

Male reproductive system alterations by SARS-CoV-2 and its pathophysiology: A review

Alterações do sistema reprodutor masculino pelo SARS-CoV-2 e sua fisiopatologia: Uma revisão

Alteraciones del aparato reproductor masculino por SARS-CoV-2 y su fisiopatología: Una revisión

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Abstract

This integrative literature review aimed to analyze the findings about the SARS-CoV-2 action on the male genital tract. The database used in the search was PubMed, Scielo and Google Scholar with the following descriptors: “Male fertility”, “COVID-19”, “Infertility”, in addition to the use of the Boolean operator (AND). The final sample was 25 baseline studies. The entry of the coronavirus takes place through the interaction of its proteins with ACE-2 and TMPRSS2. Such proteins were identified in the male reproductive system, which explains several clinical findings in patients who were infected. This interaction of the virus with cells prevents the formation of Ang 1-7, which has anti-inflammatory properties, so its reduction would cause local tissue damage in the testicular tissue. Such findings ranged from histological changes with the formation of an inflammatory infiltrate to possible autoimmune orchitis. In addition, there are controversies on certain topics, such as the carriage of the virus in semen and its potential to cause embryological damage. The study showed the different pathophysiological possibilities of the virus in causing changes in male fertility, through the inflammatory effect, direct cytopathological action of the virus, fever, infections of other structures of the reproductive system, direct alterations in the hypothalamic pituitary axis and use of drugs as a treatment. All these results show the complexity of this virus in other systems and its mechanisms, which requires further studies for its full understanding.

Keywords: Male fertility; Coronavirus; Pandemics; Angiotensin-converting enzyme 2.

Resumo

Esta revisão integrativa da literatura teve como objetivo analisar os achados sobre a ação do SARS-CoV-2 no trato genital masculino. A base de dados utilizada na busca foi o PubMed, Scielo e Google Scholar com os seguintes descritores: “Male fertility”, “COVID-19”, “Infertility”, além do uso do operador booleano (AND). A amostra final foi de 25 estudos de linha de base. A entrada do coronavírus ocorre por meio da interação de suas proteínas com ACE-2 e TMPRSS2. Tais proteínas foram identificadas no sistema reprodutor masculino, o que explica vários achados clínicos em pacientes que foram infectados. Essa interação do vírus com as células impede a formação de Ang 1-7, que possui propriedades anti-inflamatórias, de modo que sua redução causaria dano tecidual local no tecido testicular. Tais achados variaram desde alterações histológicas com formação de infiltrado inflamatório até possível orquite autoimune. Além disso, há controvérsias sobre determinados temas, como a presença do vírus no sêmen e seu potencial de causar danos embriológicos. O estudo mostrou as diferentes possibilidades fisiopatológicas do vírus em causar alterações na fertilidade masculina, através do efeito inflamatório, ação citopatológica direta do vírus, febre, infecções de outras estruturas do sistema reprodutor, alterações diretas no eixo hipotalâmico-hipofisário e uso de drogas como tratamento.

Todos esses resultados mostram a complexidade desse vírus em outros sistemas e seus mecanismos, o que requer mais estudos para seu completo entendimento.

Palavras-chave: Fertilidade masculina; Coronavírus; Pandemia; Enzima conversora de angiotensina 2.

Resumen

Esta revisión integrativa de la literatura tuvo como objetivo analizar los hallazgos sobre la acción del SARS-CoV-2 en el tracto genital masculino. La base de datos utilizada en la búsqueda fue PubMed, Scielo e Google Scholar con los siguientes descriptores: “Male fertility”, “COVID-19”, “Infertility”, además del uso del operador booleano (AND). La muestra final fue de 25 estudios de referencia. La entrada del coronavirus se produce por la interacción de sus proteínas con ACE-2 y TMPRSS2. Estas proteínas se han identificado en el sistema reproductor masculino, lo que explica varios hallazgos clínicos en pacientes infectados. Esta interacción del virus con las células impide la formación de Ang 1-7, que tiene propiedades antiinflamatorias, por lo que su reducción provocaría un daño tisular local en el tejido testicular. Los hallazgos fueron desde cambios histológicos con la formación de un infiltrado inflamatorio hasta una posible orquitis autoinmune. Además, existen controversias sobre ciertos temas, como la presencia del virus en el semen y su potencial para causar daño embriológico. El estudio mostró las diferentes posibilidades fisiopatológicas del virus en causar cambios en la fertilidad masculina, por medio del efecto inflamatorio, acción citopatológica directa del virus, fiebre, infecciones de otras estructuras del aparato reproductor, alteraciones directas en el eje hipotálamo hipofisario y uso de drogas como tratamiento. Todos estos resultados muestran la complejidad de este virus en otros sistemas y sus mecanismos, lo que requiere más estudios para su total comprensión.

Palabras clave: Fertilidad masculina; Coronavirus; Pandemia; Enzima convertidora de angiotensina 2.

1. Introduction

The virus called SARS-CoV-2 emerged in the city of Wuhan (China) at the end of 2019, with terrible consequences for those infected, and responsible for the pandemic officially announced in March 2020. This beta coronavirus belongs to the coronaviruses, and had a great impact as it is a disease transmitted by respiratory secretions, and with a potential effect on the lungs through a strong cytokine storm, triggering signs and symptoms of pneumonia, but especially in more severe cases, Severe Acute Respiratory Syndrome (SARS) (Kumar et al., 2021).

