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SARS-COV-2 causes male infertility

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ABSTRACT: The review was undertaken to figure out the chances of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection that is the source of male infertility. The unfolding novel Coronavirus (CoV) SARS-CoV-2 that causes the COVID-19 disease, expeditiously spread into a global pandemic CoV are enveloped positive-sense RNA virus, which is host-specific and can infect the human and a large number of animals. It binds to the receptor Angiotensin Converting Enzyme 2 (ACE 2) and Transmembrane Protease 2 (TMPRSS 2). It raises the possible presence of testis being a potential target for SARS-CoV-2 infection. From literature search, transcriptome sequencing data revealed ACE2 expression in the germ, sertoli and leydig cells. The presence of ACE2 on almost all testicular cells and the report of a significant impact of previous SARS coronavirus-19 on testes suggest that SARS-CoV-2 is highly likely to affect testicular tissue, male fertility. In this review, we highlighted the current knowledge related to Coronavirus Disease 2019 (COVID-19) infectious risk status to cause male infertility.

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INTRODUCTION:

The unfolding novel coronavirus (CoV) SARS-CoV-2 that source the COVID-19 disease, which was introductory point out in Wuhan, Hubei province, China, expeditiously spread into a global pandemic. Often signs accompanying with coronavirus disease 2019 (COVID-19) include cough, fever, and shortness of breath with several threats to health due to a high raise transmissibility rate, being spread in 213 countries and territories around the world have reported a total of 28,026,967 confirmed cases of COVID-19 and 908,002 deaths of September 10th 2020 [1]. By the time you would read this article, the figures would have changed to more threatening numbers, that is how fast this virus is affecting and killing people, due to potentially severe

complications in elderly or comorbid patients who have hypertension [2], diabetes mellitus [3], cardiovascular diseases [4], and chronic obstructive pulmonary disease (COPD) [5-6]. CoV are enveloped positive-sense RNA viruses, which are host-specific and can infect the human and a large number of animals [7]. It belongs to the *Coronaviridae* family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named coronavirus. It is minute in size (65 to 125 nm in diameter) and contains enveloped single-stranded positive-sense RNA as nucleic material, with a size ranging from 26 to 32 kilobases (kb) in length. It is phylogenetically classified as subgroups into four major genera: Alpha CoV (α), Beta CoV (β), Gamma CoV (γ), and Delta (CoV) (δ) [8-10]. Several CoV can infect humans, like HCoV-229E [11], HCoV-NL63 [12], HCoV-HKU19 [13], and HCoV-HKU1 [14]. It tends to cause mild respiratory disease, and the zoonotic Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV). All two highly pathogenic coronaviruses for humans are owned by the Beta CoV (β) genus that has a towering case fatality rate [15]. The COVID-19 is genetically more adjacent to SARS-CoV than MERS coronavirus with the presence of 380 amino acid substitution differences in the encoded proteins [16–18]. The most accepted transmission routes of novel CoV include cough, sneeze, and droplet inhalation are direct transmission orelse contact with oral, nasal, and eye mucous membranes are contact transmission [19]. Respiratory droplets and physical intimacy, which signify being indoor someone's personal space like kissing, hugging, caressing, are the two main transmission routes of SARS-CoV-2 [20]. In this review, we aimed to document the current knowledge related to Coronavirus Disease 2019 (COVID-19) infectious risk status in order to cause male infertility.

COVID-19 AND ACE RECEPTOR, FRIEND OR FOE?

COVID-19 shares the same receptor as SARS CoV (2002-2004), i.e., ACE 2 and TMPRSS 2. It reinforces the prospect of testis being a potential target for SARS-CoV-2 infection. The first known human homologue of the ACE is ACE2. While ACE expression is usually omnipresent, ACE-2 transcripts are observed in the heart, kidney [21]. The mechanism involved in SARS-CoV-19 adheres to ACE receptors is the FURIN cleavage site in the SARS-CoV-2S protein may provide a priming mechanism [22]. The ectodomain S1 binds to the peptidase domain of the ACE-2 enzyme, while the S2 is cleaved further by the host cell serine protease TMPRSS2 resulting in membrane fusion [23]. Mention a couple of steps are important for the viral introgression into the cells and it source of hyper-inflammation and immunosuppression are marked featured in COVID-19 [24-25], developing in a cytokine storm [26], finally leading to augment of micro-thrombosis and disseminated intravascular coagulation (DIC). Cytokine storm which leads to pneumonia. Pneumonia is the primary symptom of COVID-19. Recent studies on adult human testis explain that single-cell transcriptome sequencing of ACE2 expression is chiefly limited to the Leydig and Sertoli cells in the human testis [27]. The infection leads to arise sooner through well-differentiated ciliated cells with higher ACE-2 expression [28]. Gene Set Enrichment Analysis (GSEA) suggested that categories of gene ontology associated with viral replication and transmission are distinctly enriched in ACE-2 positive spermatogonia, whereas related terms for male gamete generation are down-regulated [29]. A study done in China, showed that ACE-2 expression was related to the age of men, with the highest number seen in ACE-2 positive cells in 30-year-old men when compared to 20-year and 60-year-old men [30]. This result support that the statement, incidence, and severity of SARS-CoV-2 are reported to be higher in males than females, Shastri *et al*. performed a study to determine the time to viral clearance, observed that females were able to bring out the viral clearance undoubtedly prior than males [31].

