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LETTER TO THE EDITOR

COVID-19 and male infertility: An update

To the Editor:

Last year *Andrology* published an Opinion Article raising the possibility that COVID-19 virions might interact with human spermatozoa and disrupt male fertility.[1] This prediction was based upon a proteomic analysis of these cells, indicating that they possess the entire repertoire of receptors needed to support angiotensin signaling, including ACE2—the cellular entry point for coronavirus infection. Because the angiotensin system is known to play such an important role in the maintenance of sperm viability and function, it was proposed that contact with the virus would have adverse reproductive consequences for infected males.[1] It was also speculated that infection would lead to a series of detrimental changes in the male tract associated with the creation of significant oxidative stress. These changes include (i) the generation of reactive oxygen species (ROS) by the sperm mitochondria as these cells engage the intrinsic apoptotic pathway[2]; (ii) an increase in local ROS generation as a result of sperm phagocytosis by leukocytes responding to elevated levels of angiotensin II[3]; and (iii) oxidative stress created by the proinflammatory cytokine storm that accompanies COVID-19 infection.[4] The suggested involvement of oxidative stress in mediating the impact of COVID-19 on male reproductive competence has led Marin et al.[5] to advocate the potential benefits of antioxidant (astaxanthin) treatment in the accompanying Letter to the Editor. Now that we have been living with this virus for around 2 years, it may be good time to review the information that has come to light, to determine whether any evidence has emerged to support the proposed impacts of COVID-19 on sperm vitality and function, and whether oxidative stress is indeed a key contributor to any of the changes observed.

At this point in our journey, it seems incontrovertible that the virus can gain access to the testes[6] possibly because the inflammatory response triggered by the virus disrupts the blood–testes barrier. Furthermore, persistence of the virus in this tissue may also be facilitated by testicular immune privilege and the local availability of regulatory T cells.[7] The presence of live virus in human semen samples is far less certain. A majority of studies have failed to detect COVID-19 in human semen,[8,9] although sporadic positive reports[10] indicate that this does occasionally happen. These observations therefore leave open the door to sexual transmission,[11] even if this is a relatively rare event.

While the virus may be an infrequent and uncertain constituent of human semen, there is much more certainty concerning the impact of viral infection on semen quality and endocrine status. For example, Ma et al.[12] observed a clear increase in circulating LH levels and a reduced testosterone:LH ratio in COVID-19 patients, suggesting a negative impact on Leydig cell function. Koç and Keseroğlu[13] confirmed a reduction in circulating testosterone levels post infection, while Cinislioglu et al.[14] demonstrated that this decline was related to the severity of the disease, as might be anticipated. In terms of semen quality, the results are more variable. Some studies have detected a significant impact of COVID-19 infection on multiple aspects of semen quality including semen volume, percentage of total motility, percentage of progressive motility, and normal sperm morphology.[13] Other studies have recorded a more limited impact of COVID-19 infection. Thus, Temiz et al.[9] could only detect a deterioration of sperm morphology following infection, while Ruan et al. found that the criteria of semen quality remained within the WHO definitions of normality in COVID-recovered patients.[15] By contrast, Gacci et al.[16] concluded that 25% (11/43) of men recovering from COVID-19 infection exhibited a severe disruption of their semen profile, with a majority (8/11) being azoospermic, the degree of spermatogenic disruption being significantly correlated with disease severity. In another small study, Li et al. found that 39% (9/23) of recovering COVID patients were suffering from oligozoospermia, while their semen profile was frequently characterized by elevated levels of leukocytic infiltration.[17]

The limitations associated with most of these investigations are small sample size, inter-patient variation in the severity of COVID-19 infection, and inadequate study design. None of the major studies conducted in this area present pre-infection data as a reference point and, instead, rely on cross-sectional comparisons with uninfected controls. One of the few published longitudinal studies where semen profile data were available before and after COVID-19 infection was a case report from an IVF clinic in India.[18] In this example, the male partner was normozoospermic prior to COVID-19 infection but revealed a dramatic decline in sperm number, motility, morphology, and DNA integrity when tested 1 month after this disease took hold. Moreover, this patient had still not recovered to pre-COVID levels when his semen was examined 4 months post infection. Fortunately, the prolonged suppression of semen quality following infection does not seem to be a consistent feature of this disease state. Several studies have not only confirmed a significant impact of infection on all aspects of semen quality but have also reported a progressive return to normality following infection.[19,20] Again, much presumably depends on the severity of the disease and the extent to which spermatogenesis was impaired in the first instance.

To date, very little research has been conducted on the mechanisms underlying the observed impacts of COVID infection on semen quality. One of the most informative studies conducted thus far, confirmed the above-mentioned suppression of semen volume, progressive motility, morphology, sperm number, and DNA integrity as a result of COVID-19 infection.[20] Significantly, the reduction of semen quality as well as the increase in sperm DNA damage were correlated with markers of oxidative stress and inflammation.[20] These data, suggesting oxidative stress is a significant contributor to the compromised semen quality seen in patients following COVID-19 infection, have been supported in independent studies.[21] However a causative link between oxidative stress and the decline in semen quality observed following COVID-19 infection has yet to be formally demonstrated.

So, in summary, considerable progress has been made over the past 12 months in our understanding of the link between COVID-19 infection and male infertility. Although the data are still limited, sufficient information is available to draw some general conclusions and suggest future avenues of research. Immediately after infection, semen quality appears to be suppressed via mechanisms that appear to lower testosterone levels and disrupt all aspects of the semen profile (sperm count, motility, and morphology as well as leukocyte infiltration), the magnitude of the effect depending on the severity and duration of the disease.[22] It is also suggested that sperm DNA damage is a feature of the disease that may impact not only the fertility of affected patients but also the health and well-being of their offspring.[23] Importantly these effects on semen quality seem to subside with the passage of time, although further studies are needed to substantiate this point. Critically, at present we do not know whether any observed changes in semen quality reflect a direct impact of the virus on spermatogenesis and sperm function or whether this is an indirect reflection of the cytokine storm precipitated by the disease and the accompanying increase in oxidative stress.[23] Careful application of antioxidants in conjunction with oxidative stress biomarkers to monitor the latter's efficacy would be a rational approach to toward the resolution of this issue as suggested by Marin et al.[5]

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