This pandemic was responsible for major instabilities, accounting for more than 250 million cases worldwide, and 5 million deaths, leading to several ethical-medical dilemmas and scientific studies to understand this virus. It is known that it is a coronavirus with properties and biochemical formation similar to SARS and MERS, responsible for regional outbreaks, but which did not become pandemics (WHO, 2021).

In addition to causing SARS, the virus also acts in other systems, in which it has become responsible for multiple organ failure, neurological symptoms, anosmia, kidney injury, clotting effects on blood vessels... Increasing importance is the male genital tract, which raises concern about possible effects of the virus on fertility (Groner et al., 2021).

It is known that the male genital tract has a privileged immunological status, due to his blood-testis barrier (BTB), his unique local immune system, and specialized cells involved in testosterone production and sperm maturation and formation. Therefore, an imbalance in these systems can predispose to manifestations of autoimmune orchitis and consequently affect fertility (Rojas et al., 2011).

Moreover, testicular tissue also has its own renin-angiotensin system that mediates several of these functions. This process is characterized by the conversion, through ACE-2 (angiotensin-converting enzyme 2), of Ang II, which is a pro-inflammatory, into Ang 1-7, which has anti-inflammatory, protective and spermatogenesis properties. However, recent studies analyze the relationship of SARS-CoV-2 infection with the imbalance of angiotensin concentration, which could explain the possible deleterious effects on testicular tissue (Prestes et al., 2017).

However, the action of SARS-CoV-2 begins with its input the cell, through a peculiar entry route. Its protein S (spike) binds to ACE-2, along with a link with the coenzyme TMPRSS2, which will ensure its entry into the cell and subsequent effects. This binding to ACE-2 ensures the possible reduction of this enzyme, and subsequent local inflammatory effects. In addition, studies show other ways the virus acts to guarantee local injury, with probable cytopathic effects, greater affinity of the virus for

specific cells, due to the concentration of the entry enzyme, or even autoimmune effects due to changes in the BTB (Oliveira et al., 2020).

Thus, this work aims to expose and analyze the consequent of the SARS-CoV-2 action in the male reproductive system, which will be demonstrated by the clinical manifestations recorded in the literature, as well as the possible mechanisms of action of this virus for the findings described, including the microscopic, immunological and cellular changes caused by this virus.

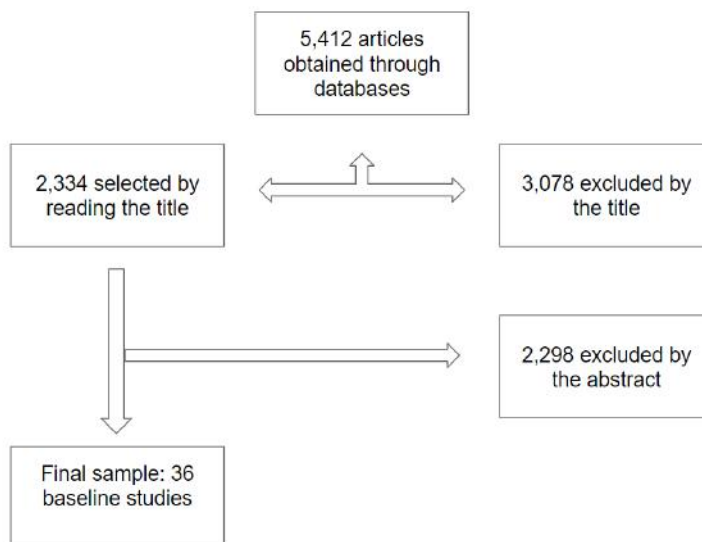
2. Methodology

This study was carried out in December 2021, through an integrative review (Pereira et al., 2018), used within the scope of Evidence-Based Practice, in which previous studies are analyzed, in order to synthesize knowledge and assist in conduct and decisions. This review method is consisting of six steps: 1) identification of the theme and guiding question; 2) establishment of inclusion and exclusion criteria; 3) data collection from selected articles; 4) critical analysis of the articles in order to classify the evidence found; 5) interpretation of results; 6) synthesis of knowledge.

The database used in the search was PubMed, Scielo and Google Scholar, without restricting the publication date, with the following descriptors: “Male fertility”, “COVID-19”, “Infertility”, in addition to the use of the Boolean operator (AND). Only full-text articles in English, Spanish and Portuguese that referred to the topic and brought theories about pathogenesis of coronavirus in the male fertility or case reports that proved its action in the reproductive system were considered. Those whose theme did not correspond to the proposal of the present study or did not present an abstract or title according to the theme, as well as those with deficient methodology, letters to the editor and opinion articles were excluded.

Initially, using the descriptors in the databases, 5,412 references were identified, as exposed in Figure 1. After reading the titles and abstracts, 5,376 articles were excluded because they were not case reports or because they did not deal with the topic. Finally, 36 articles were read in full and made up the sample of the integrative literature review.

Figure 1. Flow diagram for selecting articles for integrative review.



Source: Authors (2022).

3. Results and Discussion

How does the male genital tract work?

