

Review Article

Male infertility in patients diagnosed with COVID-19: a narrative review*Infertilidade masculina em pacientes com diagnóstico de COVID-19: uma revisão narrativa***Laura Faustino Gonçalves¹, Janaína Viana Stolz², Patrícia Haas³**

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RESUMO: *Introdução:* A literatura relata acerca do potencial impacto do vírus coronavírus (COVID-19) nos órgãos reprodutivos masculinos e na fertilidade masculina. *Objetivo:* Apresentar evidências científicas, com base em revisão narrativa, da associação de infertilidade masculina em pacientes com diagnóstico de COVID-19. *Materiais e Métodos:* Os artigos foram pesquisados nas bases de dados SciELO, LILACS, PubMed, Scopus, BIREME e Web of Science, sem restrição de local ou idioma. O período estabelecido para a avaliação foi de 2015 a 2020. Os estudos foram selecionados por meio de combinações baseadas no Medical Subject Headings (MeSH). Dois estudos que responderam à questão de pesquisa foram incluídos nesta pesquisa; sua pontuação foi ≥ 6 pontos no protocolo qualitativo proposto por Pithon et al.⁷. *Resultados:* O receptor da enzima conversora de angiotensina 2, facilita o vírus da COVID-19 infiltrar-se nas células hospedeiras, é intensamente expresso nas células testiculares. Além disso, as respostas inflamatórias induzidas pela infecção por COVID-19 podem levar ao estresse oxidativo sistêmico. *Conclusão:* Os testículos são um alvo potencial da COVID-19, resultando em danos testiculares. Portanto, os impactos imediatos ou tardios na fertilidade masculina acarretados pela COVID-19 não podem ser descartados. Ainda não foram obtidos dados definitivos para rastrear as funções reprodutivas em homens que se recuperaram da COVID-19, embora estudos estejam em andamento para estabelecer essa associação na saúde masculina.

Palavras-chave: Infecções; COVID-19; Infertilidade; Vírus; SARS-CoV-2.

ABSTRACT: *Introduction:* Literature reports on the potential impact of the coronavirus 2019 (COVID-19) on male reproductive organs and male fertility. *Objective:* To present scientific evidence, based on a narrative review, of the association of male infertility in patients diagnosed with COVID-19. *Materials and Methods:* The articles were searched in the SciELO, LILACS, PubMed, Scopus, BIREME and Web of Science databases, without restriction of location or language. The period established for the evaluation was from 2015 to 2020. The studies were selected through combinations based on Medical Subject Headings (MeSH). Two studies that answered the research question were included in this research; its score was ≥ 6 points in the qualitative protocol proposed by Pithon et al.⁷. *Results:* The angiotensin-2 converting enzyme receptor, facilitates the COVID-19 virus to infiltrate host cells, is intensely expressed in testicular cells. Furthermore, inflammatory responses induced by COVID-19 infection can lead to systemic oxidative stress. *Conclusion:* The testes are a potential target of COVID-19, resulting in testicular damage. Therefore, the immediate or late impacts on male fertility brought about by COVID-19 cannot be ruled out. Definitive data to track reproductive functions in men who have recovered from COVID-19 have not yet been obtained, although studies are underway to establish this association in male health.

Keywords: Infections; COVID-19; Infertility; Viruses; SARS-CoV-2.

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INTRODUCTION

Fertility is defined as the adequate functioning of the female and male reproductive systems. In broader terms, the function of these systems is to synthesize ova, spermatozoa, and the hormones involved in reproduction. Hence, infertility is a disease of the reproductive organs, which makes a couple incapable of reproducing after 12 months of unprotected sexual relationships. Infertility can be caused by female, male, both, and idiopathic disorders¹.

It is important to point out the difference between infertility and sterility, which are often misunderstood. Sterility is the incapacity to conceive or beget a child, whereas infertility is the inability to get herself/the partner pregnant². Since infertility can be caused by various factors, even the most comprehensive examination – including physical, serological, and hormone tests – can fail to detect the etiology of reproductive disorders³.

