

The relationship between covid-19 disease and male infertility

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Introduction

- In December 2019, cluster of a novel type of pneumonia were reported in Wuhan city, China
- Defined by WHO as a coronavirus disease 2019 (Covid-19) in February 2020
- The severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) was identified as the causing viral pathogen
- It has been declared a pandemic by WHO on 11th March 2020

- SARS-COV-2 Virus is most closely related to SARS-COV(2002) however the infection with covid-19 is much more contagious and has already infected a much higher proportion of people worldwide
- Mortality recorded with covid-19 is lesser to SARS
- Covid-19 is affecting more males than females, which contrasts with the SARS
- SARS-COV-2 may persist in humans for a much longer duration than SARS-COV, Projected that a recurrence of SARS-COV-2

- Although the testes are immunologically privileged in case of viremia, some viruses can cross the BTB, causing local inflammation.
- To date, our knowledge of the male reproductive system indicates its fragility, and there is substantial recorded evidence that the male reproductive system is vulnerable to viral infections
- Viruses like MUMPS, ZIKA, Hepatitis B virus (HBV), Hepatitis C, virus (HCV), HIV, HPV, Herpes, EBOLA, and several others have been shown to exert varying impacts on male reproductive health
- A few prominent examples of the adverse impact of these virus includes: disarrayed spermatogenesis, reduction in Sperm count, impacting sperm motility altered hormonal levels

- How do viruses create these impacts and how do they gain access to the male reproductive tract (MRT)?
 - ✓ Direct virus invasion to MRT cells (It is suggested that direct virus access is not required to damage the male reproductive system)
 - ✓ BTB damage (Persistent high body temperature as such during viral infections may tamper with the blood-testis barrier (BTB) even mild scrotal heat stress could lead to the BTB leakage and allowing the passage for macromolecular substances to testis)
 - ✓ Increase reacting oxygen species (ROS) level
 - ✓ Increase apoptosis of germinal cells
 - ✓ Injuries due to activation of immune response

- It is known that the coronavirus is predominantly transmitted through respiratory droplets
- Attention has rightly focused on the respiratory system, because this is a life-and-death battle

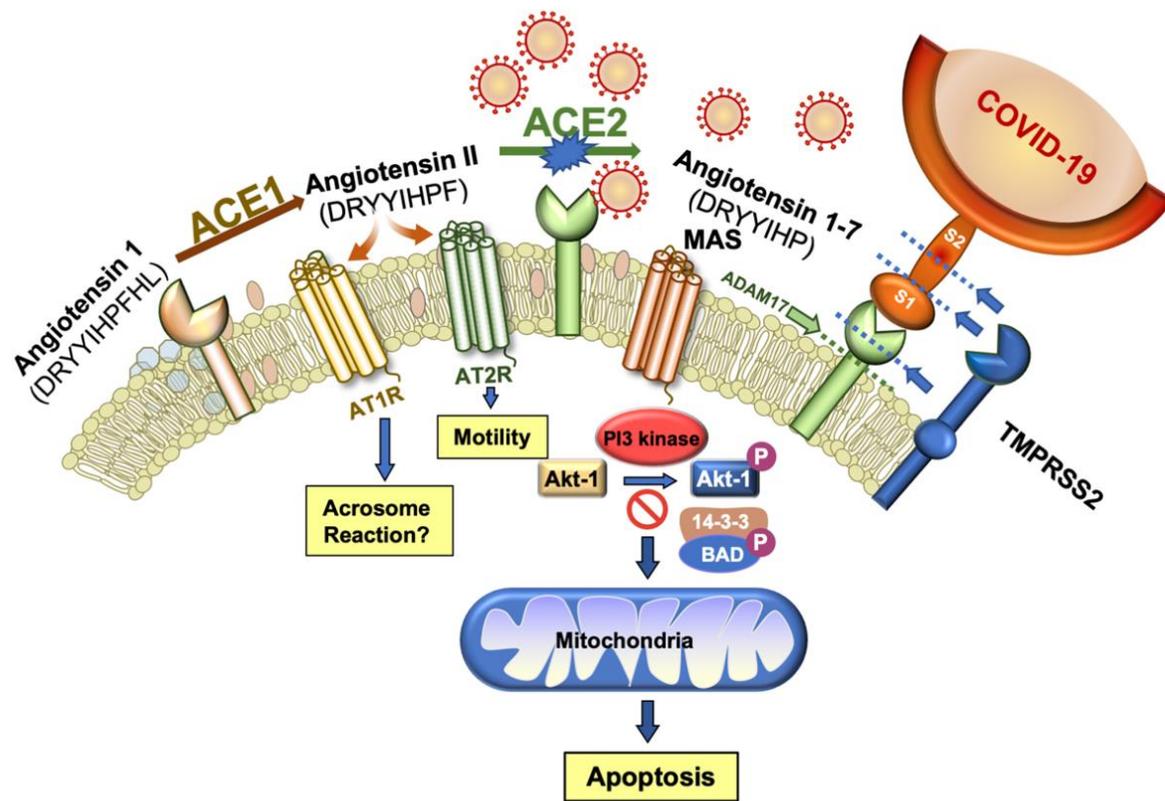
- Why do we think about involvement of MRT by covid19?
 - ✓ The clinical characteristics of covid-19 are quite similar to SARS
 - ✓ Noticeable impacts of COVID-19 on non-respiratory systems such as cardiovascular, gastrointestinal and neurologic systems. Does this pandemic spare the male reproductive system?
 - ✓ Covid-19 RNA has been detected in various biological samples, such as feces, urine and blood.
 - ✓ Our knowledge of the MRT about other viruses like MUMPS, ZIKA, HBV, HCV, HIV, HPV, HSV, EBOLA and several others that have been shown to exert varying impacts on male reproductive health.

