The effect of COVID-19 on spermatogenesis

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Abstract

Background : The viral pandemic of the coronavirus disease 2019 (COVID-19) has become a serious worldwide public health emergency, evolving exponentially. While the main organ targeted in this disease is the lungs, other vital organs may be implicated. 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 involved 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 +ve. As the SARS-CoV-2 may have the potential to infect the testis via ACE2 and adversely affect male reproductive system. From this point the purpose of this study is how covid-19 affect spermatogenesis.

methods: Aim: how covid-19 affect spermatogenesis. Design and setting of the study: a100 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 million /ml , mean concentration in the second sample 104.67 million /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.

1. Background

The viral pandemic of the coronavirus disease 2019 (COVID-19), generated by a novel mutated severe acute respiratory syndrome coronavirus (SARS-CoV-2), has become a serious worldwide public health emergency, evolving exponentially. While the main organ targeted in this disease is the lungs, other vital organs, such as the heart and kidney, may be implicated. 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 involved in testicular male regulation of steroidogenesis and spermatogenesis. As the SARS-CoV-2 may have the potential to infect the testis via ACE2 and adversely affect male reproductive system.

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, we have no idea whether the actual virus was viable and infectious. Nevertheless, the possibility that this coronavirus could have a pathophysiological impact on the testes was suggested by additional data indicating that active COVID-19 infection dramatically reduced the testosterone-to-LH ratio, suggesting a significant impact on the responsiveness of Leydig cells to LH stimulation

In many ways, we should not be surprised by these observations because the blood-testes barrier is known to offer little defense against viral invasion, given the wide range of pathogenic viruses (HIV, hepatitis, mumps, papilloma) that are known to be capable of damaging the testes and rendering the host infertile.

The angiotensin system plays a critical role in the survival and functionality of human spermatozoa but also creates a vulnerability to COVID-19 attack. Angiotensin 1 is a biologically inactive decapeptide that is cleaved by ACE1 to create angiotensin II, which in turn activates the AT1R and AG2R receptors, both of which are present in these cells. Angiotensin II is further processed by ACE2 to generate angiotensin 1-7 which binds the MAS receptor activating PI3K. The latter then phosphorylates AKT, which maintains cell viability by phosphorylating key regulators of sperm apoptosis such as BAD. As long as BAD is phosphorylated, it is held in abeyance by a 14-3-3 keeper protein. However, if the PI3/AKT pathway becomes compromised, BAD dephosphorylates, is released from its association with 14-3-3, and moves to the mitochondria where it inactivates anti-apoptotic factors and promotes the intrinsic apoptotic cascade. The spike protein on COVID-19 specifically targets ACE2 and in so doing removes an important stimulus for PI3K/AKT, thereby compromising sperm viability. Subsequent to COVID-19 binding, the ectodomain of ACE2 may be removed by ADAM proteases and shed from the sperm surface. Alternatively proteases from the TMPRSS-family, either as intrinsic components of the sperm plasma membrane or delivered by seminal prostasomes, can facilitate fusion between the virus and the sperm surface 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.

An additional concern of the COVID-19 pandemic that might impact male fertility is fever. Particularly high and sustained elevation in body temperature is a major manifestation of the COVID-19 pandemic, which complicates more than 80% of patients. The concept that fever and elevation of testicular temperature result in impairment of spermatogenesis is widely accepted.

More importantly, emerging evidence indicates that a subgroup of patients with severe COVID-19 might have a secondary cytokine storm syndrome (hemophagocytic lymphohistiocytosis). This is an underrecognized, hyperinflammatory syndrome characterized by sustained fever, with fulminant and fatal hypercytokinemia with multiorgan failure. These patients have a particular serum blood cytokine profile

with cytopenia and hyperferritinemia. These findings also suggest that immunomodulatory therapy (IL-6 antagonist) may improve mortality rate considerably in these patients.

As cytokines contribute to testicular function and maintenance of male reproductive health, and to the pathologies associated with their abnormal activity in this organ, COVID-19-induced changes in cytokines profile may have further implications to male fertility. In addition, immunomodulatory therapies may provoke potential long-term effects on male fertility and are a matter of concern. Furthermore, cytokine microenvironment deviations within the testis may have tumorigenic adverse effects on the cellular level, leading eventually to testicular cancer, a second long-term matter of concern figure(1) .

2. Methods

Aim of the study: Know the Effect of covid-19 on spermatogenesis

Type of the study: prospective clinical

Study subjects:

a. 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

b Exclusion criteria:

- congenital anomalies of the testis
- chronically ill patients
- problems of male fertility
- males with varicocele
- sexual performance disorders.

c. Sample Size Calculation:

All cases that fulfill the selection criteria (non probability sample size) with expected size of 100 patients starting from 01/04/2020 to 28/12/2021.

