19 attachment, the ectodomain of ACE2 may be removed by ADAM proteases and shed from the sperm surface [10]. Alternatively, proteases from the TMPRSS family may promote fusion between the virus and the sperm surface, either as intrinsic components of the sperm plasma membrane or provided by seminal prostasomes, by cleaving ACE2 and the viral spike proteins (S1 and S2) at the sites indicated by dashed lines, thereby completing the transformation of this cell from procreating gamete to viral vector [11].

Fever is an added risk in the COVID-19 pandemic that could affect male fertility [12]. A important manifestation of the COVID-19 pandemic is an especially high and prolonged rise in body temperature, complicating more than 80 percent of patients [13,14]. The belief that fevers and testicular

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**Received:** May 30, 2021; **Accepted:** June 14, 2021 ; **Published:** June 21, 2021

temperature elevation result in spermatogenesis deficiency is generally accepted (Figure 1).

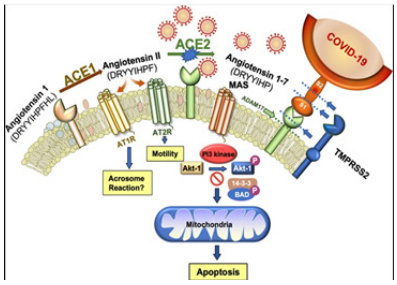


**Figure 1.** In addition, cytokine microenvironment variations within the testis can have tumorigenic cellular adverse effects, potentially contributing to testicular cancer, a second long-term problem of concern.

# Methods

## Molecular docking

Know the Effect of covid-19 on spermatogenesis.

## Type of the study

Prospective clinical trial.

## Study subjects

**Inclusion criteria:** Adult patient younger than 45 years old, no history of fertility disorders, good body built and secondary sexual character, CT chest free to exclude stress from medical illness.

**Exclusion criteria:** Congenital anomalies of the testis, chronically ill patients, problems of male fertility, males with varicocele, sexual performance disorders.

**Sample size calculation:** All cases that fulfill the selection criteria (nonprobability sample size) with expected size of 100 patients starting from 01/04/2020 to 28/12/2021 [15]. Patients whose follow-ups will be lost because of death or any other cause will be excluded from this study (expected to be 25%).

**Study tools:** All the patients will be included within inclusion criteria after giving an informed consent from patients or from hospital board to review patients medical records, it will include:

- Full history taking.
- General examination.
- Laboratory examination.

## Study setting

A 100 patients had been enrolled in the study by a criteria suggesting good semen analysis (adult younger than 45 years old, no comorbidities, no special habits, no history of fertility problems, with genital examination free, no genital previous surgery) [16]. two sets of semen analysis done, the first after 72 days of first positive swab for covid-19 to show changes in semen analysis from normal values in the cycle of spermatogenesis during infection, the other sample after 72 days from the first sample to show if the changes regress to normal and to compare it with the first sample [17].

## Research outcome measures

- Changes of semen parameter after 72 days of infection by COVID-19.
- Follow up semen analysis after 72 days of the first sample to see if it's permanent change and to compare with the first sample [18].

# Results

More importantly, emerging evidence suggests that secondary cytokine storm syndrome can occur in a subgroup of patients with extreme COVID-19 (hemophagocytic lymphohistiocytosis). This is a hyperinflammatory, underrecognized syndrome characterized by sustained fever, with fulminant and fatal hypercytokinemia with multiorgan failure. With cytopenia and hyperferritinemia, these patients have a clear serum blood cytokine profile. These results also indicate that immunomodulatory therapy (IL-6 antagonist) in these patients will dramatically increase mortality rates. Since cytokines contribute to the testicular function and preservation of male reproductive health and to the pathologies associated with their irregular organ activity, changes in the cytokine profile caused by COVID-19 may have additional consequences for male fertility. Furthermore, immunomodulatory therapies may have possible long-term effects on male fertility and are a matter of concern. In addition, cytokine microenvironment variations within the testis can have tumorigenic cellular adverse effects, potentially contributing to testicular cancer, a second long-term problem of concern (Tables 1 and 2), (Figures 2 and 3).