The disease caused by the new Coronavirus 2019 (COVID-19) has caused a worldwide viral pandemic, emerging in East Asia and rapidly spreading to other continents. The COVID-19 is a pandemic infection with unpredictable levels of morbidity and mortality in many populations, associated with different comorbidities due to changes in the biological function – including cardiac dysfunction, gastrointestinal changes, chronic kidney disease, diabetes mellitus, liver injury, lung injury, central nervous system risks, ocular risks, and cancer risks⁴. Male patients are at greater risk of infection and symptoms than women diagnosed with COVID-19. The evidence concerning the supposed impact of COVID-19 infection on male reproduction, as well as the potential of virus transmission through the seminal fluids, remains inconclusive. Nevertheless, authors suggest potential testicular damage and subsequent infertility resulting from either a direct viral invasion or a secondary immune or inflammatory response, which may negatively affect fertility in adults⁵.

The aim of this study was to analyze the occurrence of male infertility in patients diagnosed with COVID-19, in order to answer the following research question: What is the extent of male infertility in patients diagnosed with COVID-19?

METHODS

Protocol and registry

This narrative review complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations⁶, aiming at the

most rigorous scientific evidence protocol criteria. Two independent researchers searched for the scientific articles in the MEDLINE (PubMed), LILACS, SciELO, Scopus, Web of Science, and BIREME databases, with no restriction of language and place of publication, encompassing the period from 2015 to 2020.

The research was structured and organized in the PICOS framework, an acronym that stands for target **P**opulation, **I**ntervention, **C**omparison, and **O**utcomes. The population of interest or health problem (P) correspond to men with no age restriction; intervention (I): COVID-19 diagnosis; comparison (C), infertility; outcome (O): COVID-19; (S): cross-sectional studies, observational studies, descriptive studies, case-control studies, controlled clinical trials, and opinion pieces.

Research strategy

The descriptors were selected from the dictionaries in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), due to their wide use by the scientific community to index articles in the PubMed database. The search in the other databases was adjusted based on the descriptors. At first, the following Boolean operators were proposed for the search: (COVID-19) or (infertility) and (male) or (male infertility).

Eligibility criteria

Studies were included with no restriction of language, date, and place of publication. The studies readable according to the protocol by Pithon et al.⁷ which evaluates their quality.

Risk of bias

The quality of the methods used in the studies included here was independently evaluated by the reviewer, following the PRISMA recommendations⁷. The evaluation gave priority to clearly described information. In this stage, the review was blind, masking the names of authors and journals to avoid any potential bias and conflict of interest.

Exclusion criteria

Studies published as letters to the editor, guidelines, literature reviews, systematic reviews, meta-analyses, and abstracts were excluded. Studies with absent or unclear descriptions, or not fully available were also excluded.

Data analysis

The data were extracted for the study eligibility process using an appropriate spreadsheet for narrative reviews, developed by two researchers in Excel software, version 16.0 (Microsoft, EUA). The extracted data were entered into the spreadsheet by one of the researchers and

then checked by another one. The studies were selected at first by their title; then, the abstracts were analyzed, and only the potentially eligible ones were selected. Based on their abstracts, the articles were selected to be fully read. Those that met all the pre established criteria were included.

Study selection process

Initially, the eligibility reviewer was calibrated to conduct the narrative review. After calibrating and answering questions, the titles and abstracts were independently examined by an eligibility reviewer, who was not blind to the name of the authors and journals. Those whose title was within the context, but the abstract was unavailable, were also retrieved and analyzed in full. Studies not within the context, case reports, letters to the editor and/or editorials, literature reviews, meta-analysis, indexes, abstracts, and studies on animals were excluded. Afterward, the preliminarily eligible studies had their text retrieved and fully analyzed. In specific cases when a

potentially eligible study had incomplete data, the authors were contacted via email for further information.

Collected data

The year of publication, place of the research, language of publication, type of study, sample, method, result, and conclusion of the study were identified.

RESULTS

Initially, 532 articles were selected, narrowed down to 494 after excluding the repeated ones; then, the titles and abstracts were analyzed, and 490 papers were excluded for not being in the scope proposed for the research. Hence, two articles were included in the final analysis of the present research^{8,9}. The selected studies were designed as descriptive study.

The databases were consulted based on the selected descriptors, obtaining the results presented in Table 1.

