Chapter 63
What is the impact of COVID-19 and vaccines for COVID-19 on sexual and reproductive health?

R. John Aitken

In 2019 the world was gripped by a COVID pandemic that has, to date, infected 500 million individuals and taken over six million lives. This virus is generally thought to target the lungs, kidney and heart, although there is growing evidence that it can also invade the reproductive system, particularly in the male. As a result, there is increasing concern over whether this virus can have a detrimental impact on the male reproductive function, whether such an attack can seriously impact semen quality and/or the biogenesis of androgens, whether such impacts induce transient infertility or sterility, and whether vaccination might be a help or a hindrance in managing the reproductive impacts of this disease. This article summarises the data currently available on this topic and provides a snapshot of our current understanding of how COVID-19 infection influences male fertility.

COVID-19 infection of the male reproductive tract

Initial awareness of the male reproductive system's vulnerability to COVID-19 attack was predicated upon proteomic analyses indicating that the male germ line contains the entire repertoire of proteins needed to facilitate the binding and incorporation of viral particles. Thus, the viral spike glycoprotein (S) that gives this corona virus its name, has a particular affinity for ACE2 (angiotensin-converting enzyme 2), which is highly expressed on the surface of several cell types in the testes including Leydig cells, Sertoli cells, macrophages and the germ line. The presence of ACE2 on the surface of human spermatozoa is thought to be responsible for the generation of angiotensin 1-7 at the cell surface (Fig. 1). This endocrine product of ACE2 processing, is potentially important to spermatozoa because it binds to the MAS receptor, thereby activating phosphoinositide 3-

kinase (PI3K) which in turn phosphorylates a number of proteins that are essential for sperm survival, preventing these cells from defaulting to an apoptotic fate (Fig. 1). A COVID-19 attack on ACE2 is therefore predicted to result in proteolytic cleavage of this enzyme, leading to a loss of PI3 kinase activity and a consequential impairment of sperm viability and function (Fig. 1). Furthermore, since both Leydig- and Sertoli- cells are also known to express the ACE2/angiotensin 1-7/MAS receptor/ PI3 kinase pathway, any impact of COVID-19 infection on these cells could involve the induction of apoptosis/loss of function via similar mechanisms.

Actual fusion between the virus and a target cell requires the presence of the protease, TMPRSS2, to cleave the viral spike protein (S) at the S1/S2 boundary or within S2 subunit, thereby removing the structural constraint of S1 on S2, and releasing the internal membrane fusion peptide (Fig. 1). TMPRSS2 protein is abundantly expressed in the prostate, but can also be found in the epididymis, Leydig cells, spermatids and spermatogonia. This protease is also known to be present in seminal prostasomes that transfer their contents, including proteins, to the spermatozoa following ejaculation. Via this mechanism the incorporation of TMPRSS2 into the sperm plasma membrane has been proposed. Furthermore, a close examination of the sperm proteome reveals the presence of related proteases, TMPRSS11B and TMPRSS12 as well as FURIN in these cells, all of which have the potential to facilitate viral entry. The presence of these activating proteases as well as ACE2 in the sperm plasma membrane would be expected to allow the COVID-19 virus to bind to the cell surface and ultimately fuse, either in the testes or during the prolonged sojourn of these cells in the epididymis. On this basis it has been argued that spermatozoa would well act as a vector for COVID-19 infection making this, potentially, a sexually transmitted disease. Notwithstanding such theoretical considerations, at present, there is no convincing evidence to demonstrate that this is the case. COVID-19 infection seems to be spread primarily via an airborne means of dissemination. However, given the publication of occasional reports describing the presence of viral RNA in human semen, we cannot completely exclude the possibility that when viral loads are extremely high, then sexual transmission of COVID-19 might occur.

Whether or not the virus can infiltrate human semen and remain active, the testes can certainly become heavily infected with this virus and is even thought to be a sanctuary for COVID-19 replication.