COVID-19 AND MALE REPRODUCTION SYSTEM:

BTB is not inhibiting the viruses:

The Blood-Testis Barrier (BTB) is not supported by the entry of viruses, significantly with the dawning of local inflammation or septicemia or viraemia. Ultimately, few viruses could be seen in semen like Japanese encephalitis virus, parainfluenza virus, paravaccinia virus and foot and mouth disease virus in mammals [32-34]. Likewise, 27 viruses have been established in semen to date. The scientists have concluded that, more than 3,000 research papers show that at least 11 viruses live in the testis, including those causing pneumonia, dengue and extreme acute respiratory syndrome [35]. Nevertheless of the measure they enter, viruses have been identified in the human ejaculate, though the degrees to which infection and reproduction occur inside

the spermatozoa or germ cells stay indistinct [36]. Some inclusion viruses, such as Zika, HIV/AIDS, and hepatitis virus, can be transmitted via semen [37]. Zika virus can be seen indoors in spermatozoa and perhaps transferred to the oocyte onset of fertilization. It is proposed that sexual transmission of the ZIKA virus will increase infected people in endemic countries and territories [38]. The harmful upshot of viruses carryout overt damage to spermatozoa, testis, irregular sex-hormone expression, hyperinflammation and immunesuppression are markedly identify in COVID-19, emerge in a cytokine storm finally leading to outcome of micro-thrombosis and disseminated intravascular coagulation (DIC) [39]. The testes are made chiefly of seminiferous tubules and intratubular tissue. In seminiferous tubules, spermatozoa are produced, composed of sperm-producing cells (spermatogonia) and the supporting sertoli cells [40-41]. Underneath LH regulation, the interstitial Leydig cells are liable for the testosterone production. Since sertoli and leydig cells are showered by blood, the virus effect on these cells is sufficient to cause infertility, even though the BTB were impermeable to viruses. Testicular damage in COVID-19 might, therefore, induce a state of hypogonadism as shown by lower testosterone to LH ratio in patients with COVID-19, reminiscent of impaired steroidogenesis emerge from subclinical testicular dysfunction [42-43]. Post-mortem examinations of testicular tissue from COVID-19 patients showed undoubtedly lower Leydig cells, as well as inflammation edema in the interstitium [44] and seminiferous tubular injury was reported despite no evidence of the virus in the testis [45]. This does not rule out the chances of viral transmission via sexual behavior (e.g., oral/ anal contacts). Undoubtedly, viral particles may be transmitted over oral sex and saliva is act as lubricant. However, it should be accepted that the testis is target for SARSCoV-2 and the chance for long-lasting outcome on the endocrine function exists, even for recovered patients [46].

LITERATURE SCAN:

Effect of SARS Coronaviruses on testis:

The related studies were searched from the electronic databases such as PubMed, Scopus, Google Scholar, EMBASE, and COVID-19 specific databases such as LitCovid and WHO website till the 22nd of September 2020. Nevertheless, in another similar study from China, the virus was not detected in the semen samples of 34 COVID-19 patients after a median of 31 days [47]. Only two studies have looked for the presence of SARS-CoV-2 in semen samples and present contrasting findings. Xu J, *et al*., performed on 31 male COVID-19 patients in Italy identified that some patients develop hypergonadotropic hypogonadism subsequent to the dawning of the disease. In the same study, a reduced degree of serum testosterone (total and free) performs as a prognosticator of insufficient development in SARS-CoV-2 men [48].

Testosterone act as a modulator for endothelial function [49] and curb the inflammation by it boosting levels of anti-inflammatory cytokines (such as IL-10) and decreasing levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β [50]. The suppression of testosterone levels might be one of the reasons for the considerable changes in regarding hospitalization and mortality rate between males and females and might as well give an explanation of why SARS-CoV-2 almost frequently infects old men [51]. In one more study, the authors examined the pathological variations in the testis of six patients affected by COVID-19 and compared it with controls. They establish that SARS-CoV-2 caused the orchitis, and the testis displayed damage of germ cells with absolute few or no spermatozoa in the seminiferous tubules. Still, SARS-CoV-2 genome sequences were not dappled in the affected testis. This study apparently advised that SARS coronaviruses cause orchitis and may lead to infertility even if they do not enter the seminiferous tubules or are not detected in semen samples [52].

Effect of SARS Coronaviruses on Prostate gland:

The prostate gland is a male genital organ whose response to secrete prostate fluid, one of the main seminal components [53]. The prostate gland muscles still comfort in presuming this seminal fluid over the urethra during ejaculation [54]. A prostate-excreted fluid reports around one-third of allover semen volume and compresses calcium, numerous proteins, and citric acid [55,56]. The prostate is well-known to ACE2 expression on normal and benign prostate hyperplasia, so it is presumably to get SARS-CoV-2 infection and may disturb its secretions. Nevertheless the respiratory tract fluid, the researchers also adequately acknowledged SARS-CoV-2 in the patient's saliva, urine, and conjunctiva [57-59]. It suggested that the virus may have distinct courses of transmission. Till now, no more studies available to confirm whether the prostate is affected or not.

CONCLUSION:

From the evidence cited above, it is reasonable that SARS-CoV-2 can disturb multiple reproductive organs, increasing the chance of its cause of infertility. ACE2 is highly expressed in the testis, offering the chance of testicular infection till in the early stage of the disease. Being expressed in both leydig and sertoli cells, ACE2 performs key roles in spermatogenesis also in the regulation of steroidogenesis. In especially teenage people who attain puberty, SARS-CoV-2 infection could substantially disturb sexual development and fertility because of its impact on testicular and prostate development. In the adult male population, the viral infection may cause notable damage to the testicular tissue, and affect on spermatogenesis. Till now, no more studies available to confirm whether the prostate is affected or not. Since comorbidities have an impact on the outcome of SARS-CoV-2 infection, who have notable oxidative stress, another predisposing factor of infertility is even more accessible to SARS-CoV-2 induced infertility.

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