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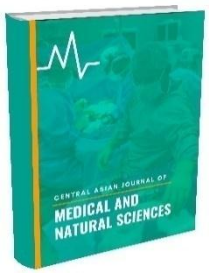

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Potential Impact of SARS-Cov-2 on the Male and Female Reproductive Systems

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Abstract: On 29 December 2019, four cases of pneumonia of unknown etiology were reported in Wuhan, the capital of Hubei Province of China. In January 2020, sequencing the next generation of a full-size genome from respiratory tract samples of pneumonia patients revealed a new coronavirus (CoV) that had not previously been associated with an infection in humans.

Key words: SARS-CoV-2, COVID-19, ACE2, TMPRSS2, reproductive system, steroidogenesis, spermatogenesis, hormones, pregnancy, vertical transmission.

Introduction

On February 11, 2020, the International Committee of Virus Taxonomy recognized the etiology of this infection and named it «Coronavirus-2 of severe acute respiratory syndrome» (SARS-CoV-2), and the World Health Organization (WHO) named the disease as COVID-19 [18]. COVID-19 was originally described as a purely respiratory tract infection. As our understanding of the virus has grown, it has become clear that the virus is also capable of causing disturbances in other organs of the human body, such as the liver, kidneys, and the gastrointestinal tract, and it has been suggested that this viral infection has the potential to disrupt the reproductive functions of men and women [17].

Susceptibility of human reproductive tissues to SARS-CoV-2

As is known, ACE2 are functional receptors for SARS-CoV-2 spikes (S-proteins), which are among the key components of the renin-angiotensin-aldosterone system (RAAS), modulating the cleavage of angiotensin II (Ang II) and angiotensin 1-7 (Ang (1-7)) [8]. The S-protein SARS-CoV-2 itself has a strong affinity to ACE2, and after its attachment to the receptor, the viral genome and nucleocapsid are released into the host cell cytoplasm. It should also be noted that SARS CoV-2 requires TMPRSS2 (transmembrane, serine protease-2) to split the viral S-protein and ensure fusion between the membranes of the virus and the host cell [15]. It is the co-expression of ACE2 and TMPRSS2 genes that is important for infection, where SARS-CoV-2 uses the ACE2 receptor to enter the cell and TMPRSS2 serine protease to prime the S protein [15]. As is well known, one of the functions of the RAAS is to regulate the basic functions of the male and female reproductive systems. In women, this

regulation includes effects on folliculogenesis, steroid genesis, oocyte maturation, ovulation, and endometrial regeneration. In men, the presence of ACE2 testicular receptors contributes to the regulation of normal testicular function and is therefore the most important component in steroid regulation, testosterone production, and sperm development. Since SARS-CoV-2 enters the cell by binding to ACE2 receptors, reproductive cells and tissues expressing it are potentially vulnerable to the virus, and their functions could theoretically be impaired [6]. As we know, ACE2 receptors themselves are much more represented in the male reproductive system than in the female. Low expression of ACE2, during histopathological studies, was determined in the fallopian tube, ovaries, endometrium, vagina, and cervix. In contrast, in men, ACE2 expression in the testicles is one of the highest, especially in the Leydig and Sertoli cells, and there is also an average expression in the glandular cells of the seminal vesicles. Accordingly, these histopathological studies suggest that it is the testicles may be more vulnerable than the ovaries to the harmful effects of SARS-CoV-2 infection [11].

Impact of SARS-CoV-2 on the male reproductive system

The male reproductive system is known to be vulnerable to many viruses, and previous research and observation has documented this effect associated with viral infections such as hepatitis B, mumps, and HIV, where the pathogens of these infectious diseases can enter the male reproductive tract, and thereby causing orchitis, can lead to a decrease in male fertility [16]. Given this property of viruses, one of the goals of several initial studies of patients with COVID-19 was to focus efforts to detect the full-fledged virus or some of its components in the male reproductive tract (MRT). But so far, contradictory results have been obtained [9]. Diangeng Li et al. revealed [3] that 6 out of 38 men infected with COVID-19 had an identifiable virus in their sperm. This was established with the help of RT-PCR. A significant proportion of positive semen samples were found in male patients with acute infection (26.7%), compared with those who were already recovering from COVID-19 (8.7%). It was also possible to determine the presence of SARS-CoV-2 particles in male testicles by American scientists headed by Justin K. Achua et al. [11], who, during histopathological analysis of testicular tissue material in 6 deceased patients from COVID-19 and one living patient, were able to detect viral particles in two samples exposed to transmission electron microscopy (TEM), one of which was from a living seroconverted patient who had previously tested positive for COVID-19.