Table 1. Classification of the references obtained from the PubMed, SciELO, LILACS, Web of Science, and Scopus databases.

Descriptors	Total number of articles	Number of excluded references	Reason for exclusion	Number of selected articles	Database
(COVID-19) and (SARS-CoV-2) or (infertility) and (male) or (male infertility)	0	-	-	-	SciELO
(COVID-19) and (SARS-CoV-2) or (infertility) and (male) or (male infertility)	0	-	-	-	LILACS
(COVID-19) and (SARS-CoV-2) or (infertility) and (male) or (male infertility)	0	-	-	-	Web of Science
(COVID-19) and (SARS-CoV-2) or (infertility) and (male) or (male infertility)	0	-	-	-	Scopus
(COVID-19) and (SARS-CoV-2) or (infertility) and (male) or (male infertility)	104	102	Excluded by title (60); excluded by abstract (30); Duplicated (¹⁰); other types of study (2)	2	BIREME
(COVID-19) and (SARS-CoV-2) or (infertility) and (male) or (male infertility)	428	428	Excluded by title (300); excluded by abstract (100); Duplicated (28)	0	PubMed
Total	532	530		2	BIREME

Source: Developed by the authors

The main characteristics of the pieces of research selected for this study are shown in Table 2.

Table 2. Summary of included articles.

Author/Year/Place	Objective	Results	Conclusion
Dutta; Sengupta ⁹ 2021 Malaysia	To precisely present the possible impact of COVID-19 on the male reproductive functions and highlight the speculations that require in-depth research on the exact underlying mechanisms of how COVID-19 is associated with men’s health and fertility.	The angiotensin-converting enzyme 2 receptor, which helps SARS-CoV-2 enter the host cells, is intensely expressed in the testicular cells. Also, the endogenous androgenic environment and their receptors are associated with ACE2 activation, indicating that increased testosterone levels can trigger the COVID-19 pathogenesis. On the contrary, hypogonadism has also been reported in the acute phase of some COVID-19 cases. Also, the uncontrolled inflammatory responses induced by SARS-CoV-2 infection can lead to systemic oxidative stress (OS), whose severe disruptive effects on the testicular functions are well documented.	The testicles are a potential SARS-CoV-2 target, and testicular damage can be theoretically explained, as well as infertility after COVID-19 infection. A direct invasion of SARS-CoV-2 is caused by angiotensin-converting enzyme 2 receptors, probably causing direct testicular damage, or affecting the testicular functions with secondary immune and inflammatory responses.
Aitken ⁸ 2021 Australia	To highlight the evidence that the male reproductive system, particularly the spermatozoa, is another vulnerable target, raising the possibility that COVID-19 can eventually induce male infertility and/or facilitate the sexual transmission of this virus, depending on the level of infection.	The destination of angiotensin-converting enzyme 2 after interacting with COVID-19 is complex and depends on the type of cell. Also angiotensin-converting enzyme 2 cleavage after being exposed to COVID-19 decreases the viability and function of the sperm, causing a loss of fertility. With the presence of these activating proteases along with angiotensin-converting enzyme 2 on the plasmatic membrane of the sperm, the COVID-19 virus is expected to connect to the cell surface and merge with it, in both the testicles and epididymis when these cells stay there for long.	So far, no definite data has been obtained to screen the reproductive functions in men who recovered from COVID-19. Since male infertility has already been showing a global decline trend – which is a great threat to humankind – it is essential to conduct complete research to reveal the exact impact and mechanism through with the COVID-19 pandemic can affect the parameters of male fertility.

Source: Dutta; Sengupta⁹, Aitken⁸.

Legend: Angiotensin-converting enzyme 2 - ACE2

COVID-19 and angiotensin-converting enzyme (ACE2)

The first study indicates that COVID-19 may have a physiopathological impact on the testicles, suggesting that the virus infection reduces the testosterone with a significant impact on these cells’ response capacity⁸. The second study expounds that the ACE2 receptor plays an essential role in COVID-19 pathogenesis⁹. The SARS-CoV-2 connection to the ACE2 receptors allows its entrance and cell replication, as the testicles have a large amount of ACE2 receptors. The four main types of testicular cells with ACE2 expression are those of the seminiferous tubules, the spermatogonia, Leydig cells, and Sertoli cells⁹. The presence of COVID-19 in human spermatozoa affects the activity of the ACE2, causing it to accumulate and thus increase the phagocytosis of spermatozoa. Since ACE2 also stimulates the acrosome reaction in human spermatozoa, the prolonged exposure to high ACE2 levels because of COVID-19 infection may lead to premature acrosomal exocytosis and aged sperms⁸.