Cells in the male genital tract are responsible for spermatogenesis, as well as promoting primary and secondary sexual characters. It is worth remembering that initially in the testes there are the seminiferous tubules, which are surrounded by interstitial tissue. This interstitial tissue is formed by vessels, connective tissue and especially Leydig cells, responsible for the generation of testosterone. This production of testosterone begins in the hypothalamic-pituitary axis, where the hypothalamus produces GnRH, which will stimulate the pituitary to produce FSH and LH. LH acts on Leydig cells, stimulating them to produce testosterone, while FSH stimulates Sertoli cells to produce androgen-binding protein, which will act by concentrating the produced testosterone in order to induce spermatogenesis (Meng et al., 2021).

Thus, with testosterone, the spermatogonias begin to mature, some remain as stem cells, while others grow into spermatocytes, spermatids, until they become spermatozoa. This maturation is aided by Sertoli cells, which also function by nourishing the germ cells, providing mechanical support to them, and above all maintain gap junctions with other Sertoli cells, such junctions form the BTB, which provides the testicular environment with a site condition. immunologically privileged, furthermore there is a local anti-inflammatory environment, with expression of TGF-beta by testicular cells, immunomodulatory cytokine and Treg (Aitken, 2021).

However, spermatogonia are found at the base of Sertoli cells, which makes them more susceptible to external immune damage, and without the protection of the BTB. After the formation of sperm, these cells are concentrated in the epididymis to finish their maturation, until they are expelled through the vas deferens, where they will receive other contents that will form the semen, such as prostatic secretions and seminal vesicles, to finally being ejected through the urethra (Rojas et al., 2011).

RAAS in the male genital tract

The angiotensin-converting enzyme-2 (ACE-2) is an enzyme encoded by the gene located on the short arm of the X chromosome, specifically in the Xp22.2 gene, and is closely related to the renin-angiotensin aldosterone system (RAAS). In this system, the juxtaglomerular cells of the nephrons detect low glomerular filtration pressure and thus release the enzyme renin, responsible for converting angiotensinogen into angiotensin I (Ang I), a protein that will be catalyzed by ACE I (angiotensin-converting enzyme I) and will be converted to angiotensin II (Ang II). This Ang II has several properties when interacting with ART1 receptors, including pro-inflammatory, vasoconstrictor, fibrosis, stimulation of aldosterone production, which increases sodium retention and increases blood pressure... There is even evidence of heart, lung, brain and kidney damage from the strong effect of Ang II (Pascolo et al., 2020; Younis et al., 2020).

On the other side, the ACE-2 enzyme will act by converting Ang II into Ang 1-7, which will act on ART2 and MAS receptors in the opposite direction to cause vasodilation, anti-fibrotic, diuresis and anti-inflammatory effects. Thus, the balance between Ang II and Ang 1-7 establishes blood and inflammatory properties (Illiano et al., 2020; Younis et al., 2020; Fathi et al., 2021).

Such enzymes have already been discovered in several tissues, including testicular tissue. It was verified, for example, there was a strong presence of ACE-2 in Sertoli cells, seminiferous duct cells, Leydig cells and spermatogonia, there is also MAS and Ang 1-7 in the seminiferous tubule and Leydig cells. Besides that, there is evidence that infertile people do not have any of these RAAS components (Figueredo, 2021; Reis et al., 2010; Abobaker & Raba, 2021).

There is the idea that testicular RAAS is independent of systemic RAAS, because the BTB shows the chance that local renin is produced by Leydig cells, testicular ACE is involved with sperm capacitation, and ACE-2 in the regulation of

spermatogenesis. So, when the virus enters the cell, it ends up saturating the ACE-2 receptors, which consequently prevents the conversion of Ang II, which will increase his concentration and inflammatory effects (Illiano et al., 2020; Pascolo et al., 2020).

Through the produced review, it was possible to realize ACE-2, Ang 1-7 and MAS in the testes, especially in Leydig and Sertoli cells. Thus, taking in consideration the Leydig cells function in producing steroids such as testosterone, MAS receptor in this cell shows that Ang 1-7 may modulate testosterone production (Illiano et al., 2020).

Entry into cells

SARS-CoV-2 is a coronavirus with about 80% biomolecular homology with SARS-CoV-1, in addition both act on the ACE-2 receptor as a form of entry into the cell. The current coronavirus has the S protein (Spike), which will bind to this enzyme. However, later studies showed that there is also a need for a co-receptor called TMPRSS2 (transmembrane serine protease 2), which acts by cleaving the S protein in order to mediate the entry of the coronavirus into the host cell. The S protein divides into S1, which will bind to ACE-2, and the S2 portion mediates membrane fusion (Oliveira et al., 2020).

This ACE-2 protein is found in many tissues, such as the lung, kidneys, heart, brain and testis, which makes these systems targets for studies on possible interactions with the virus. ACE-2 is present in testicular tissue, but TMPRSS2 (slightly expressed in prostate, epididymal cells, spermatogonia, spermatids, semen, and Leydig cells) is required for viral entry. Due to the event that this serine protease is poorly expressed in this tissue, there is a possibility that SARS-CoV-2 interacts with other local testicular tissue proteins to ensure its entry into cells, such as cathepsin L (CTSL) or BSG, which may also act by cleaving the S protein (Batiha et al., 2020; Entezami et al., 2020; Pascolo et al., 2020).

Possible effects of the virus on fertility

Based on the literature review carried out, it was possible to detect the possible effects of the virus on fertility or even fertilization. The main findings are detailed in Table 1.

Table 1. Possible effects of SARS-CoV-2 in male fertility.