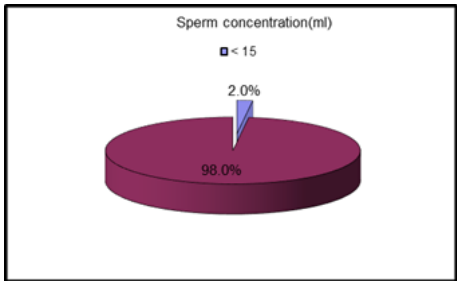


**Figure 2.** Distribution of the studied cases according to sperm concentration (ml).

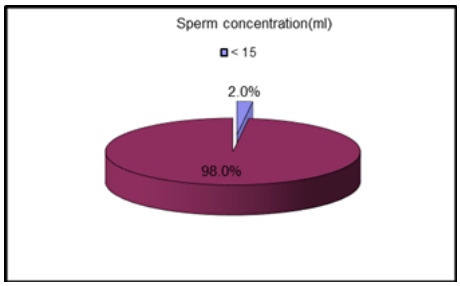


**Figure 3.** Distribution of the studied cases according to morphology (normal forms).

**Table 1.** Distribution of the studied cases according to age, length, weight, BMI, DM, HTN, cardiac, special habit, other and previous surgery.

| | | **No.=100** |
|---|---|---|
| Age | Mean ± SD | 24.61 ± 3.34 |
| | Range | 21-35 |
| Length | Mean ± SD | 1.71 ± 0.06 |
| | Range | 1.5-1.78 |
| Weight | Mean ± SD | 75.42 ± 10.41 |
| | Range | 55-99 |
| BMI | Mean ± SD | 25.97 ± 3.73 |
| | Range | 18.59-37.11 |
| DM | No | 100 (100.0%) |
| HTN | No | 100 (100.0%) |
| Cardiac | No | 100 (100.0%) |
| Special habit | No | 100 (100.0%) |
| Other | No | 100 (100.0%) |

| | | |
|---|---|---|
| Previous surgery | No | 100 (100.0%) |

**Table 2.** Distribution of the studied cases according to PH, volume, sperm concentration (ml), motility (A+B)%, morphology (normal forms)%, Rbcs and pus cell.

| First semen analysis | | No=100 |
|---|---|---|
| PH | Mean ± SD | 7.63 ± 0.26 |
| | Range | 7-8 |
| Volume | Mean ± SD | 3.27 ± 0.75 |
| | Range | 2-4.6 |
| | >1.5 | 100 (100.0%) |
| Sperm concentration(ml) | Mean ± SD | 96.49 ± 35.87 |
| | Range | 12-154 |
| | <15 | 2 (2.0%) |
| | >15 | 98 (98.0%) |
| Motility(A+B)% | Mean ± SD | 44.52 ± 6.67 |
| | Range | 34-58 |
| | >32 | 100 (100.0%) |
| Morphology (normal forms)% | Mean ± SD | 23.41 ± 17.64 |
| | Range | 1-55 |
| | <4 | 36 (36.0%) |
| | >4 | 64 (64.0%) |
| Rbcs | Mean ± SD | 1.07 ± 0.78 |
| | Range | 0–2 |
| Pus cell | Mean ± SD | 1.20 ± 0.99 |
| | Range | 0-6 |

The Previous table shows that there was highly statistically significant difference found between First semen analysis and Second semen analysis Regarding Morphology(normal forms)%, and there was statistically significant difference found between first semen analysis and Second semen analysis Regarding sperm concentration (ml) and Motility (A+B)% , and there was nonstatistically significant difference found between First semen analysis and Second semen analysis Regarding PH , Volume , Rbcs and Pus cell (Tables 3 and 4), (Figures 4-11).

**Table 3.** Spreading of the studied cases according to PH, volume, sperm concentration(ml), motility(A+B)%, morphology (normal forms)%, Rbcs and pus cell.

| Second semen analysis | | No.=100 |
|---|---|---|
| PH | Mean ± SD | 7.61 ± 0.26 |
| | Range | 7-8 |
| Volume | Mean ± SD | 3.25 ± 0.76 |
| | Range | 2-4.6 |
| | >1.5 | 100 (100.0%) |
| Sperm concentration(ml) | Mean ± SD | 104.67 ± 33.80 |
| | Range | 15-154 |
| | <15 | 0 (0.0%) |
| | >15 | 100 (100.0%) |
| Motility(A+B)% | Mean ± SD | 46.47 ± 7.09 |
| | Range | 34-58 |
| | >32 | 100 (100.0%) |
| Morphology(normal forms)% | Mean ± SD | 30.55 ± 12.98 |
| | Range | 2-60 |
| | <4 | 4 (4.0%) |
| | >4 | 96 (96.0%) |
| Rbcs | Mean ± SD | 1.06 ± 0.76 |
| | Range | 0-2 |
| Pus cell | Mean ± SD | 1.07 ± 0.76 |
| | Range | 0-2 |