The destination of ACE2 after interacting with

COVID-19 is complex and depends on the type of cell. Likewise, ACE2 cleavage after exposure to COVID-19 decreases the feasibility and function of the sperm, inducing a loss of fertility. Also, the ACE2 processing on the surface of human spermatozoa can effectively transform these cells into viral vectors, capable of sexually transmitting the virus. The COVID-19 virus aims to connect to the cell surface and merge with it, both in the testicles and in the epididymis when these cells stay there for long. In this regard, it must be highlighted that the spermatozoa can carry viral infections from the male to the female reproductive tract, as in the sexual transmission of the Zika virus, for instance⁸.

COVID-19 and oxidative stress (OS)

SARS-CoV-2 can work through mechanisms that may interrupt male reproductive functions. It has been suggested that this virus activates routes sensitive to the oxidants through inflammatory responses, thus OS – which has a common pathological mechanism to interrupt various physiological functions with oxidative damage to the person’s tissues. The OS can affect the quality of

the semen and interrupt the functions and morphology of the spermatozoa. Moreover, the SARS-CoV-2 infection causes psychological stress, one of the main causes of systemic OS⁹.

Patients post-COVID-19 infection and infertility

Few opportunities are left to study the reproductive competence of patients who recovered from COVID-19 infection, which can make research more difficult. It must also be evaluated to what extent COVID-19 triggers an early ACE2 discharge on the spermatozoa surface and whether the loss of this enzyme increases the rate of sperm aging and cell death⁹. Besides the direct relationship between SARS-CoV-2 infection and OS, COVID-19 treatment includes antiviral drugs such as ribavirin, which has been proved to be associated with OS induction, decreased testosterone level, impaired spermatogenesis, and spermatid abnormalities in studies with animals⁹.

DISCUSSION

Even though up to now no study has confirmed the influence of SARS-CoV-2 on the testicles or semen parameters, data from a previous coronavirus outbreak furnish critical information on its possible impact on male fertility¹⁰. ACE converts angiotensin I to angiotensin II. ACE2 is an endogenous counter-regulator of the ACE system that deactivates angiotensin II. SARS-CoV-2 enters human cells using ACE2 as a receptor with strong connection affinity¹¹.

Authors participation: *Laura Faustino Gonçalves*: Conception and/or study design; preliminary writing. *Janaina Viana Stolz*: Analysis or interpretation of data. *Patricia Haas*: Conception and/or design of the study; analysis or interpretation of data. All authors approved the final version and agreed to be accountable for all aspects of the work.

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According to the authors, ACE2, angiotensin, and their receptors in the testicles are present specifically in the Leydig and Sertoli cells. Although the testicular ACE2 expression can indicate the possible entrance of the virus into the testicles, there is yet no consensus in the literature on this subject¹².

Despite the lack of consensus in the scientific literature, there evidently are testicular injuries and inflammatory infiltration, changes in semen parameters, and an increase in the number of spermatozoa with fragmented deoxyribonucleic acid (DNA). These results suggest that the SARS-CoV-2 infection may lead to fertility problems¹³. There is currently limited data on the potential SARS-CoV-2 infection routes in the respiratory, cardiovascular, digestive, urinary, and reproductive systems. In this regard, the data on virus load in the semen or testicular biopsies of patients infected with SARS-CoV-2 are minimal¹⁴.

CONCLUSION

The impact of COVID-19 on fertility must be studied in recovered patients, with enough evaluations to result in more significant evidence since this viral disease has a long-lasting impact. Recovered COVID-19 patients form an ideal group of people to study its impact on spermatogenesis and fertility. COVID-19 uses ACE2 as a receptor to enter the human cells, and it has been verified that angiotensin-converting enzyme 2, angiotensin, and their receptors are present in the testicles, particularly in the Leydig and Sertoli cells.

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