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Review Article

Potential effects of COVID-19 on reproductive health: a mini review

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Abstract: Coronavirus disease 2019 (COVID-19) is now a major public health problem worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity is extremely strong. One major target of the virus is the lung, which can lead to death due to the development of respiratory distress syndrome and even multiple system organ failure. The possible pathophysiology by which SARS-CoV-2 affects the object is by way of the receptor, angiotensin-converting enzyme 2 (ACE2). From the study of the viral structure and infection mechanisms, researchers have discovered that the ACE2 acts as a receptor for SARS-CoV-2. According to previous studies, ACE2 is one of the key enzymes in the RAS system. Physiological functions can be found in angiosarcomas and in the kidney, liver, intestine and so on. Whether SARS-CoV-2 infection leads to male fertility impairment has recently received attention. Nevertheless, the association between SARS-CoV-2 infection and reproductive health is currently poorly understood. Using key words including "SARS-CoV-2", "reproductive health", "ACE2" and "2019-nCoV", we retrieved original articles and reviews from the PubMed and WEB OF SCI databases published before December 16, 2020 and performed a thorough review of them. Compared with females, we discovered that infected person with SARS-CoV-2 was higher in males. Men who were infected with SARS-CoV-2 may be easy to suffer from impaired reproductive health. These investigations would help for a comprehensive grasp of the relationship between SARS-CoV-2 infection and reproductive health.

Keywords: SARS-CoV-2, ACE2, sperm, 2019-nCoV, reproductive health

Introduction

Coronavirus disease 2019 (COVID-19) is a communicable disease due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) announced that the COVID-19 outbreak entered a global pandemic on March 11, 2020 [1]. As of December 16, 2020, 7,2196,732 cases and 1630,521 deaths have been confirmed globally (WHO,2020). The sequence of the major genes is 5'-orf1a/b-s-e-m-n-3', including a 5'-end methylated cap and a 3'-end poly A tail [2], which is similar to the mRNA structure of eukaryotes. The virus was found to specifically recognize receptors via the S protein on the surface of cell membranes, angiotensin-converting enzyme 2 (angiotensin I-converting enzyme 2, ACE2) [3, 4] and modulate cell membrane fusion between virus and host. The 5' end Orf1a/B gene is translated by cell protein translation system and RNA polymerase complex is produced. Then applying the template of viral genome produces a negative chain and positive chain. Because templates are from RNA genomes, the infection can therefore lead to viral genome replication [5] (**Figure 1**). In the early stage of COVID-19 infection, most of patients show reduced or normal counts of white blood cell, reduced counts of lymphocyte, high level of C-reactive protein, normal level of procalcitonin and positive findings of imaging examinations. Patients who were severely infected by COVID-19 showed increased

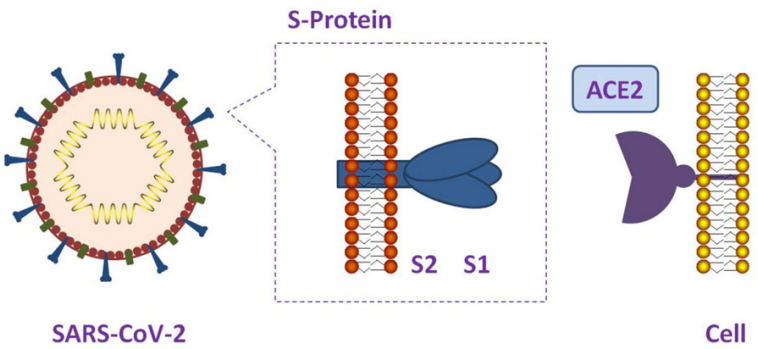

Figure 1. Schematic diagram of the SPIKE protein interaction with the ACE2 protein.