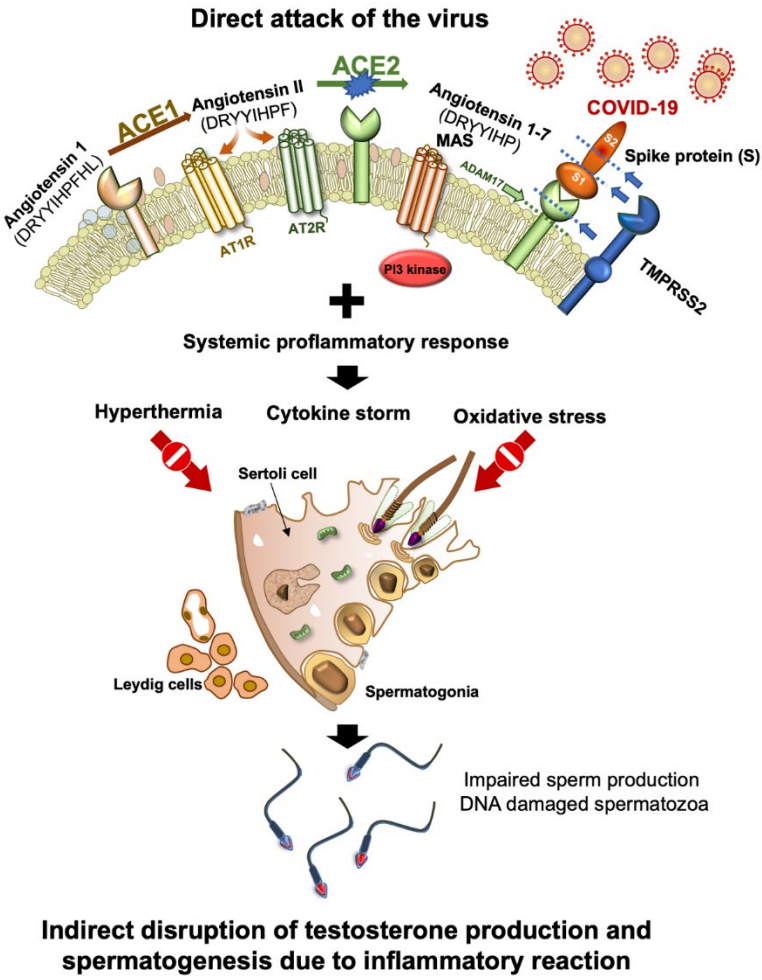

Figure 1. Mechanisms by which COVID-19 can impact male fertility. Several key cell types within the reproductive system (Sertoli cells, germ cells, Leydig cells, epididymal epithelia, prostate gland epithelia) are vulnerable to viral attack because they express ACE2, which is targeted by the viral spike glycoprotein (S). Disruption of ACE2 will lead to a local loss of angiotensin 1-7, which is a key ligand for the MAS receptor which drives PI3 kinase activity. In the case of spermatozoa, a loss of PI3 kinase activity will cause these cells to default to the intrinsic apoptotic pathway. The presence of the viral fusion transmembrane protease, serine 2 (TMPRSS2) protease on the surface of

reproductive cells allows COVID-19 to enter the cell and initiate viral replication. Within the testes, both spermatogonia and macrophages appear to be major viral factories supporting high levels of replication and acting as a reservoir ensuring the prolonged supply of active virions. In addition to the direct impact of viral infection on reproductive function, COVID-19 also induces a pro-inflammatory state characterized by a cytokine storm accompanied by high levels of oxidative stress and hyperthermia. These conditions actively suppress spermatogenesis and disrupt testosterone production by the Leydig cells. This combination of direct and indirect actions on the part of COVID-19 has a devastating effect on male reproductive function, which generally abate once the infection resolves.

Thus, there is recent evidence to indicate that the virus gains access to both testicular macrophages and spermatogenic cells and can actively replicate at these sites forming an intratesticular repository of active virus, which may prolong the impact of COVID-19 infection on male reproductive function. Furthermore, the inward migration of infected macrophages from distant sites such as the lung may represent one of the key mechanisms by which COVID-19 infection is delivered to the testes - acting as Trojan horses and exploiting the capacity of this organ for immune tolerance.

The pro-inflammatory state and male reproduction

In addition to the direct effects of the virus on the male reproductive tract, it is also probable that male fertility is impacted by the cytokine storm that accompanies infection by COVID-19. The latter triggers a hyperactive immune response associated with the release of key cytokines (for example, IL-1β, IL-6, IL-8, IL-10, TGF-β, TNF-α, IFN-αand IFN-γ) that, in turn, generate a proinflammatory state. Several of these cytokines (for example IL-10, IL-6, IFN-γ, and TNF-α) are known to signal the development of inflammatory conditions that are harmful to semen quality and male fertility. Furthermore, certain cytokines, such as TNF-α, can have a direct impact on the functionality of human spermatozoa. In addition, the induction of an inflammatory state is associated with an increase in testicular temperature and the associated induction of oxidative stress. The deleterious impact of such stress on testicular function reflects the vulnerability of Leydig- and germ- cells to both lipid peroxidation and the induction of oxidative DNA damage. Furthermore, oxidative stress is known to have a negative influence on the integrity of the

blood testes barrier, which will only serve to reinforce COVID-19's disruptive effect on spermatogenesis.