Author	Sample	Main findings
Xu <i>et al.</i> (2006)	Testicular autopsy of 6 men who died of COVID	<ul style="list-style-type: none"> ● Orchitis ● Leukocyte infiltration ● Damaged testosterone production ● Destruction of the seminiferous tubule epithelium
Duarte-Neto <i>et al.</i> (2020)	10 autopsies (COVID-19)	<ul style="list-style-type: none"> ● Orchitis ● Microthrombi
Entezami <i>et al.</i> (2020)	15 patients in the acute phase of the virus infection and 23 patients in the recovery phase	<ul style="list-style-type: none"> ● Presence of virus in semen
Gagliardi <i>et al.</i> (2020)	14 years old boy	<ul style="list-style-type: none"> ● Orchi-epididymitis ● Testicular edema
Li <i>et al.</i> (2020)	Autopsy of 6 patients killed by COVID-19	<ul style="list-style-type: none"> ● Thinning of the seminiferous epithelium ● Red cell exudate ● Oligozoospermia ● Leukocytospermia ● Orchitis

Li <i>et al.</i> (2020)	4 patients in the acute phase of infection, and 2 of them in the recovery phase	•	SARS-CoV-2 RNA in semen
Ling <i>et al.</i> (2020)	66 patients	•	Virus genetic material in urine
Pan <i>et al.</i> (2020)	6 patients infected with COVID-19	•	Scrotal discomfort
Paoli <i>et al.</i> (2020)	31 year old male infected with COVID-19	•	No viral RNA in semen
Schroeder <i>et al.</i> (2020)	88 male patients positive for SARS-CoV-2	•	Low levels of testosterone and dihydrotestosterone
Shen <i>et al.</i> (2020)	Gene Expression Omnibus	•	ACE-2 expression is highest in men at age 30 and decreases at age 60
Song <i>et al.</i> (2020)	Semen from 12 patients recovering from COVID-19	•	No viral RNA in semen
Yang <i>et al.</i> (2020)	Autopsies of 12 people who died from COVID-19	•	Vacuolization
		•	Cell debris in the lumen of the seminiferous tubules
		•	Lower number of Sertoli cells
		•	Edema
		•	T lymphocyte infiltration.
Gacci <i>et al.</i> (2021)	43 men infected by COVID-19	•	Severe disturbance of his semen profile
		•	Azoospermia
Mannur <i>et al.</i> (2021)	Patient who would undergo in vitro fertilization	•	Oligo-asene-teratozoospermia
		•	Severe damage to sperm DNA
		•	Grade 2 embryo formation

Source: Authors (2022).

Due to the fact that SARS-CoV-2 has a biomolecular similarity with the 2002 SARS-CoV, it is important to highlight the findings of the early coronavirus and its influences on the male reproductive tract, which were studied by Xu et al. (2006) through the testicular autopsy of 6 men who died of COVID. In their findings, all the patients had orchitis and leukocyte infiltration, which could interfere with the activity of Leydig cells, thus damaging the production of testosterone and destroying the epithelium of the seminiferous tubules, as well as generating a strong cytokine response.

On the other hand about SARS-CoV-2, there are increasing reports of findings that show a relationship between the virus and the male genital tract. With regard to histopathological and immunohistochemical findings, the research carried out by Li *et al.* (2020) performed with autopsy analysis of 6 patients who died from COVID-19, revealed in the histopathology of testicular tissue interstitial edema, congestion of the testes and epididymis, thinning of the seminiferous epithelium, higher rate of apoptosis, epididymitis and red cell exudate; immunohistochemically, they showed T lymphocytes and macrophages in the interstitium and IgG in the seminiferous tubules, however there was no presence of the virus in the semen. Furthermore, in these infected patients there were findings of oligozoospermia and leukocytospermia, which is indicative of orchitis, as well as an

increase in IL-6 and TNF in the semen. This leukocyte infiltration and cytokines certainly impact Leydig cells and BTB, which causes problems in testosterone production and damage to seminiferous tubule cells.

Yang *et al.* (2020) analyzed autopsies of 12 people who died from COVID-19 and found vacuolization, edema of Sertoli cells, also found cellular debris in the lumen of the seminiferous tubules, lower number of Sertoli cells, edema and T-lymphocyte infiltration and histiocytes in the interstitial tissue.

In Brazil, there was a finding of orchitis with associated micro thrombus in a study carried out with 10 autopsies by MIA-US (minimally invasive autopsy guided by ultrasound) (Duarte-Neto *et al.*, 2020).

Gacci *et al.* (2021) reported in their work that 25% (11/43) of men recovering from COVID-19 infection exhibited a severe disturbance of their semen profile, with the majority (8/11) being azoospermic, and the degree of spermatogenic disruption was significantly correlated with disease severity. There was also the report by Mannur *et al.* (2021) who showed a case of a patient who was going to undergo in vitro fertilization, however 43 days after his recovery from a mild infection by COVID-19, he presented oligo-asene-teratozoospermia, with strong damage to the sperm DNA, with embryo formation of grade 2 (severe fragmentation and low degree of implantation). 135 days later, his semen was analyzed, there was normal sperm count and motility, but there was still a change in her morphology, with teratozoospermia. The authors also explain that intrinsic apoptosis may have occurred, causing sperm senescence and death. Therefore, there was a long-term change of his sperm (greater than 4 months). The authors also postulate that there would be TMPRSS2 in the sperm membrane, which would contribute to direct infection by SARS-CoV-2 (Pascolo *et al.*, 2020).