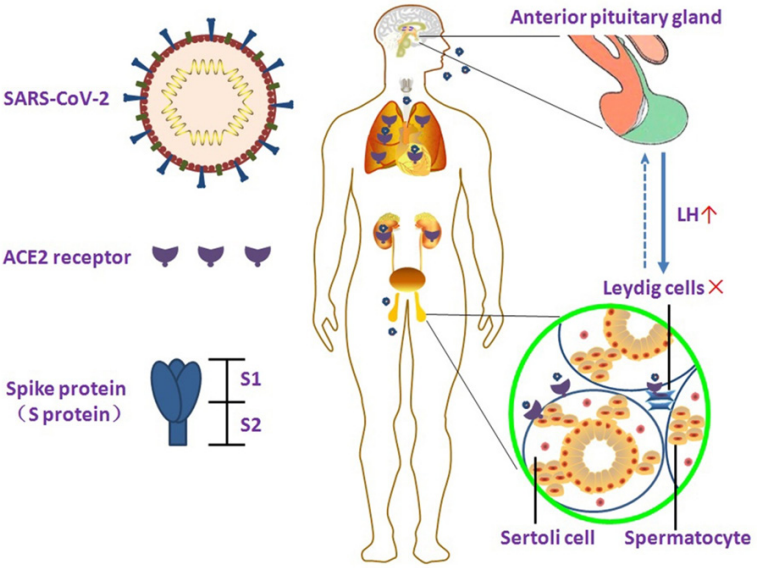

Figure 2. A review of severe acute respiratory syndrome coronavirus 2 infection in the reproductive system [19]. The transmission pathway of SARS-CoV-2 and the impact of male genital organ infection. Several organs (lung, kidney) and male genital cells (Sertoli cells, Leydig cells) that have the ACE2 receptor could be infected by SARS-CoV-2. The damage to Leydig cells caused by viral infection may result in an increased level of LH from the pituitary gland, which could consequently stimulate Leydig cells. Note: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; S protein, spike protein; LH, luteinizing hormone.

proinflammatory cytokines including TNF-α, IFN-γ and IL-6. And some patients even had cytokine storm characteristics [6, 7]. An autopsy of the first patient who died of COVID-19 found diffuse alveolar injury and pulmonary clear membrane formation [8], which was consistent with the manifestations of acute respiratory distress syndrome and similar to the pathological features of SARS and MERS (Middle East respiratory syndrome). More and more data and information about the histopathological changes in multiple organs have been found, especially in the lungs [9, 10]. Nevertheless, data or information about the COVID-19 impact on reproductive health is scarce.

A recent research applying single-cell RNA sequencing showed that the ACE2 receptor can be expressed in germ cells, Leydig cells, and sertoli cells of testes [1] and ovaries [11], which suggests that the testes are a possible target for SARS-CoV-2 infection.

Possibility of the molecular basis of testicular injury by SARS-CoV-2

The cell membranes of relevant tissues (the lung, heart, kidney endothelial cells and/or epithelial cells) express a functional receptor, ACE2, which can be bound by the novel coronavirus. However, ACE2 alone is not enough to induce virus infection in host cells, and the assistance of other viral receptors or "co-receptors" in different tissues is needed to mediate the invasion of the virus into cells [12, 13]. In virus-infected cells, infection depends on the presence of transmembrane serine protease 2 (TMPRSS2) on the cell membrane, which activates the S protein and mediates the entry of the virus into host cells [14, 15]. The expression of ACE2 in Sertoli cells, spermatogonia cells in the tubules of human testes and Leydig cells in the interstitial region, indicates the widespread presence of the novel coronavirus receptors in testicular tissue. Support cells expressed ACE2 at a high level, while early spermatocytes, late spermatocytes and sperm cells expressed ACE2 at very low levels [16, 17] (**Figure 2**). Among the different testicular cell types, the expression patterns of the

TMPRSS2 and ACE2 genes are different, among which, the expression level of the TMPRSS2 gene is the highest in supporting cells, while the expression level of the ACE2 gene is very low, and the TM-PRSS2 gene is also expressed in the interstitial cells [18]. In addition, the BSG, CTSL and CTSB genes associated with COVID-19 were also expressed in different degrees in spermatogenic cells and stromal cells at different developmental stages [18, 19]. Therefore, both spermatogenic cells and somatic cells in the human testis have a molecular basis for the attachment of the novel coronavirus; therefore, the testis has a potential risk for infection by the novel coronavirus. However, whether the novel coronavirus damages the testis and invades the testicular cells and the mechanism involved have not been confirmed.

