Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)
ISSN: 2349-2759
Available online at www.jipbs.com

Review article

SARS-COV-2 and female reproductive system

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Received on: 24/03/2022, Revised on: 22/04/2022, Accepted on: 10/05/2022, Published on: 15/07/2022.

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Keywords: COVID-19; female reproductive system; ACE 2.

Vol. 9 (3): 01-05, Jul-Sep, 2022.

DOI: http://doi.org/10.56511/JIPBS.2022.9301

Abstract

Virus SARS-CoV-2, which causes COVID-19 infection, is transmitted mainly by respiratory droplets and its clinical manifestations vary according to the severity of the disease. The respiratory system is the most affected, but other possible forms of transmission are hypothesized. SARS-CoV-2 enters the cell through the binding of the spike protein of the virus with the ACE2 receptor (angiotensin-converting enzyme 2), but it can also be mediated by proteases or cathepsins. The aim of this study is to evaluate the relationship between the COVID-19 virus and the female reproductive system, and to investigate the possibility of transmission of SARS-CoV-2 through the vaginal fluid. A literature review was carried out in the PubMed, Scielo and Web of Science databases, using the terms: "covid and female genitourinary tract", "covid and cervical sample", "covid and HPV", "covid and intraepithelial lesions", "covid and female genital tract". Despite the few reports on the subject, some of them point to the presence of SARS-COV-2 in samples of vaginal fluid, identified by the PCR technique. Additional studies are needed in order to establish a relationship between the findings in the vaginal fluid and the correlation with infection and viral load.

Introduction

Although the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) preferentially affects the respiratory system, its presence has already been identified in multiple organs [1], including heart, lung, liver and pancreas. Furthermore, there is increasing evidence that the virus can also reach the genitourinary system, involving testis, ovary, vagina, uterus and placenta [2, 3]. Recently, the hypothesis that the virus attacks the cervix has been raised, considering that it is commonly affected by another virus, the human papillomavirus (HPV). This hypothesis is supported by the fact that HPV, a virus with tropism for the cervix, and coronavirus share common characteristics in terms of transmission processes and life cycle, although they do not have genetic similarities [1].

When the coronavirus invades the target cell, it binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which modulates the levels of angiotensin II and angiotensin 1-7 in cell process, and so, human cells with ACE2 expression are believed to be the target of SARS-CoV-2 infection. In the female reproductive tract, ACE2 is related to oocyte maturation, ovulation and spermatogenesis [4], steroid secretion, and can still be found in endometrial cells. Based on this, it is hypothesized that SARS-CoV-2 could interfere with female reproductive functions through the regulation of this enzyme, which could cause infertility and menstrual disorders [5], although the potential risk of COVID-19 infection in female fertility must be secured afterwards.

Given the limited knowledge regarding SARS-CoV-2 viral infection in the uterine cervix and female reproductive system, the aim of this study is to verify whether SARS-CoV-2 interferes with the physiology of the female reproductive system as well as its relationship with ACE2. For this purpose, the literature was evaluated regarding the presence of the virus in the vaginal fluid, as well as the relationship of ACE2 activity in the female reproductive system and its relationship with COVID-19.

Materials and Methods

This study consists of a literature review using *PubMed*, *Scielo* and *Web of Science* databases. As a research strategy, the keywords were used: "covid and female genitourinary tract", "covid and cervical sample", "covid and HPV", "covid and intraepithelial lesions", "covid and female genital tract". For this research, no date filters or language restrictions were used.

The studies that were eligible for this review described the expression of SARS-CoV-2 in vaginal fluid. Articles that dealt with this virus with other pathologies or with the male reproductive system were excluded.

Duplicate citations were removed and all remaining studies were selected for eligibility by reviewing their titles and abstracts. Studies that contained only the abstract were excluded due to the limited availability of information that would satisfy the eligibility for analysis of the results of interest. After applying these criteria, an in-depth review of the studies was carried out and the data were extracted in an Microsoft Excel spreadsheet.

Results

Based on the search terms, 647 articles were initially found and after initial analysis and application of inclusion and exclusion criteria, 15 articles reached the objective of this review. The search strategy and the method used for the selection of studies are shown in Figure 1.