However, some studies postulate that there are no such risks, due to the absence of co-expression of ACE-2 and TMPRSS2 in sperm, although there is the basigin (BSG / CD147), as well as another protease, cathepsin L (CTSL), that could act by cleaving the viral protein S, thus facilitating the entry of the virus (Pascolo *et al.*, 2020).

In the clinical findings, Pan *et al.* (2020) showed that 19% of men in their study had orchitis-like scrotal discomfort during COVID-19 infection. Furthermore, another evident factor is the study by Shen *et al.* (2020), who postulated that the number of ACE-2 in male patients is higher at age 30 and decreases at age 60, which shows that young patients are likely to be more susceptible to testicular damage. Gagliardi *et al.* (2020). presented a case of orchiepididymitis concomitant with COVID-19 infection in a 14-year-old boy, who presented with right testicular edema and findings of leukocytosis and lymphocytopenia (Abobaker & Raba, 2021).

The virus in semen is somewhat a contradictory analysis, which demands further studies. Entezami *et al.* (2020) performed a cohort study, in which 4 of 15 patients in the acute stage of virus infection and 2 of 23 patients in the recovery stage tested positive for this finding. Li *et al.* (2019) in their work reported 6 cases of SARS-CoV-2 RNA in semen, 4 of them in the acute stage of infection, and 2 of them in the recovery stage. However, Song *et al.* (2020) when analyzing by RT-PCR the viral RNA in the semen of 12 patients recovering from COVID-19 did not obtain any results, as well as the studies by Paoli *et al.* (2020) who also did not identify samples in the semen.

Also controversial is the relationship between hypogonadism and SARS-CoV-2. Infertile men have a natural reduction in ACE-2, one of whose functions is to regulate steroidogenesis, epididymal contractility and sperm cell function. Thus, comorbidities, for example, diabetes, pulmonary, renal, cardiovascular and coronary heart diseases, can impair the production and activity of ACE2. Therefore, obese individuals tend to have hypogonadism, due to low ACE-2, high Ang II and greater inflammation and local fibrosis when faces a viral infection (Pascolo *et al.*, 2020).

Studies by Schroeder *et al.* (2020) showed that many men with low levels of testosterone and dihydrotestosterone had COVID-19, which perhaps shows that hypogonadism is a comorbidity factor, this argument may be confirmed by evidences that testosterone acts in immunomodulatory, anti-inflammatory function, and regulate T lymphocyte differentiation. Since

hypogonadism is a common finding in systemic diseases, it is not known whether the low testosterone levels seen in patients with COVID-19 are the cause or the result of severe infection (Khalili et al., 2020)

It is also worth mentioning that there is a certain epidemiological profile in SARS-CoV-2 infection, when male patients are more infected with COVID-19, such findings can be explained by the fact that testicular cells have more receptors than the ovaries, which increases the cases of gonadal damage in men, as well as the fact that there is a protein called Androgen Receptor (AR) in men, responsible for the transcription of TMPRSS2, which is regulated by androgenic hormones, thus increasing the predisposition to SARS-CoV-2 infection by increased serine protease (Khalili et al., 2020; Qiao et al., 2020; Dutta & Sengupta, 2021).

In addition, the female immune system is more resistant, with better antibody production, more expression of TLR7 and lower expression of IL-6, a cytokine that characterizes the cytokine storm in COVID-19 inflammation. Finally, estradiol reduces ACE-2, which represents less interaction with the virus, while androgens act as promoters of TMPRSS2 (Navarra et al., 2020; Stelzig et al., 2020; Delamuta et al., 2021).

Regarding findings from patients with COVID-19 that may demonstrate the presence and indirect effect of the virus in the genital tract, Ling *et al.* (2020) showed genetic material of the virus in the urine in only 6.9% of patients positive for COVID-19 and it was also present in 3 recovered patients, which is worth remembering that the urinary tract in humans converges with the genital tract, where there may be the possibility of SARS-CoV-2 in the genital tract being released in the urine. Many studies have shown a return to normality in semen production after infection, although the period of normality varies, since semen parameters such as concentration and motility can remain altered from 72 to 90 days after infection by COVID-19, which it will depend a lot on the extent of the lesion, severity and time of initial lesion by the virus. Although affected aspects of the sperm, such as count, morphology and motility, and DNA damage itself may be potential risks for the possible future embryo (Abdel-Moneim, 2021; Aitken, 2021).

Possible virus action mechanisms on fertility

Through the literature review, it was detected possible mechanisms of action of the virus on fertility. The main findings are compiled in Table 2 and graphic 1.