Female reproduction

Although there is no report about the effect of the novel coronavirus on the female reproductive system, evidence suggests that renin-angiotensin-aldosterone system (RAS) is involved in the female reproductive process, including follicle formation, steroid production, oocyte maturation and ovulation, while there is no effect of the novel coronavirus on the female reproductive tract. Reis et al. [20] confirmed that the Ang (1-7)-MAS receptor-ACE2 axis exists in human ovaries, and ACE2 markers are present at all levels in follicles. ACE2 has also been found in the bovine follicular membrane and in granulosa cells, and its expression has been significantly increased in granular cells that produce dominate follicles, confirming its involvement in follicular development [21]. ACE2 is expressed in the endometrium, mainly in the epithelial cells, but less in the stromal cells. Moreover, its expression level can change with the menstrual cycle, and its expression level is significantly higher in the secretion stage than in the proliferation stage [22]. Combined with the relationship between the expression and distribution of ACE2 and the reported viral pneumonia, it is speculated that novel coronavirus may attack the follicular membrane and granular cells of the ovary, affect the growth of follicles and the quality of oocytes, reduce the ovarian reserve function, and cause female infertility or pregnancy loss. At the same time, it may damage the endometrial epithelial cells and affect early embryo implantation. Previous studies have shown that the incidences of maternal and infant complications such as spontaneous abortion, premature delivery, intrauterine growth restriction and disseminated intravascular coagulation (DIC) in pregnant women infected with SARS are high [23]. Two recent studies, from the Weill Cornell Medical College in New York and Northwestern University, found that some of the placental maternal vessels were damaged and blood clots (which limit the delivery of oxygen and nutrients to the fetus) were significantly increased in women who were pregnant and infected with COVID-19. In general, infection with SARS-COV-2 may indirectly affect fetal growth in pregnant women. A study by the fetal medicine specialist, Malavika Prabhu, suggests that it is necessary to closely monitor fetal growth during the second half of pregnancy in women infected with SARS-COV-2 [24].

At present, the report about COVID-19 affecting pregnancy outcomes is rare. On account of the small number of “susceptible cells” at the maternal-fetal interface in the first trimester, the potential for vertical transmission between mother and child is extremely low [25]. The latest study also indicated that there was no evidence of vertical mother-to-child transmission of SARS-CoV-2. However, relevant literatures regarding SARS-CoV-2 infection in pregnancy, especially pregnancy outcomes are still lacking, which should be considered along with the pregnant woman’s illness and pregnancy situation. If the pregnancy continues, the health of the fetus and the newborn should be closely observed with appropriate follow up. Interestingly, recent literature has shown significant changes in breast milk proteins and metabolism associated with COVID-19 using proteomics and metabolomics. It is worth noting that the altered proteins in the breast milk of COVID-19 patients are mainly involved in the immune response. In breast milk, the downstream metabolites of AAAs metabolized by microorganisms were also significantly altered. Changes in breast milk composition may reflect the mother’s systemic physiological response to SARS-CoV-2 or may be caused by SARS-CoV-2-mediated effects on breast milk production and/or breast secretion. In addition, COVID-19 may affect the microbes in the maternal body, leading to changes in the microbial metabolites secreted into the breast milk. Taken together, this work suggests that

the lack of immune-related components of the breast milk may be detrimental to the early development of the immune defenses in newborns, a possibility that needs further investigation [26]. However, expectant mother who are infected with COVID-19 have higher risk of complications. Although there are regional differences in the rates of undesirable effect, vertical transmission is still possible [27, 28].