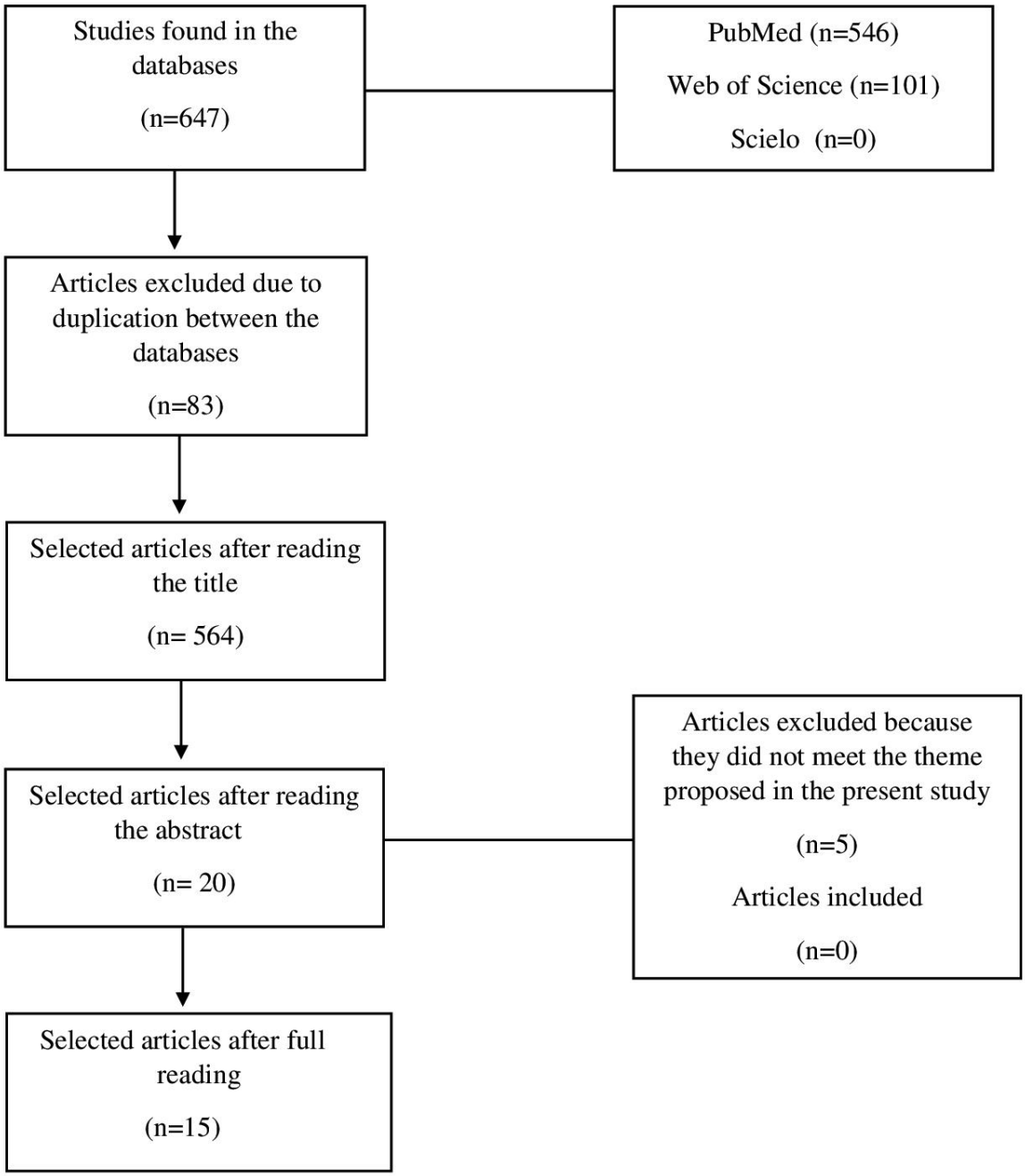

Figure 1. Flowchart of the study selection process for this review.

The table below (Table 1) briefly explains the perspective in each of the following studies eligible for the formulation of this article, regarding the possible expression of the SARS-CoV-2 virus in the Female Reproductive System.

Table 1. Studies included in the review that relate the number of women tested or studies and expression of SARS-CoV-2 in the Female Reproductive System.