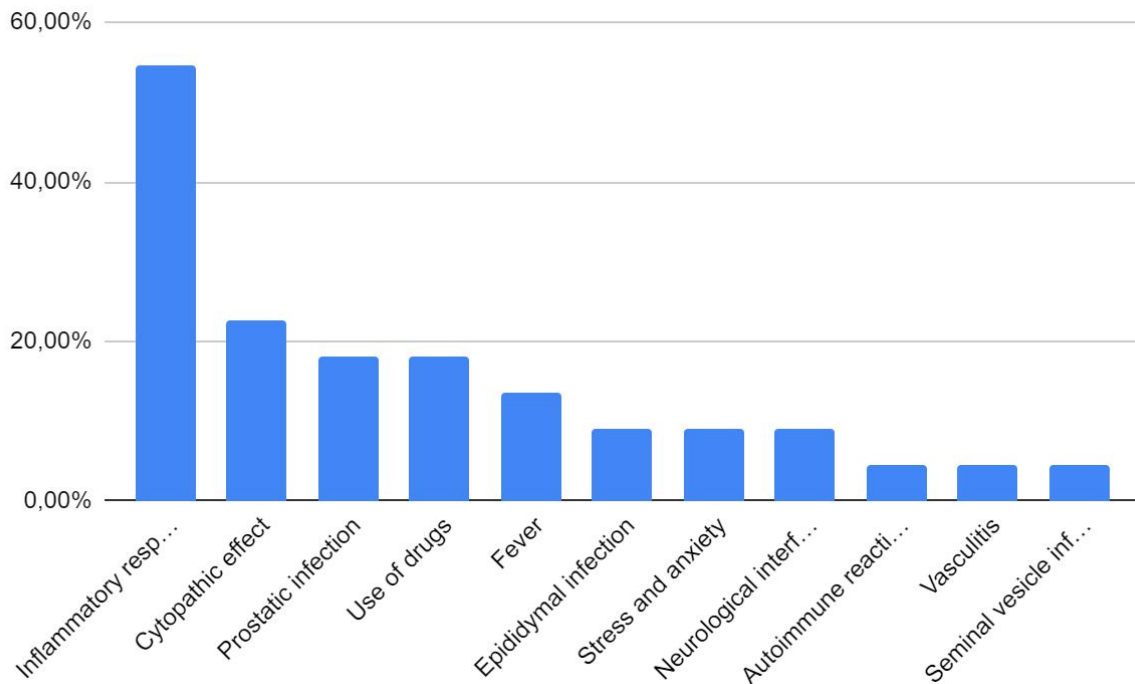
Table 2. Possible mechanisms of virus action on fertility according to the review performed.

Author	Mechanisms
Leal <i>et al.</i> (2009)	• Inflammatory response
Veldhuis <i>et al.</i> (2016)	• Inflammatory response
Abobaker (2020)	• Inflammatory response
Corona <i>et al.</i> (2020)	• Vasculitis
Figueredo <i>et al.</i> (2020)	• Inflammatory response
Huang <i>et al.</i> (2020)	• Inflammatory response • Cytopathic effect • Use of drugs with oxidative potential
Illiano (2020)	• Inflammatory response

Ma <i>et al.</i> (2020)	<ul style="list-style-type: none">• Inflammatory response
Navarra <i>et al.</i> (2020)	<ul style="list-style-type: none">• Epididymal infection• Seminal vesicle infection
Pascolo <i>et al.</i> (2020)	<ul style="list-style-type: none">• Use of drugs with oxidative potential
Quan <i>et al.</i> (2020)	<ul style="list-style-type: none">• Prostatic infection
Seymen <i>et al.</i> (2020)	<ul style="list-style-type: none">• Prostatic infection• Cytopathic effect• Stress and anxiety• Neurological interference
Sun <i>et al.</i> (2020)	<ul style="list-style-type: none">• Cytopathic effect
Vishvkarma <i>et al.</i> (2020)	<ul style="list-style-type: none">• Prostatic infection• Neurological interference
Younis <i>et al.</i> (2020)	<ul style="list-style-type: none">• Inflammatory response• Fever
Abdel-Moneim (2021)	<ul style="list-style-type: none">• Inflammatory response• Cytopathic effect• Use of drugs with oxidative potential
Delamuta <i>et al.</i> (2021)	<ul style="list-style-type: none">• Fever
Dutta <i>et al.</i> (2021)	<ul style="list-style-type: none">• Inflammatory response• Use of drugs with oxidative potential• Stress and anxiety
Fathi <i>et al.</i> (2021)	<ul style="list-style-type: none">• Epididymal infection• Prostatic infection
Mannur <i>et al.</i> (2021)	<ul style="list-style-type: none">• Cytopathic effect
Meng <i>et al.</i> (2021)	<ul style="list-style-type: none">• Inflammatory response• Autoimmune reaction• Fever
Zhao <i>et al.</i> (2021)	<ul style="list-style-type: none">• Inflammatory response

Source: Authors (2022).

Graphic 1. Most frequent pathophysiological mechanisms associated with the virus in the literature review performed



Source: Authors (2022).

Based on the study, the inflammatory response caused by the viral infection was present in 54.55% of the articles analyzed, and taking into account the various findings and case reports in the review conducted, several pathophysiological mechanisms are postulated to explain the mechanism of action of the virus on the testicular tissue. As an example of comparison of this mechanism, some patients contaminated with SARS-CoV (2002) presented orchitis and in the analysis of biopsies, there was destruction of germ cells, without viral material, but there was IgG, which leads to the hypothesis of autoimmune inflammatory orchitis by the coronavirus (Meng et al., 2021).

Among the findings that point to inflammatory reasons, there is the study by Li *et al.* (2020) of patients infected with COVID-19 with thinning, apoptosis and edema of the testicular tissue that reveal the probable action of cytokines, such as IL-1 and TNF, responsible for increasing capillary permeability and leukocyte recruitment.

