



Does COVID-19 affect male fertility?

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Dear Editor,

Multiple cases of pneumonia caused by a novel corona virus (SARS-COV2) have been reported in Wuhan city in China in December 2019 [1]. Since then, the infection has spread world-wide, leading to acute respiratory distress syndrome (SARS) named as “COVID-19” by the World Health Organization (WHO) [1]. On 11/03/2020, the disease has been declared as a global pandemic by WHO [1]. Angiotensin converting enzymes 2 (ACE2) receptors play a key role in pathogenesis of COVID-19. Binding of SARS-COV2 virus to ACE2 receptors facilitate its cell entry and replication [2]. Therefore, cells that show high level of ACE2 expression have the potential to be targeted and damaged by the virus [2]. Multiple studies detected high ACE2 expression level in testicular cells, mainly in seminiferous duct cells, spermatogonia, Leydig cell and Sertoli cells [2–4]. Based on the results of these studies, it is concluded that the testis could be a potential target for direct damage by SARS-COV2 virus. Another study performed following the outbreak of SARS-COV infection in 2002 showed that orchitis was a recognised complication of SARS [5]. The main question is whether COVID-19 has the potential to cause testicular damage and infertility in male patients. So far there is no definitive answer as a follow-up of reproductive function of recovered male patients is required.

SARS-cov2 virus binds to ACE2 receptors and enter the cells to complete its replication cycle [2]. This is considered as the main pathological mechanism of direct cell infection and damage by the virus. Therefore, cells with increased ACE2 expression are potential target of viral invasion [2]. Among different body tissues, testis shows nearly the highest level of ACE2 mRNA and protein expression [2]. At

the level of testicular cells, four main cell types; seminiferous duct cells, spermatogonia, Leydig cells and Sertoli cells, show higher rate of ACE2 mRNA expression [2–4]. If the virus causes damage to these cells, the process of spermatogenesis could be affected which might pose risk to male fertility. Interestingly, the testicular expression of ACE2 is age related [4]. The highest expression recorded in patients aged 30, which is higher than those in their twenties, whereas 60-year-old patients show the lowest level of expression [4]. This might indicate that young male patients are at higher risk of testicular damage by COVID-19 than older patients. In one study, examination of autopsy specimen of testis of six patients who died due to SARS-Cov infection in 2002 showed an evidence of orchitis [5]. Histopathological examination revealed inflammatory infiltrates, mainly in seminiferous tubules [5]. Immunohistochemistry showed IgG deposition mainly in seminiferous epithelium, interstitium, degenerated germ cells and Sertoli cells [5]. These are almost the same cell types that show high ACE2 expression [2–4]. Interestingly, in-situ hybridization does not detect viral genomic materials in the testicular tissue specimens [5]. This indicates that testicular damage is due to inflammatory and immunological response rather than direct damage by the virus.

There is a theoretical possibility of testicular damage and subsequent infertility following COVID-19 infection. The possibility of testicular damage is caused by either direct viral invasion through binding of SARS-COV2 virus to ACE2 receptors or secondary to immunological and inflammatory response. Follow-up studies of reproductive function of recovered male patients is required to investigate this possibility.

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Compliance with ethical standards

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