Male reproduction

Xu et al. [29] showed that all SARS patients had orchitis at autopsy. The specific symptoms are extensive destruction of germ cells, the thickening of the basement membrane in testicular tissue, the decrease or even complete loss of sperm cells in the spermatogenic tubules, and a large amount of leukocyte infiltration. Recently, Wang et al. [30] reported the high expression of ACE2 in renal tubule cells, testicular stromal cells and spermatogenic cells. Fan et al. studied the expression pattern of ACE2 and the transcription level of TMPRSS2 in single cells of adult testes and showed that ACE2 was mainly concentrated in the spermatogonia cells, stromal cells and supporting cells.

TMPRSS2 expression was concentrated in spermatogonial cells and sperm cells. GO analysis showed that in ACE2-positive spermatogonial cells, the expressions of genes related to virus reproduction and transmission were upregulated, while the expressions of genes related to spermatogenesis were downregulated [31]. In ACE-positive mesenchymal cells and supporting cells, the expressions of intercellular connection genes and immune-related ge nes were increased, and the expressions of reproductive-related genes were decreased [29]. These findings in support cells are particularly important because stromal cells are in charge of androgen biosynthesis and play an important role in the testicular microenvironment. Recent literature has also shown that age is associated with the expression of ACE2 in testicular cells, with the lowest ACE2 expression in the 60-year-old group and the highest expression in the 30-year-old group (2.84%). To some extent, these results suggest that SARS-COV-2 infection may affect the male reproductive system [32].

It is suggested that SARS-CoV-2 infection could influence the male reproductive system. The occurrence and development of SARS-CoV-2 is thought to be due to direct cell infection, which leads to cellular damage. Just as stated previously, ACE2 receptors permit the virus to get into host cells and then accomplish the process of replication cycle. Cells with higher ACE2 mRNA expression have a higher risk of SARS-CoV-2 infection, which may cause male sterility, including a decrease in spermatogenesis, thereby worsening the survival of male gametes [33, 34].

In addition, SARS-CoV-2 may lead to more severe testicular damage in young men of childbearing age than that in older men. Constant high-temperature changes in the testes can cause the degeneration and destruction of germ cells. Fever is a very common symptom related to SARS-CoV-2 and can indirectly cause testicular dysfunction. Pan et al. analyzed semen samples from 34 recovered men diagnosed with COVID-19. There was no SARS-CoV-2 detected in the investigation samples (semen analysis was not performed in the study). Whether semen could transmit SARS-CoV-2 is unclear. During the acute phase of SARS-CoV-2 infection, only 3 semen samples (8.82%) were provided. Moreover, the disease severities of the men recruited in the study were classified as mild. It suggests that the presence of the virus in semen cannot be ruled out (especially in cases of acute infection or severe symptoms) [35]. A total of 38 semen samples were provided. 23 participants were undergoing recovery period and 23 participants were in the acute phase. Semen analysis discovered that the total positive rate was 15.8%. The positive rate of patients who were in the acute stage of infection and undergoing recovery period was 26.7% and 8.7%, respectively [36]. At the same time, a research was conducted to get a better understanding of the effect of SARS-CoV-2 infection by using semen analysis results. Holtmann et al. [37] investigated the semen parameters for 20 patients and 14 healthy volunteers. And 20 patients consisted of 18 recovered patients and 2 acute stage patients. Furthermore, further classification of patients (mild or moderate) was performed according to whether patients were admitted to hospital during the stage of active infection. Patients with an infection of moderate degree showed lower sperm concentration, lower total number of sperm per ejaculate, motile sperm and prog-

ressively motile sperm than patients with mild symptoms and healthy volunteers.