**Table 4.** Comparison between first semen analysis and second semen analysis regarding PH, volume, sperm concentration(ml), motility(A+B)%, morphology(normal forms)%, Rbcs and pus cell

| Semen analysis | | First | Second | Paired T-test | P-value | Sig. |
|---|---|---|---|---|---|---|
| PH | Mean ± SD | 7.63 ± 0.26 | 7.61 ± 0.26 | 0.554 | 0.581 | NS |
| | Range | 7-8 | 7-8 | | | |
| Volume | Mean ± SD | 3.27 ± 0.75 | 3.25 ± 0.76 | 0.237 | 0.813 | NS |
| | Range | 2-4.6 | 2-4.6 | | | |
| Sperm concentration(ml) | Mean ± SD | 96.49 ± 35.87 | 104.67 ± 33.80 | -1.871 | 0.054 | S |
| | Range | 12-154 | 15-154 | | | |
| Motility(A+B) % | Mean ± SD | 44.52 ± 6.67 | 46.47 ± 7.09 | -0.047 | 0.043 | S |
| | Range | 34-58 | 34-58 | | | |
| Morphology (normal forms)% | Mean ± SD | 23.41 ± 17.64 | 30.55 ± 12.98 | -7.035 | 0.000 | HS |
| | Range | 1-55 | 2-60 | | | |
| Rbcs | Mean ± SD | 1.07 ± 0.78 | 1.06 ± 0.76 | 0.107 | 0.915 | NS |
| | Range | 0-2 | 0-2 | | | |
| Pus cell | Mean ± SD | 1.20 ± 0.99 | 1.07 ± 0.76 | 0.935 | 0.352 | NS |
| | Range | 0-6 | 0-2 | | | |

