The Impact of COVID-19 on Gametes and Endometrium: A Narrative Review

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ABSTRACT

The Coronavirus disease 2019 (COVID-19) has been affecting our lives since December 19. Naturally, during the COVID-19 outbreak, it has become a point of interest whether severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection might affect oocyte, and sperm and influence the implantation during the assisted reproductive technology cycles. In the current narrative review, we aimed to scrutinize articles about SARS-CoV-2 infection and infertility concerning the safety of gametes and the endometrium. Whereas the available data suggest that SARS-CoV-2 interferes with various types of molecular pathways in the oocyte, spermatozoa, and endometrium, the lack of co-expression in angiotensin-converting enzyme 2 and transmembrane protease serine 2 in those cell lines theoretically avoid concerns by patients and reproductive endocrinologists. However, one should consider that those observations were based on a few case series and should be confirmed with further observational studies including a larger sample size with various clinic spectrums. Alternative pathways that can be utilized by the virus to invade gametes and individual differences in molecular expression are other potential limitations that should be considered.

Keywords: Assisted reproductive technology, COVID-19, Fertility

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Introduction

Each of these pandemics was frightening and had high fatality individually. However, none of them had a worldwide invasion such as COVID-19. The COVID-19 pandemic had affected about 108 million people and caused about 2.4 million deaths according to World Health Organization (WHO) until the end of February 2021. This tragic pandemic has changed all clinical mechanisms around the world, because of its spreading pattern, overloading service, intensive care beds, and hence fatality rate. Many specialties stopped or reduced their routine activities except for gynecology and obstetrics. In this context, we might assume that, in a pandemic triage, there are some critical non-deferrable conditions including cancers, chronic diseases, and pregnancy. In those days, it was noticed that one of such non-deferrable conditions might be the motivation for childbearing. As scientists know more about this virus and disease, many more scientific and medical questions are raised to be answered. Besides all these questions and answers, it has become how this virus might affect reproductive organs, gonads, oocytes, sperm, gametogenesis, and embryos in humans.

As it's currently very well-known, the virus binds angiotensin-converting enzyme 2 (ACE2) receptors with its spike protein (Protein S) and transports it into the cells via transmembrane protease serine 2 (TMPPRS2). TMPRSS2 primes protein S and provides the virus to enter the target cell. That's why the virus needs not only the ACE2 receptor but also the ACE2 receptor and TMPRSS2 together to be able to infect a cell (Figure 1). There is another protein called Basigin (BSG) as a SARS-CoV-2 binding receptor (1-2). In this respect, it is important to document those receptors and proteases in gametes and embryos or endometrium to theoretically assume whether it might infect or not those cells and tissues.

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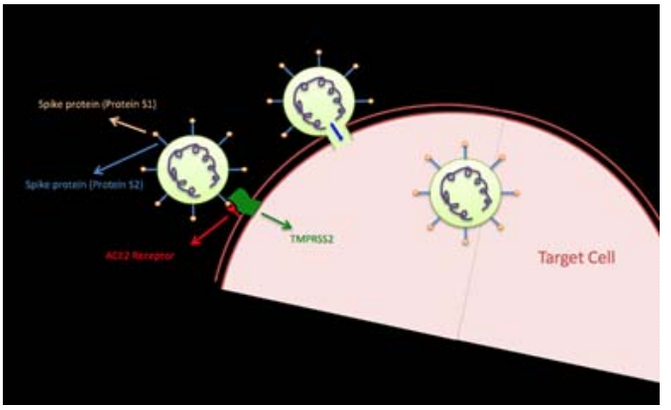

Figure 1: *It is a schematic picture showing the coronavirus is connected to ACE2 receptors with protein S on it and can move into the cell with TMPPRS2.*

The current article aims to review the association between SARS-CoV-2 and oocyte, sperm and endometrium in light of recent information.

Oocyte

SARS-CoV-2 binds certain types of receptors and activator proteins to be able to infect a tissue or a cell. Whereas ACE2 and BSG are associated receptors, TMPRSS2 and cathepsin L (CTSL) are established activator proteins (1-3). According to available data, mRNAs (messenger RNA) of these genes are expressed in most of the human female reproductive tract (4). However, not only the presence of those binding points solely but also the co-existence of those receptors and activator proteins are highly crucial to speculate about the potential host reaction of a given tissue.

In the study of Stanley et al., three non-human primate ovarian tissue and 18 human cumulus cells from 18 independent oocytes of nine patients were studied. Co-expression of ACE2 and TMPRSS2 in oocytes appeared to increase as the follicles progressed through development. Whereas oocytes in primordial follicles had minimal co-expression, 62% of antral follicles had a detectable expression of both ACE2 and TMPRSS2 (Pearson correlation value=0.37) (5). Therefore, antral follicles appear to have the highest susceptibility to infection. However, given the fact that antral follicles undergo ovulation and atrophy in each cycle, SARS-CoV-2 is not thought to have a permanent effect on female gamete cells.

Other than non-human primate studies, a total of 16 oocytes (six oocytes from patient A and 10 oocytes from patient B) were evaluated from those retrieved from two confirmed SARS-CoV-2 positive asymptomatic women (4). According to that, in a single study conducted from human material, it was noticed that the ribonucleic acid (RNA) for the SARS-CoV-2 gene was undetectable but ACE2 expression was noticed in <30% of the oocytes. In addition, TMPRSS2 expression has never been detected but BSG and CTSL were observed in all oocytes. Although those findings were significant to assume that oocytes are theoretically safe to be getting infected by SARS-CoV-2, one should be cautious that those women were asymptomatic and there might be individual differences concerning distribution in receptor and binding potential.