Then potential for infection of MRT by SARS-COV-2 cannot be ruled out

The role of ACE in pathogenesis of Covid-19

- SARS-COV-2 seems to have high affinity binding capability to the angiotensin-converting enzyme2 (ACE2) in human cells which is expressed in multiple organ system including tests
- ACE2 as the cellular receptor for SARS-COV-2 maybe the mechanism for access to the MRT
- Angiotensin converting enzyme 2 (ACE2) is a functional receptor on alveolar epithelial type 2 (AT2) cells and an entry point for the SARS-CoV-2.
- The spikes of SARS-CoV-2 (S-protein) have strong affinity for the ACE2 receptor, and after attachment, the viral genome and nucleocapsid are liberated into the host cell cytoplasm.

- SARS-CoV-2 needs TMPRSS2 (transmembrane, serin protease-2) to cleave the viral S-protein, and enable fusion between the viral and host cellular membrane.
- The co-expression of both ACE2 and TMPRSS2 genes is necessary for infection to occur, since SARS-CoV-2 uses the ACE2 receptor for entry and the serine protease TMPRSS2 for S protein priming.
- ACE2 expression is found in the heart (7.5% of myocardial cells), ileum (30%), kidney (4%), bladder (2.4%) and in the respiratory tract (~ 2%).
- All tissues that have more than 1% expression of ACE2 receptors could be a target for the SARS CoV-2.



- ACE2 is abundantly expressed in testes, including spermatogonia, Leydig, and Sertoli cells. Further, it is also hypothesized that the attachment of SARS-COV-2 to the ACE2 receptor might in turn increase the expression of ACE2 and initiate an inflammatory response that could interfere with the normal functions of Sertoli and Leydig cells.

- In the male, testicular ACE2 may regulate testicular function, plays a role in sperm function, and may be important for sperm's contribution to embryo quality.
- ACE2 receptors are much more abundant in the male reproductive system than the female reproductive system.
- ACE2 expression in the testis is among the highest observed, with high expression in Leydig and Sertoli cells and medium expression in glandular cells of the seminal vesicle. As a result, it is expected that the testes will be more vulnerable than the ovaries to the detrimental effects of a SARS-CoV-2 infection.

COVID-19 and gonadal pathology

- Although no evidence for the virus was found in the testes in the majority (90%) of the cases by RT-PCR but these patterns are reported in several studies:
 - ✓ Presents of interstitial edema and congestion both in testis and epididymis (Orchitis, epididymitis)
 - ✓ Thinning of seminiferous epithelium (decrease cell layers)
 - ✓ Increased proportion of apoptotic testicular cells (determined using the TUNEL assay)

- ✓ Impaired spermatogenesis
- ✓ Injury to Sertoli cells and seminiferous tubules
- ✓ Significant reduction of Leydig cells
- ✓ Mild inflammatory infiltrates in the interstitium
- ✓ microthrombi