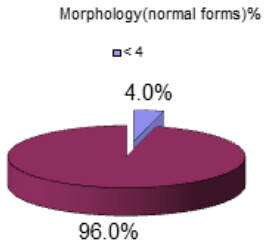


**Figure 4.** Spreading of the studied cases according to morphology (normal forms).

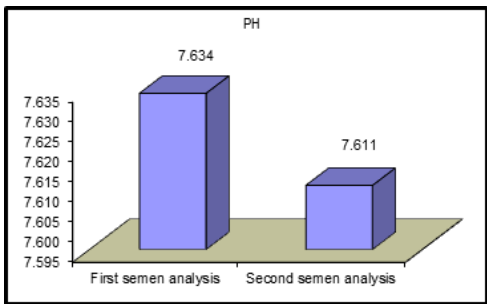


**Figure 5.** PH first semen analysis and second semen analysis.

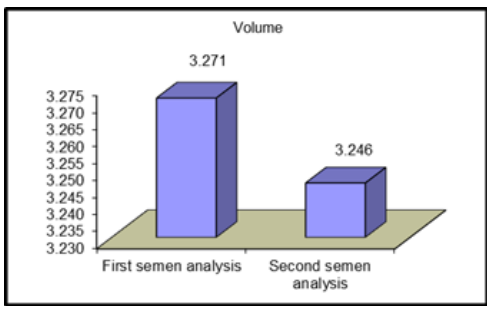


**Figure 6.** Volume first semen analysis and second semen analysis.

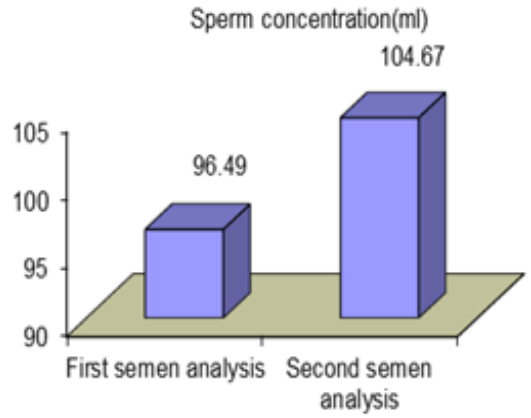


**Figure 7.** Sperm concentration (ml) first semen analysis and second semen analysis.

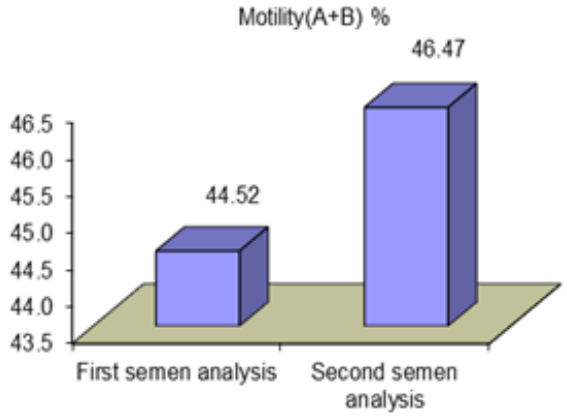


**Figure 8.** Motility (A+B)% first semen analysis and Second semen analysis.

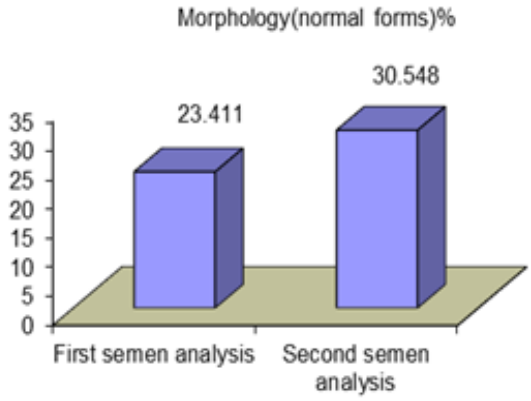


**Figure 9.** Morphology (normal forms)% first semen analysis and second semen analysis.

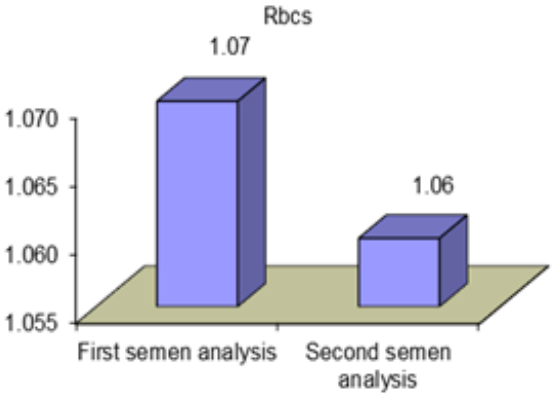


**Figure 10.** Rbcs first semen analysis and second semen analysis.

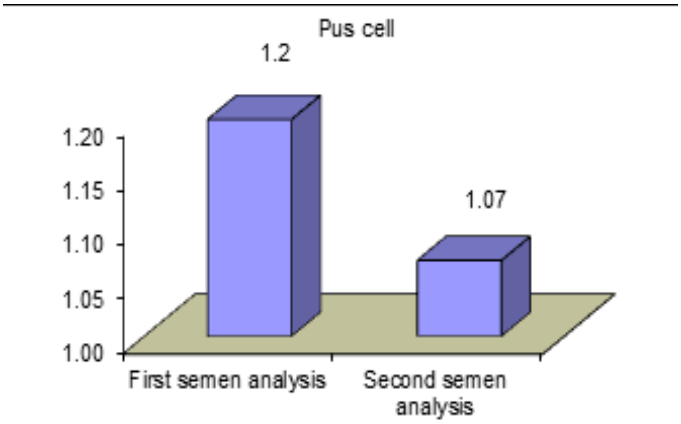


**Figure 11.** Pus cell First semen analysis and second semen analysis.

## Discussion

A total number 100 patients with mean (Age 24.6, BMI 25.97), with no comorbidity with criteria mentioned before. First sample show 2% of patients oligospermia, 36% of patients teratospermia. The second sample show 4% of patients teratospermia by comparing the two samples there is a significant increase in sperm concentration with mean concentration in the first sample 96.49 m/ml, mean concentration in the second sample 104.67 m/ml, a significant increase in motility (A+B) with mean percentage of 44% in the first sample and 46% in the second sample, a highly significant increase in the normal forms of sperms with mean percentage of 23.4% in the first sample and 30.55% in the second sample.

## Conclusion

A total number 100 patients with mean (Age 24.6, BMI 25.97), with no comorbidity with criteria mentioned before. First sample show 2% of patients oligospermia, 36% of patients teratospermia. Covid-19 affect spermatogenesis in the form of reversible teratospermia, reversable decrease sperm count but within normal level, reversable decrease in the sperm motility but also within normal level.

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**How to cite this article:** Rahman, Mostafa Kamel Abdel, Ahmed Abdel Moniem, Mohammed Zarzour, Adel Kurkar and Hosny Behnsawy. "The Effect of COVID-19 on Spermatogenesis" *Virol Curr Res* 5 (2021): 131.