Lastly, most recently, with the presentation of a 35 years old patient who received in vitro fertilization (IVF) treatment and had a positive SARS-CoV-2 polymerase chain reaction (PCR) test taken from a nasopharyngeal swab during oocyte pick-up procedure, PCR analysis for SARS-CoV-2 viral RNA was found to be negative in the follicular aspirate taken from both ovaries (6).

Sperm

Global data show that the mortality rate of SARS-CoV-2 cases is higher in men than in women (7). Therefore, one might expect distinct expression of ACE2 and associated protein expression in male than female patients. Nevertheless, there is some evidence linking the high expression of ACE2 with infertility in male human cases (8). This finding might be related to the observation that Protein-S on COVID-19 specifically targets ACE2 and in so doing removes an important stimulus for phosphoinositide 3-kinase/ protein kinase B (PI3K/AKT), thereby might compromise sperm viability (9). Interestingly, the number of cells that were ACE2 positive was found more frequently in a 30 years old male patient when compared with men in their 20s and 60s. That report might stress a particularly increased risk of infertility in male patients around 30s (10-11).

Although the blood testicular barrier has been considered an anatomical defense barrier against microorganisms, viral infections such as human immunodeficiency virus (HIV), hepatitis, and mumps have been shown to infect testicular tissue. Since it has been shown that the testosterone-luteinizing hormone ratio is decreased in SARS-CoV-2 patients; it might be possibly related to the infection of testicular tissue with SARS-CoV-2 which once again avoids the general belief of barrier theory (12-13). Nevertheless, in a study by Aitken et al., which included 38 semen samples taken from patients infected with SARS-CoV-2, RT-PCR (real time-polymerase chain reaction) analysis determined SARS-CoV-2 in six semen samples. Of those six samples, four were collected from men during the acute phase of the infection, and two were in the period of recovery (9).

In the study by Stanley et al., 11 cell types were tested, including the germ and somatic niche cells such as Leydig, endothelial, myoid cells, and macrophages. Additionally, differentiating spermatogonia, early primary spermatocytes, late primary spermatocytes, round spermatids, elongated spermatids, and spermatozoa were also assessed (5). The authors found that whereas a small proportion of spermatogonia stem cells expressed genes of ACE2 and TMPRSS2 separately, co-expressing of both genes was extremely rare with a ratio of 0.05%. In concordance, co-expression of ACE2 and TMPRSS2 was not detected in testicular somatic cells and sper-

matozoa. With regard to the fact that ACE2 and TMPRSS2 co-expression was not detected in any testicular somatic cell type; spermatozoa may not be at risk of SARS-CoV-2 infection (5). However, other than ACE2 and TMPRSS2, alternative receptors and proteases may mediate viral entry in these cells. BSG was more broadly expressed across testicular somatic cell types than ACE2 and was co-expressed with CTSL in early and late primary spermatocytes (78.7% and 90.8% of cells with mRNA transcripts, respectively).

Endometrium

The effect of SARS-CoV-2 on endometrial tissue and implantation is still mostly unknown. In a study by Henarejos-Castillo et al (14), the authors evaluated endometrial susceptibility to SARS-CoV-2 infection by measuring endometrial ACE2, TMPRSS2, TMPRSS4, cathepsin B, cathepsin L, FURIN, MX dynamin-like GTPase 1 (MX1) and BSG gene expression. Gene expression data of 112 women with normal endometrial pathology from five studies were used to determine receptor expression throughout the menstrual cycle. The study population included 29 samples in the proliferative phase, 29 samples in the early secretory phase, 43 samples in the medium secretory phase, and eight samples in the late secretory phase.

The authors reported low expression of ACE2 in the endometrium (15). However, low levels of ACE2 expression do not indicate that the virus does not affect tissue, as ACE2 expression is also poor in lung tissue but it is the primary target for SARS-CoV-2 (16).

Other findings of that study revealed that ACE2 expression in the endometrium increased gradually from the early secretory phase to the medium secretory phase (1⁄4 2.47 of the fold change). In this respect, an increase in the expression profile of ACE2 throughout the implantation window might be crucial for the risk of viral infection at this stage of the menstrual cycle. In addition, there was a positive correlation between age and ACE2 in this study.

Early pregnancy

la Cour Freiesleben et al. conducted a study to determine whether SARS-CoV-2 infection during the first three months of pregnancy affected fetal nuchal thickness and pregnancy loss (17). In this study, 18 women with SARS-CoV-2 antibodies (two women were immunoglobulin M (Ig M) and immunoglobulin G (Ig G) positive, and 16 women were Ig G positive only) and 994 women without antibodies were selected. Median nuchal thickness, free human chorionic gonadotropin (beta-hCG) and pregnancy-associated plasma protein A (PAPP-A) levels and multiple of the median (MoM) values were not significantly different between women with and without SARS-CoV-2 antibodies. Also, after taking maternal age and a gestational week into account, positive antibodies (p=0.81) did not affect nuchal translucency thickness. The authors also reported that they failed to document a significant increase in the risk of pregnancy loss in women with SARS-CoV-2 infection during the first trimester even when they were stratified according to their previous obstetric outcome (17).

Conclusion

According to recent studies, the lack of co-expression in ACE2 receptor and TMPRSS2 proteases on gametes theoretically might be considered preventive findings for viral transmission to the embryo. However, alternative pathways for viral infection, individual differences concerning receptivity, and lack of detailed information particularly in severe cases might obstruct our optimistic view. Therefore, reproductive endocrinologists should follow further data closely throughout our ages to take preventive measures immediately. We still have a lot to learn about COVID-19!

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