The relationship between covid-19 disease and male infertility

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
- 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

- 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 it’s 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 :disarrayed spermatogenesis, reduction is 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)

✓ Increase reacting oxygen species (ROS) level

✓ Increase apoptosis of germinal cells

✓ Injuries due to activation of immune response

Why do we think about involvement of MRT by covid19?

✓Noticeable impacts of COVID-19 on non-respiratory systems such as cardiovascular, gastrointestinal and neurologic systems

✓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
- 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 increases 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.
- 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

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

Immunological mediators

- Observation of T-lymphocyte (CD3+) and macrophage (CD68+) infiltration in testicular tissues of the COVID-19 patients compared to control patients testes.

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

- Dysregulation of HPG axis, may also impair testosterone secretion and sperm production.
- Increased oxidative stress 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 increased in leucocytospermia

Vaccination

- There is no evidence that covid-19 vaccine can affect the fertility of couples

- It’s suggested that ART (Assisted Reproductive Technology) 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.