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 : a100 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). 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

Research outcome measures:

- changes of semen parameter after 72days 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

3. Results

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 $\pm$ SD	24.61 $\pm$ 3.34
	Range	21 - 35
Length	Mean $\pm$ SD	1.71 $\pm$ 0.06
	Range	1.5 - 1.78
Weight	Mean $\pm$ SD	75.42 $\pm$ 10.41
	Range	55 - 99
BMI	Mean $\pm$ SD	25.97 $\pm$ 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 $\pm$ SD Range	7.63 $\pm$ 0.26 7 - 8
Volume	Mean $\pm$ SD Range > 1.5	3.27 $\pm$ 0.75 2 - 4.6 100 (100.0%)
Sperm concentration(ml)	Mean $\pm$ SD Range < 15 > 15	96.49 $\pm$ 35.87 12 - 154 2 (2.0%) 98 (98.0%)
Motility(A+B) %	Mean $\pm$ SD Range > 32	44.52 $\pm$ 6.67 34 - 58 100 (100.0%)
Morphology(normal forms)%	Mean $\pm$ SD Range < 4 > 4	23.41 $\pm$ 17.64 1 - 55 36 (36.0%) 64 (64.0%)
Rbcs	Mean $\pm$ SD Range	1.07 $\pm$ 0.78 0 - 2
Pus cell	Mean $\pm$ SD Range	1.20 $\pm$ 0.99 0 - 6

Table (3): Distribution 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 $\pm$ SD Range	7.61 $\pm$ 0.26 7 - 8
Volume	Mean $\pm$ SD Range > 1.5	3.25 $\pm$ 0.76 2 - 4.6 100 (100.0%)
Sperm concentration(ml)	Mean $\pm$ SD Range < 15 > 15	104.67 $\pm$ 33.80 15 - 154 0 (0.0%) 100 (100.0%)
Motility(A+B) %	Mean $\pm$ SD Range > 32	46.47 $\pm$ 7.09 34 - 58 100 (100.0%)
Morphology(normal forms)%	Mean $\pm$ SD Range < 4 > 4	30.55 $\pm$ 12.98 2 - 60 4 (4.0%) 96 (96.0%)
Rbcs	Mean $\pm$ SD Range	1.06 $\pm$ 0.76 0 - 2
Pus cell	Mean $\pm$ SD Range	1.07 $\pm$ 0.76 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 $\pm$ SD	7.63 $\pm$ 0.26	7.61 $\pm$ 0.26	0.554	0.581	NS
	Range	7 - 8	7 - 8			
Volume	Mean $\pm$ SD	3.27 $\pm$ 0.75	3.25 $\pm$ 0.76	0.237	0.813	NS
	Range	2 - 4.6	2 - 4.6			
Sperm concentration(ml)	Mean $\pm$ SD	96.49 $\pm$ 35.87	104.67 $\pm$ 33.80	-1.871	0.054	S
	Range	12 - 154	15 - 154			
Motility(A+B) %	Mean $\pm$ SD	44.52 $\pm$ 6.67	46.47 $\pm$ 7.09	-0.047	0.043	S
	Range	34 - 58	34 - 58			
Morphology(normal forms)%	Mean $\pm$ SD	23.41 $\pm$ 17.64	30.55 $\pm$ 12.98	-7.035	0.000	HS
	Range	1 - 55	2 - 60			
Rbcs	Mean $\pm$ SD	1.07 $\pm$ 0.78	1.06 $\pm$ 0.76	0.107	0.915	NS
	Range	0 - 2	0 - 2			
Pus cell	Mean $\pm$ SD	1.20 $\pm$ 0.99	1.07 $\pm$ 0.76	0.935	0.352	NS
	Range	0 - 6	0 - 2			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value < 0.01: highly significant (HS)

***:Paired t-test**

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 non statistically significant difference found between First semen analysis and Second semen analysis Regarding PH , Volume , Rbcs and Pus cell.

4. 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 million /ml , mean concentration in the second sample 104.67 million /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. Table (1,2,3,4) . figure (2,3,4,5,6,7,8,9,10,11)

5. Conclusion

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 .

Declarations

Ethics approval and consent to participate:

Informed written consent to participate in the study was provided by all participants. This study approved by Institutional Review Board (IRB).

Consent for publication:

Not applicable .

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests :

The authors declare that they have no competing interests.

Funding:

No

Authors' contributions:

MKA contributed to creation of new software used in the work. AMA contributed to design of the work. HMAB contributed to analysis and interpretation of data. MKA drafted the work and substantively revised

it. All authors have read and approved the manuscript.

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Informed written consent to participate in the study was provided by all participants. This study approved by Assiut University ethics committee - Institutional Review Board (IRB).

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Figures

Figure 1

cytokine microenvironment deviations within the testis may have tumorigenic adverse effects on the cellular level, leading eventually to testicular cancer, a second long-term matter of concern.

Figure 2

Distribution of the studied cases according to Sperm concentration(ml)

Figure 3

Distribution of the studied cases according to Morphology(normal forms)%

Figure 4

Distribution 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