Furthermore, patients with COVID-19 generate a strong inflammatory response characterized by hypercytokinemia, cytopenia, hyperferritinemia and multiple organ failure, with possible tumorigenic effects according to the extent of DNA damage. There is also evidence of CD68+ macrophage and anti-phospholipid IgG in the testicular tissue of infected patients, which may act against sperm (Huang et al., 2020; Younis et al., 2020).

The explanation for such findings lies in the hematogenous route, through which the SARS-CoV-2 virus reaches the testicular tissue, and the first contact occurs with the interstitial tissue, where there are Leydig cells and spermatogonia, which are not protected by BTB, thus making them possible targets for the virus, although in the acute stage of infection, histological changes in Leydig cells are not always possible to be visualized (Huang et al., 2020; Illiano et al., 2020).

Therefore, a strong inflammatory response may occur, even more as a consequence of intra cytosolic sensors of viral RNA after the viral entry in local cells, which stimulates a release of cytokines by Leydig and Sertoli cells and promotes autoimmune responses, orchitis, leukocyte infiltration and generation of interferons that reduce the production of testosterone. Moreover, the inflammatory state increases the formation of reactive oxygen species (ROS), which cause DNA damage, apoptosis and impair semen quality. In addition, the virus does not replicate in testicular tissue, but its permanence is sufficient

to stimulate the immune system and inflammatory responses (Abdel-Moneim, 2021; Abobaker & Raba, 2021; Dutta & Sengupta, 2021).

Excess cytokines can lead to damage to the integrity of BTB, in a proportion that this damage may be the access route of the coronavirus to other cells, such as Sertoli cells, which express ACE-2, and thus are potential hosts. Furthermore, the occupation of ACE-2 receptors reduces the number of this enzyme so important in the anti-inflammatory effect, increases the Ang II and thus potentiates inflammation. The absence of production of Ang 1-7 will not stimulate the MAS receptor in Leydig cells, with a subsequent reduction in testosterone production, this can also be explained in the experience that the absence of MAS receptor in rats caused problems in steroidogenesis testicular (Leal et al., 2019; Illiano et al., 2020;).

Such pro-inflammatory states will generate consequences in testicular tissue, the inflammatory action on spermatogonia can lead to infertility by disrupting spermatogenesis. The inflammatory state can also act on the hypothalamic-pituitary axis, reducing GnRH or LH and, consequently, testosterone, although there are controversies on this issue. According to Ma *et al.* (2020) in their studies with 81 men of fertile age and infected with COVID-19, found in these patients a low rate of testosterone, a high rate of LH and prolactin and a low Testosterone/LH ratio, this can be explained by a brief initial negative feedback by the low testosterone, which stimulated LH and helped maintain normal testosterone levels, perhaps long-term hypogonadism effects may occur (Veldhuis et al., 2016; Dutta & Sengupta, 2021; Figueredo, 2021).

Another possible mechanism occurs through the autoimmune reaction, in which macrophages and leukocytes stimulated by the inflammatory environment can end up destroying the BTB and spermatogonia, which can activate an autoimmune response with the formation of IgG autoantibodies. This autoimmune response was present in 4.54% of the publications and occurs because the testicular tissue is an immunologically privileged environment, so without BTB, testicular proteins are seen as antigens by the immune system (Meng et al., 2021).

There is also the possibility that prolonged fever can be the factor responsible for reproductive disorders, a very common situation in patients infected with SARS-CoV-2 and reported by 3 authors. The ideal temperature for spermatogenesis is 37°C, but high temperatures caused by fever stimulate apoptosis of gonadal cells. Such fever is a direct effect of the inflammatory process, with the action of IL-1, IL-6, TNF... which act on the hypothalamic centers. However, this possibility is controversial, due to the fact that in countries with endemic diseases characterized by febrile signs, such as malaria, male infertility is not so common (Younis et al., 2020; Delamuta et al., 2021; Meng et al., 2021).

On the other hand, there are hypotheses of virus infection in specific structures of the genital tract. There have been reports of infected individuals who have had orchiepididymitis, which shows the possibility of infection of epididymal cells. Such cells have furin domains that predispose them to SARS-CoV-2 virus infections, as well as evidence of TMPRSS2 in their tissue (Navarra et al., 2020; Fathi et al., 2021).

Although there is still a lack of studies on the seminal vesicle, in a way that only 4.54% of the analyzed articles presented such theory, the SARS-CoV-2 virus in the semen may be an indication of impairment of this vesicle, responsible for most of the seminal volume (approximately 70%). There is also expression of ACE-2 and TMPRSS2 in the seminal vesicles, so they can be targets of the virus (Navarra et al., 2020).

Finally, there are high expressions of TMPRSS2 in the prostate gland tissue, especially by luminal cells, and discrete expression of ACE-2. The expression of TMPRSS2 is stimulated by androgens, so the prostate may be the gateway to the male reproductive system. TMPRSS2 can also be released into semen through proteasomes, which will help sperm function. Therefore, the expression of TMPRSS2 may be an indicative factor of probable infection of the prostate tissue by SARS-CoV-2 and may explain the alterations found in semen. Besides that, about 1/3 of the semen volume comes from prostatic content. Nevertheless, studies such as by Quan *et al.* (2020) with 18 people infected with COVID-19 did not identify SARS-CoV-2 gene expression in prostatic secretion in RT-PCR analysis (Seymen, 2020; Vishvkarma & Rajender, 2020; Fathi et al., 2021).