Immunological mediators

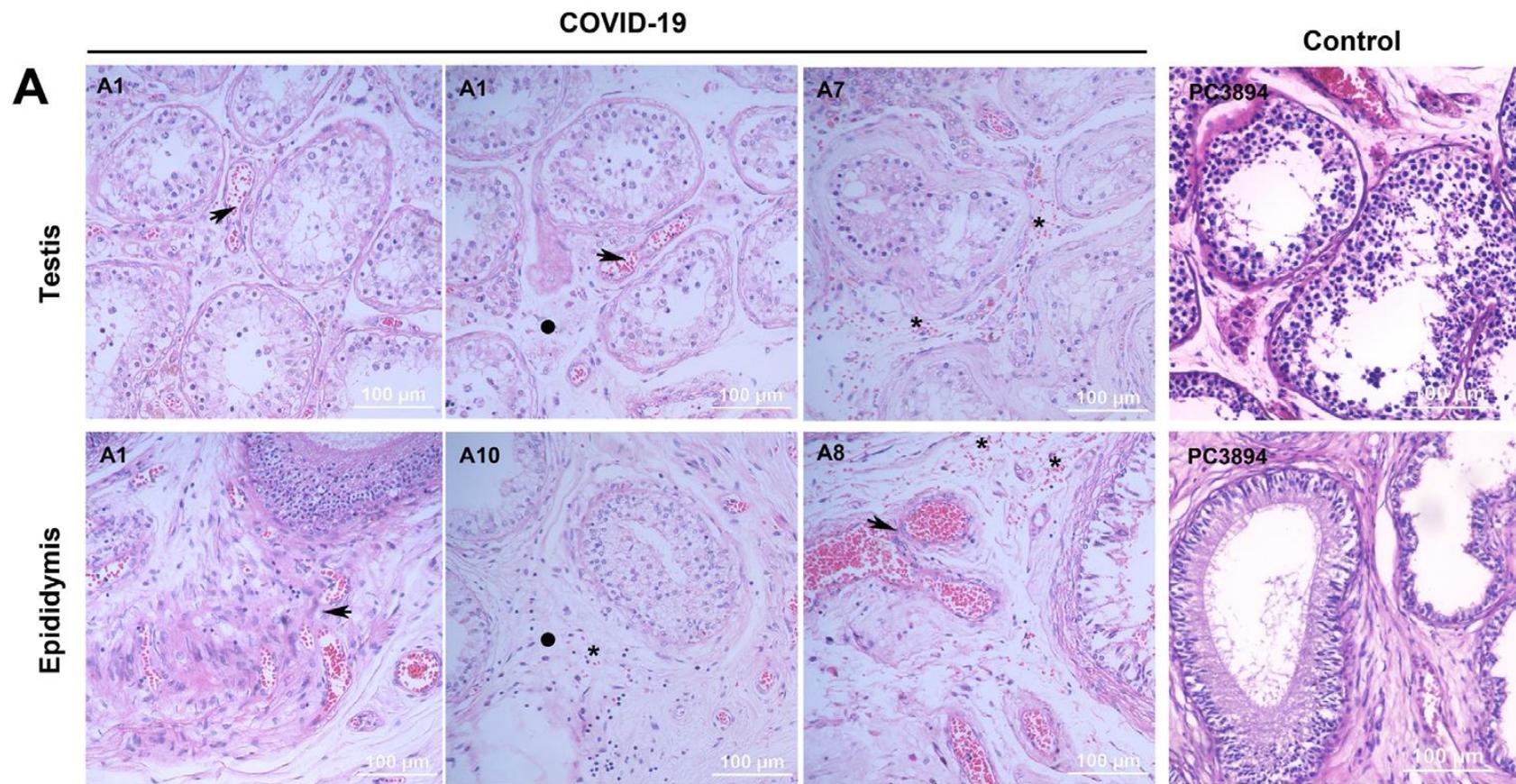
- Observation of T-lymphocyte (CD3+) and macrophage (CD68+) infiltration in testicular tissues showed an increased concentration of T-lymphocyte and macrophage in the interstitium of testicular tissue of the COVID-19 patients compared to control patients testes.
- Obvious infiltration of T-lymphocytes around the blood vessels of the testes and epididymis tissue and noticed occasional Tlymphocytes presence around the epididymal duct of the COVID-19 patients.
- Increase of seminal IL-6, TNF-a, and MCP-1 levels were observed in COVID-19 patients

COVID-19 effect on reproductive hormones

- A higher serum luteinizing hormone (LH) and a lower ratio of T to LH are observed in the COVID-19 patients.
- Worsening of clinical status is coupled with a progressive reduction in T levels and increase in LH levels
- Suggesting a significant impact on the responsiveness of Leydig cells to LH stimulation.

COVID-19 and semen parameters

- Aspects of the viral illness, such as fever, inflammation, and dysregulation of HPG axis, may also impair testosterone secretion and sperm production. Increased oxidative stress, as may be caused by COVID-19, could reduce sperm motility and increase sperm DNA fragmentation.
- The preliminary data suggest that mild disease does not appear to have a negative effect on spermatogenesis.
- Patients with moderate to severe disease have impairment of semen volume, low sperm concentration and motility with higher sperm DFI; they may also have poor sperm morphology.
- An increase in seminal leucocytes of more than $1 \times 10^6/\text{ml}$, which is the recommended criteria of WHO for leucocytospermia



Sexual transmission of COVID-19

- Should sexual contact be a matter of concern in the case of COVID-19?
 - ✓ Some may claim it is unnecessary to investigate
- However other researchers believe that it is important because:
 - ✓ Delayed outbreaks risk
 - ✓ Infertile patients under going ART

- The results of studies about sexual transmission in men are conflicting most of these studies show that the semen and testis specimen are negative for SARS-COV-2 RNA
- Only one study demonstrate that SARS-COV-2 can be present and detected in semen samples of covid-19 patients.
- However, there is still no definitive data to prove that spermatozoa serve as vectors for transmission of COVID-19

Vaccination

- There is no evidence that covid-19 vaccine can affect the fertility of couples
- It is recommended that people of reproductive age are advised to have the vaccine when they receive their invitation for vaccination these include those who are trying to have baby as well as those who are thinking about having a baby.
- It's suggested that ART procedures and fertility treatments should not be delayed due to the covid-19 pandemic but to consider immunizing infertile couples with vaccination before ART/IVF.
- Some people may get bothersome side effects in few days after vaccination, in men and women who receive the vaccine it seems prudent to postpone assisted ART for at least a few days after