At the same time, other studies have attempted to determine the presence of the virus in the semen of infected or recovering men and have received conflicting results so far. Ci Song et al. tested semen samples from 12 recovering men and one sample of testicular tissue from a deceased patient. Both sperm and testicular samples were negative for SARS-CoV-2 RNA [2]. Liqiang Guo et al. reported no SARS-CoV-2 RNA in the semen samples of 23 patients who had recently infected or recovering from COVID-19. or were recovering from COVID-19. The average interval between diagnosis and sample submission in these studies was 32 days [14]. Similar results were obtained by Feng Pan et al. from 34 recovering male patients [5]. It is worth noting that all these studies were limited to small sample sizes, the lack of ability to estimate the long-term effects of SARS-CoV-2 on spermatogenesis, and the significant interval (average of 5 weeks) in the collection of samples from convalescent patients. Considering the conflicting results of previous published works, it is necessary to wait for further research data to confirm or deny the ability of SARS-CoV-2 to cross the blood-epididymis barrier, and thereby be detected using the available instrumental methods of research. Therefore, the possibility of the presence of SARS-CoV-2 in semen cannot be completely ruled out, and further research is needed in men with symptoms of this viral infection, as well as in asymptomatic patients, before any definitive conclusions can be drawn.

This controversy in research to detect virion in MRT should not diminish the possible vulnerability of the male reproductive system to SARS-CoV-2 virus infection. Some studies since the start of the

COVID-19 pandemic have found significant coronavirus effects on male fertility and pathological changes in in the male gonads, which may well affect the reproductive well-being of male patients with COVID-19 in the long term. Chinese scientists led by Honggang Li et al. [9], in a histopathological assessment of testicles in six deceased COVID-19 patients, compared to a control group of the same age, found in all six cases congestion, edema and the presence of red blood cells in both the testicular appendages and in the testicles themselves. Detachment of spermatogenic epithelium in the seminiferous tubules was also observed in these patients. The fraction of apoptotic testicular cells, the researchers determined using the TUNEL assay. As a result, it was found that most of the apoptotic cells were located inside the seminiferous tubules. The number of apoptotic cells in the testicles of COVID-19 patients was significantly higher, almost three times, compared to the average value of apoptotic cells in the tests of patients of the control group. These results made it possible to establish a life-threatening sperm defect in these deceased patients from COVID-19. It should also be noted that the result of this study was the discovery of infiltration of T lymphocytes (CD3+) and macrophages (CD68+) around blood vessels of interstitial testicular tissue in patients with COVID-19, and IgG precipitation in the seminiferous tubules compared to the control group has also been identified. It can be assumed that the observed IgG precipitation in the seminiferous tubules in these patients was caused by a secondary autoimmune response to viral infection, like the autoimmune orchitis previously observed in patients infected with SARS-CoV [9]. Similar infiltration of testicular tissue with lymphocytes and macrophages, as well as varying degrees of impaired spermatogenesis, were found in 3 out of 6 deceased patients from COVID-19 by American scientists led by Justin K. Achua et al. [11]. In addition, using the method of immunofluorescence, it was found that the density of ACE-2 receptors was inversely proportional to the degree of impairment of spermatogenesis. Accordingly, it has been suggested that damage to cells involved in spermatogenesis, by the SARS-CoV-2 virus, may cause men with more ACE-2 expression to be at greater risk of impaired spermatogenesis, while in men with lower ACE-2 receptor expression spermatogenesis will be within normal range.

As we know, the hypothalamic-pituitary-gonadal (HPG) axis plays a vital role in reproduction. Hypothalamic neurons expressing gonadotropin-releasing hormone (GnRH) activate the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. Low GnRH levels cause a decrease in FSH and LH, which leads to dysfunction of Sertoli and Leydig cells. Chinese researchers Ling Ma et al. [13] found that COVID-19 patients had significantly higher serum LH levels, but at the same time lower testosterone/LH and FSH levels than healthy men, suggesting potential hypogonadism. Taken together, the data obtained showed that patients with COVID-19 had a reduced testosterone/LH ratio, indicating a possible subclinical dysfunction of the male gonads. In addition, HPG activation and subsequent changes in hormone concentration may play a critical role in poor sperm quality in active patients or in COVID-19 survivors. Honggang Li et al. [9] found, when examining semen samples in 9 out of 23 inpatients infected with COVID-19, a low sperm concentration, and less than 15 x 10^6 / ml, meeting the WHO recommended criteria for the diagnosis of oligozoospermia. Although all nine patients with oligozoospermia had offspring at the time of taking the material and there was no history of use of assisted reproductive technology or references to fertility treatments in the past. Moreover, the average sperm concentration in all 23 inpatients with COVID-19 was significantly reduced compared to that in males of the same age group.