Observed clinical impacts on male reproduction

When infection does occur, it seems to result in the rapid impairment of sperm quality decreasing sperm number and motility in the ejaculate and increasing the incidence of morphological abnormalities in these cells. In addition, COVID-19 infection has been found to induce profound changes in overall testicular architecture and function including thickening of the tunica propria, germ cell apoptosis, Sertoli cell barrier loss, haemorrhage, angiogenesis, Leydig cell inhibition, inflammation, and fibrosis. Even a relatively mild infection that does not require hospitalization, has been linked with the rapid induction of azoospermia (complete absence of spermatozoa in the ejaculate) in longitudinal studies on single individuals monitored before, during and after COVID-19 infection. In addition, COVID-19 infection may result in reduced testosterone levels in infected males, accompanied by increases in pituitary gonadotrophin (LH and FSH) output. These observations are consistent with the direct suppression of Leydig cell function rather than an indirect action mediated by changes to the hypothalamic-pituitary axis. Happily, such impacts on sperm production and function, as well as testosterone biosynthesis, seem to be readily reversible, with several studies documenting a return to normality within a matter of weeks. Notwithstanding such observations, there are also clear inter-individual differences in the rate at which normal reproductive function returns, that will have to be carefully monitored in future studies. Furthermore, long term impacts on male fertility associated with sperm DNA damage and/or the generation of anti-sperm antibodies cannot be excluded at this stage.

Relative importance of viral infection and oxidative stress

Present data suggest that the negative impact of COVID-19 infection on male reproductive function involves a combination of direct cellular damage induced by the virus and indirect damage mediated by the accompanying inflammatory reaction and oxidative stress. The apparent capacity of the virus to rapidly induce complete azoospermia may reflect its ability to replicate within spermatogonia, leading to high

levels of germ cell apoptosis and the cessation of sperm production. The suppression of spermatogenesis may also involve a direct viral attack on Leydig- and/or Sertoli- cells, both of which have been found to harbour viral particles following infection.

Indirect mechanisms are also important in determining the reproductive response to COVID-19 infection. It is well known that a range of viral infections that do not directly target the germ line (e.g. mumps or HIV) can have a disruptive impact on male reproduction as a consequence of inflammation and the resulting induction of oxidative stress and hyperthermia in the testes. The oxidative stress associated with COVID-19-induced inflammation induces significant oxidative DNA damage and lipid peroxidation in spermatozoa, that appears to persist, even when normal semen parameters have been restored. The oxidative stress associated with COVID-19 infection has also been found to reduce testicular glutathione levels and precipitate a concomitant increase in ROS generation and apoptosis in the male germ line. Interestingly, treatment with antioxidants such as N-acetyl cysteine has been shown to significantly improve semen quality in COVID-19 patients. In light of these data, a systematic, case-controlled analysis of the protective impact of antioxidant therapy during and after COVID-19 infection is certainly warranted.

Impact of anti-COVID vaccines

Several studies have examined the impact of anti- COVID-19 vaccination on semen quality and all are unanimous in finding no discernible impact on spermatogenesis or testosterone production. In addition, the fertilizing potential of spermatozoa following vaccination was found to be unimpaired.

Conclusions

The COVID-19 virus impacts male fertility via two major mechanisms : (i) direct interaction of the virus with ACE2 on the surface of key reproductive cell types including Sertoli cells, Leydig cells and the germ line, and (ii) the generation of a cytokine storm and the subsequent appearance of a proinflammatory state associated with raised testicular temperature and clear evidence of oxidative stress. In a vast majority of patients, the impact of the virus on semen quality and testosterone output is sudden, and occasionally severe, but generally reversible within a few weeks.

However, the persistence of oxidative DNA damage in the germ line and the occasional presence of anti-sperm antibodies may have long term implications for the fertility of a small minority of patients. There is limited evidence to suggest that antioxidant therapy might be beneficial in counteracting the impact of the virus on male fertility although additional studies will be required to confirm the therapeutic benefit provided by such therapy and to refine the precise nature of the antioxidants to be used in this context. There is also consistent evidence to indicate that COVID-19 vaccines have no impact on male fertility per se. Indeed, by controlling the onset of severe febrile disease, vaccination should do nothing but support male reproductive health in the face of this pernicious virus.

Suggested reading

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