Year/Country	Title	Number of individuals or studies	SARS-CoV-2 Expression in the Female Reproductive System
2020/Greece	SARS-CoV-2 infection and impact on female genital tract: An untested hypothesis [1].	21 studies	Although it elucidates that further studies are needed to define this hypothesis, it suggests that the presence of COVID-19 genetic material in cervical cytology sample.
2021/China	SARS-CoV-2 effects in the genitourinary system and prospects of sex hormone therapy [2].	88 studies	The SARS-CoV-2 virus can invade the genitourinary system, causing urological symptoms, in this way, it is necessary to identify potential compromises of genitourinary organs and protect them from damage.
2020/USA	Female reproductive tract has low concentration of SARS-CoV2 receptors [3].	19 studies	The findings suggest that the uterus is unlikely to be susceptible to infection by SARS-CoV 2 in humans.
2020/China	A review of severe acute respiratory syndrome coronavirus 2 infection in the reproductive system [4].	27 studies	The risk of SARS-CoV-2 attacking the reproductive system is higher in men than women. Furthermore, no damage to the female reproductive system of COVID-19 patients has been reported.
2020/China	Potential influence of COVID-19/ACE2 on the female reproductive system [5].	91 studies	It concluded that the SARS-CoV-2 virus can infect the ovary, uterus, vagina and placenta through the ubiquitous expression of ACE2. And also the SARS-CoV-2/ACE2 link can disrupt female reproductive functions.
2021/China	Potential effects of COVID-19 on reproductive systems and fertility; assisted reproductive technology guidelines and considerations: a review [6].	59 studies	It revealed low overall endometrial susceptibility to SARS-CoV-2, and an increased susceptibility to endometrial infection in older women, and during the secretory phase.
2011/Brazil	Angiotensin-(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary [7].	24 patients	Angiotensin-(1-7) and the receptor Mas were localized to primordial, primary, secondary, and antral follicles, stroma, and corpora lutea of reproductive-age ovaries.
2020/Georgia	Endometrial susceptibility to SARS CoV-2: explained by gene expression across the menstrual cycle [8].	5 studies	The findings suggest a low risk of endometrial infection with SARS-CoV-2. However, existing evidence suggests that the expression of genes related to SARS-CoV-2 infection varies with age and menstrual cycle phase.
2020/China	Severe acute respiratory syndrome coronavirus 2 detection in the female lower genital tract [9].	35 patients	SARS-CoV-2 was not found in vaginal fluid and cervical exfoliated cells. Results showed that the lower female genital tract might not be a transmission route for SARS-CoV-2.
2020/China	SARS-CoV-2 Is Not Detectable in the Vaginal Fluid of Women With Severe COVID-19 Infection [10].	10 patients	The findings indicate that the SARS-CoV-2 virus is not present in the vaginal fluids of critically ill COVID-19 patients.
2020/Israel	Detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vaginal swabs of women with acute SARS-CoV-2 infection: a prospective study [11].	35 patients	Positive vaginal RT-PCR was found in 2 women, one of them in perimenopause and the other, after premenopause.
2021/Czech Republic	SARS-CoV-2 RNA may rarely be present in a uterine cervix LBC sample at the asymptomatic early stage of COVID 19 disease [12].	23 patients	Presence of SARS-CoV-2 RNA in liquid-based cervical cytology (LBC) samples in 01 asymptomatic 26-year-old patient.
2021/USA	Detection of COVID-19 in a Vulvar Lesion [13].	1 case report	Case report of 01 pregnant patient with a positive vulvar lesion for severe acute respiratory syndrome-COVID by viral swab.
2020/Turkey	SARS-CoV-2 is not present in the vaginal fluid of pregnant women	12 patients	SARS-CoV-2 was not present in the vaginal fluid of pregnant women, which may indicate that the female genital tract is not a

	with COVID-19 [14].		transmission route for SARS-CoV-2.
2020/Turkey	Evaluation of the presence of SARS-COV-2 in the vaginal fluid of reproductive-aged women [15].	18 patients	The SARS-CoV-2 virus has not been detected in the vaginal fluid of patients who tested positive for COVID-19 in the reproductive period.

Discussion

The SARS-CoV-2 virus enters the body by binding the spike protein (S protein) with ACE2 enzyme, which is present in host cells. The entry into cells is also mediated by Transmembrane Serine Protease 2 (TMPRSS2), and in the absence of these, the cathepsins CTSB and CTSL [3]. Although ACE2 may facilitate virus entry into the epithelial surface, the ACE2/Angiotensin 1-7 Axis may reduce SARS-CoV-2 infection, providing protective effects against lung and kidney damage in patients with COVID-19, which represents a potential target for therapeutic intervention [2].

It is suspected that SARS-CoV-2 can infect the ovary, uterus, vagina and placenta through the expression of these genes in cells of the female reproductive system [6]. In that case, the oocytes and embryos are therefore susceptible to the SARS-CoV-2 infection, once ACE2 receptors are present in the female reproductive system and gonadotropin-dependent expression of ACE2 has been reported in human ovaries. Therefore, ACE2 Mrna transcripts could be detected in ovaries from reproductive-aged women to postmenopausal women [7]. It is suggested that downregulation of ACE2 by SARS-CoV-2 has an impact on oocyte quality and fertility; however, further studies are needed to prove the possible relationship of the SARS-CoV-2 virus on female fertility [6].

Angiotensin-converting enzyme 2 (ACE2) are also present in male reproductive system, and based on that, some positive tests using the polymerase chain reaction (PCR) technique were found in sêmen [6]. There are few data regarding vaginal colonization by the virus, which is clinically significant especially due to the risk of sexual and vertical transmission during childbirth [6].