There is also the possibility of vasculitis caused by COVID-19 as an impact factor on reproduction, and this effect has already been observed and proven, which can cause changes in the coagulation and segmental vascularization of the testis, with consequent orchitis. It is also known that LH has a role in inducing greater vascularization in the testis, so neurological changes in the hypothalamic-pituitary axis could also alter the concentration of LH and hence local vascular effects (Corona et al., 2020). Furthermore, there was a case report of a patient recovered from COVID-19, who showed oligo-asene-teratozoospermia, which suggests a possible direct infection of the virus on the sperm via TMPRSS2. In addition to the inflammatory effect caused by the virus, which will stimulate leukocyte recruitment and damage the BTB, there is evidence of direct interference by the virus, such as a probable presence in semen, affecting sperm fertility, as well as records of reduced autophagy in people infected with COVID-19. Studies have recorded increased expression of SQSTM1/p62 in cells infected by SARS-CoV-2, with a reduction in the rate of cellular autophagy. In practice, autophagy is important for degradation of senile organelles, reuse of structures, such as lipoproteins, to synthesize testosterone, as well as elimination of intracellular antigens, so autophagy is important in spermatogenesis. Thus, the reduction in autophagy may be linked to the formation of anomalous sperm and other possible cellular changes in the testis (Seymen, 2020; Sun, 2020; Mannur et al., 2021).

Based in the fact that Leydig cells express both ACE-2, TMPRSS2, alternative Basigin receptor (BSG) and Cathepsin L protease (CTSL), a possible cytopathic effect of SARS-CoV-2 on this cell can be hypothesized. Such mechanisms can be compared with other coronaviruses, such as IBV (infectious avian bronchitis), which have been identified in Sertoli cells and have a similar pathophysiology. In addition, high inflammation, with excess IL-6, damages the BTB, which makes it an access route for the SARS-CoV-2 virus in the testicular environment and its direct access to other cells (Huang et al., 2020). Probably the primary cell in the infection would be the Leydig cell, both because of its location in the interstitium close to the vessels, and because of the co-expression of important receptors, such as ACE-2 and TMPRSS2. Subsequently, Sertoli cells and spermatogonia appear that have the same conditions, which make them alternative routes for the virus to enter in testicular tissue (Abdel-Moneim, 2021).

It is also worth mentioning that being infected by a disease responsible for a pandemic and the death of millions of people will certainly cause anxiety and stress in the patient. Such psychological situations cause imbalance in the hypothalamus/pituitary axis and are usually accompanied by low concentrations of androgen-binding protein, high secretions of cortisol and prolactin, low sperm count and concentration, and high fragmentation of sperm DNA, with would induce sexual dysfunction (Seymen, 2020; Dutta & Sengupta, 2021).

Another pathophysiological mechanism is the neurological interference caused by the virus. It is known that several viruses have already been identified in the brain, including SARS-CoV and SARS-CoV-2. In addition, neurons and glial cells also express ACE-2, becoming targets of the virus, which can act on the hypothalamic-pituitary axis, in order to deregulate the hormonal production of GnRH (released by the hypothalamus), so that the low production can affect the synthesis of LH, FSH, prolactin, estradiol and testosterone, which certainly has an impact on fertility, although there is still a lack of studies on such hormonal interferences (Seymen, 2020).

When analyzing other classes of viruses that enter the CNS, and that can be used as a comparison to understand the mechanism of SARS-CoV-2, it is postulated that they reach the brain when entering the oral or nasal route. The entry of viral particles into the brain circulation can break the blood-brain barrier (BBB), or contaminate monocytes that cross the barrier and then replicate in the nervous tissue. Certain viruses do not cross the barrier, but can induce inflammation by cytokines that break it down (Vishvkarma & Rajender, 2020).

However, another proposed explanation for the testicular alterations was the use of drugs. Many patients, specially at the beginning of the pandemic, used a series of anti-inflammatories as a way to fight the cytokine storm caused by the infection, such as corticosteroids and steroids (methylprednisolone) which are known to have a side effect of causing loss of libido and

erectile dysfunction, besides that studies with treated rats treated with glucocorticoid showed changes in their Leydig cells. There are also antiviral drugs such as ribavirin, lopinavir and ritonavir, which also promote oxidative stress, with consequent damage to spermatogenesis and a reduction in testosterone. And the controversial continued use of chloroquine can impair sperm quality, through impact on epididymis and spermatogenesis (Huang et al., 2020; Pascolo et al., 2020; Abdel-Moneim, 2021; Dutta & Sengupta, 2021).

4. Conclusion

To conclude, the various mechanisms that can justify testicular tissue changes with SARS-CoV-2 infection are evident, and changes in the amount of sperm, inflammatory infiltrates have been reported by several studies, which demonstrates the potential for orchitis and infertility in severe infections, especially in young patients or those with comorbidities involved in the reduction of ACE-2. About the mechanisms, these are diverse, which range from fever, direct cytopathological effect, inflammatory reaction and drug reaction may be involved in the pathophysiology.

So, further studies need to be carried out to clarify the mechanisms not yet fully understood of the virus action, in order to carry out therapeutic measures to protect the infected from testicular damage, as well as to understand the contradictory reports of the coronavirus in the sperm, which could imply in embryonic alterations.

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