Accordingly, all the above data from various studies around the world indicate that COVID-19 can have a potential effect on the male reproductive system, by disrupting various functions (immune, hormonal, etc.) and causing possible sperm dysfunction with a significant decrease in sperm count. All this points to the need to take a vigilant approach to long-range studies, as well as to the implementation of more thorough screenings of infected and diseased patients, to find out whether

these effects are reversible or not and try to develop standard therapeutic algorithms for therapeutic and preventive care, thus paying special attention to the reproductive health of men.

Impact of SARS-CoV-2 on the female reproductive system

As already mentioned, the female reproductive system has less risk of being exposed to various disorders because of COVID-19 disease. This is due to the much lower expression of ACE2 receptors in the female reproductive system. However, infecting SARS-CoV-2 may raise some concerns related to pregnancy in women due to physiological changes in immunity, maternal susceptibility to various viral respiratory infections, increased oxygen requirements, as well as the risks associated with treatment during pregnancy. Statistics to date show that COVID-19 causes the same spectrum of symptoms in pregnant women as in non-pregnant women, such as: fever ~ 40%, cough 39%, shortness of breath 13.2%, muscle pain 10%. From the literature available, pregnant women infected with SARS-CoV-2 have a higher risk of premature delivery, fetal distress syndrome, premature amniotic sack rupture and increased frequency of caesarean sections, compared with uninfected pregnant women [15]. Elisheva D. Shanes et al. [4], who studied placental morphology in 16 patients with COVID-19, found the presence of morphological anomalies in the placenta, mainly related to the insufficiency of the perfusion of the mother's vessels (decimal arteriopathy, fibrinoid necrosis, and malperfusion of the fetal vessels). It was found that the signs of malperfusion of the mother vessels, observed in the placenta, were not related to the presence of chronic or gestational hypertension, as well as with the presence of any other acute or chronic inflammatory processes. This suggests that the placenta may be sensitive to COVID-19 due to increased expression of ACE2 receptors during pregnancy and emphasizes the role of other infection mechanisms in placental pathology, not just the mandatory presence of an inflammatory cytokine storm.

Despite the contradictory results and debates in the scientific community, it is also necessary to point out the possibility of vertical transmission of viral infection from mother to fetus. The most conclusive evidence of intrauterine COVID-19 transmission would be confirmation of SARS-CoV-2 replication in the lung tissues of the fetus, but it is technically impossible to perform such studies. In practice, the approach to investigating the presence of intrauterine viral infection is to check for the presence of the virus in the placenta, amniotic fluid, umbilical cord blood and pharyngeal swabs of newborns [7].

So, the initial tests and the subsequent negative results of neonatal nasal swabs, amniotic fluid, and cord blood from mothers with COVID-19 in the last trimester of pregnancy, failed to prove antenatal infection. The evidence for this conclusion is mainly because the virus itself was not detected after birth in the tested newborns [10]. Although, as the authors themselves point out, the results of these studies may have been influenced by the small size of the statistical sample and by the retrospective study method.

In turn, the results of other studies [7,12,19] indicate the detection of the presence of antibodies (IgG / IgM) against SARS-CoV-2 among infants who are negative for COVID-19 but born to infected mothers. As we know, the definition of IgG antibodies in newborns has no reliable value, as these antibodies may have been transmitted by an infected mother, but the presence of IgM, which have a large molecular structure and is not transmitted transplacental, indicates that their production were intrauterine and reflects the immune response of the fetus. Although cross-reactions between IgM SARS-CoV-2 and other immunological markers cannot be excluded, which can lead to false positive results?

Alexandre J. Vivanti et al. [1] in their work refers to a proven case of intrauterine infection of the fetus from a 23-year-old mother infected with COVID 19, who was admitted to the clinic at 36 weeks of pregnancy. Thus, the results of the PCR test of the placenta, amniotic fluid, nasopharyngeal smear, and neonatal blood, determined a positive result for the E and S genes of SARS-CoV-2. According to the

current classification system, a congenital neonatal infection is considered proven if the virus is found in the amniotic fluid collected prior to the rupture of the fetal membranes or in the blood taken from the infant immediately after birth. According to researchers, this case is one of the few that fully qualifies as congenital SARS-CoV-2. This newborn, in the weeks that followed, exhibited non-specific symptoms of mild pneumonia, as well as severe neurological symptoms because of an inflammatory reaction. MRI neuroimaging has shown damage to white matter that can be caused by vascular inflammation caused by SARS-CoV-2 infection, which has previously been observed in adult patients with COVID 19 [1].

Conclusion

Based on this review article, we can conclude that the impact of COVID-19 on the reproductive female and male systems urgently requires further detailed and in-depth study using all available instrumental research methods, especially considering the rapid mutation of SARS-CoV-2 virus strains.

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