Hypotheses suggest that the SARS-CoV-2/ACE2 binding in the female genital tract may disrupt reproductive functions, which could lead to infertility, menstrual disorders, and fetal distress [5]. The evidence of increased expression of ACE2 and Ang 1-7 receptors in the secretory phase of the menstrual cycle, raises the possibility that the endometrium is more susceptible to SARS-CoV-2 during this phase. However, one study [6] found low endometrial susceptibility to SARS-CoV-2. The authors also reported a positive correlation between age and virus gene expression, suggesting greater susceptibility to endometrial infection in older women.

Despite the low expression of ACE2 in endometrial tissue, this fact does not totally exclude the risk of infection, as other proteases such as TMPRSS4 (Transmembrane Serine Protease 4), CTSL (Cathepsin L), CTSB (Cathepsin B) and FURIN (Furin, Paired Basic Amino Acid Cleaving Enzyme) showed high expression during certain periods of the menstrual cycle. It is suggested that ACE2 expression varies with age, however, the endometrium appears to have low susceptibility to SARS-CoV-2 infection due to low expression of ACE2 and TMPRSS2 [8]. Conversely, one research [3] revealed very low expression of ACE2 in uterine stromal cells and endothelial cells, as well as not detecting TMPRSS2 expression in any uterine cell. Therefore, as no co-expression of ACE2 was found with any of the proteases involved in the entry of the SARS-CoV-2 virus, these authors indicated that the uterus is unlikely to be affected.

In agreement with the aforementioned research, a study carried out in China evaluated samples from the lower genital tract for SARS-CoV-2, and found negative results. The authors believe that the result is due to the negative expression of ACE2 in the vagina and cervix, and suggest that the lower female genital tract is not a route of transmission of SARS-CoV-2 [9]. Another study [10] corroborated these data when it evaluated samples obtained from vaginal swabs with all samples negative for the virus.

On the other hand, a study [11] evaluated 35 samples of women positive for SARS-COV2, and among them 2 had a positive vaginal RT-PCR, one patient being 86 years old and the other 21 years old, suggesting that the incidence of SARS-CoV-2 vaginal colonization is low. In another case, the virus was identified in a 26-year-old female patient, but with a low viral load, both in the cervical sample and in the nasopharyngeal swab, thus, it was assumed that the patient was at an asymptomatic early stage. This data suggests that cervical samples had a low risk of exposure to SARS-CoV-2, even during the viral incubation period after a positive nasopharyngeal test [12].

There is also a report in the literature that describes a patient who was regularly monitored due to HPV infection and was affected by SARS-COV-2. After recovery from the viral infection, the patient was diagnosed with Cervical Intraepithelial Neoplasia 1 (CIN1). Although it is not possible to correlate SARS-COV-2 infection and the development of CIN1, dysregulation of the immune system is considered a known factor for the occurrence of cervical pathology. Thus, it is pertinent to alert patients infected by HPV and contaminated by COVID-19, to be observed more regularly to optimize early detection of lesions [1], which may have contributed to the appearance of cervical lesions.

The first report of the detection of SARS-COV-2 in a vulvar lesion was published in 2020. The study described the finding in a pregnant patient with 26 years old, who in a prenatal consultation reported, in addition to mild symptoms of COVID-19, a complaint of vulvovaginitis. The presence of the virus was identified in a vulvar lesion and nasopharyngeal swab. This case shows that COVID-19 is

detectable in the vulva, serving as a warning to health professionals [13].

Although the virus mainly spreads through respiratory droplets, sexual transmission of SARS-CoV-2 has not been clearly demonstrated nor excluded to date [14]. Eighteen women who were in their reproductive years and diagnosed with severe COVID-19 pneumonia were included in a study, and all tested negative for the virus. The large number of HPV-negative cervical samples suggests that the ACE2 receptor is not present in the vaginal epithelium [15].

Conclusion

The potential risk of SARS-CoV-2 infection in the reproductive system and its effects cannot be ignored. Although scarce, data from publications in this area are still controversial and little explored. Considering the lack of descriptions and the limitations of the studies included in this research, additional studies are needed in order to provide detailed clinical data on SARS-CoV-2 in the female genital system, as well as the possible sexual transmission in patients whose virus has been detected in the vaginal fluid. Nevertheless, although vertical transmission of COVID-19 has not been definitively demonstrated, the presence of detectable virus in the lower genital tract should lead to continued studies of this possibility, which can be significant in a variety of settings in health care.

Acknowledgments

We thank all the collaborators for the writing of this study, and in particular, the Pro-rectory of Extension (PROREXT) of UFRGS.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this review article.

Authors Contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

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