However, the results of these studies were not in agreement but were limited by the sample sizes. Therefore, the relationship between SARS-CoV-2 and male fertility should be urgently investigated and explored [38]. In recent literature, sexually related hormones were compared between SARS-CoV-2-infected men of childbearing age and age-matched healthy men. Serum luteinizing hormone (LH) was significantly increased, but the testosterone (T) to LH and follicle-stimulating hormone (FSH) to LH ratios were significantly decreased in the COVID-19 men. Some of the significant products of Leydig cells are sex hormones (T, rostenedione, and dehydroepiandrosterone). Additionally, LH plays a role in stimulating Leydig cells. Due to the enrichment of ACE2 expression, Leydig cells may lead to a dysfunction as a result of SARS-CoV-2 infection [39, 40]. Considering the potential impact of the virus on the reproductive tissues, some scholars suggest that more attention should be given to the evaluation of gonadal function, especially in men of childbearing age, during hospitalization and subsequent follow-up of COVID-19 patients (**Figure 2**) [41].

Conclusion and prospects

The association of SARS-CoV-2 infection to fertility deficit in males and females is a novel research field. Current studies have shown that the testes and the female reproductive system have a molecular basis where the viruses can attach. A literature review of past and recent studies showed that COVID-19 may have potential effects on both male and female reproductive systems. More analysis of clinical specimens, the application of various experimental techniques and the establishment of effective animal models will reveal the relationship of the infection with the novel coronavirus and fertility deficit. At the same time, medical professionals should make a comprehensive assessment according to the patient's fertility needs, disease status and psychological status to provide reasonable fertility guidance and counseling.

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Disclosure of conflict of interest

None.

Abbreviations

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; LH, luteinizing hormone; S protein, Spike protein; CPR, C-reactive protein; TMPRSS2, transmembrane serine protease 2; RAS, renin-angiotensin-aldosterone system; DIC, disseminated intravascular coagulation.

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References

[1] Yang M, Chen S, Huang B, Zhong J, Su H, Chen Y, Cao Q, Ma L, He J, Li X, Li X, Zhou J, Fan J, Luo D, Chang X, Knarik A, Zhou M and Nie X. Pathological findings in the testes of COVID-19 patients: clinical implications. Eur Urol Focus 2020; 6: 1124-1129.

[2] Chen Y, Liu Q and Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol 2020; 92: 418-423.

[3] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS and McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020; 367: 1260-1263.

[4] Letko M, Marzi A and Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 2020; 5: 562-569.

[5] Mao XD, Li T, Xu Z and Liu K. Pathogenesis of COVID-19 and the quality control of nucleic acid detection. Biochem Biophys Res Commun 2021; [Epub ahead of print].

[6] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, Li W, Tong Q, Yi J, Zhao L, Xiong L, Guo C, Tian J, Luo J, Yao J, Pang R, Shen H, Peng C, Liu T, Zhang Q, Wu J, Xu L, Lu S, Wang B, Weng Z, Han C, Zhu H, Zhou R, Zhou H, Chen X, Ye P, Zhu B, Wang L, Zhou W, He S, He Y, Jie S, Wei P, Zhang J, Lu Y, Wang W, Zhang L, Li L, Zhou F, Wang J,

Dittmer U, Lu M, Hu Y, Yang D and Zheng X. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 2020; 55: 102763.

[7] Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M and Qu J. Clinical features predicting mortality risk in patients with viral pneumonia: the MuLBSTA score. Front Microbiol 2019; 10: 2752.

[8] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J and Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8: 420-422.

[9] Tian S, Hu W, Niu L, Liu H, Xu H and Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020; 15: 700-704.

[10] Zhang H, Zhou P, Wei Y, Yue H, Wang Y, Hu M, Zhang S, Cao T, Yang C, Li M, Guo G, Chen X, Chen Y, Lei M, Liu H, Zhao J, Peng P, Wang CY and Du R. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. Ann Intern Med 2020; 172: 629-632.

[11] Mosleh H, Moradi F, Mehdizadeh M, Ajdary M, Moeinzadeh A and Shabani R. Health concerns regarding the effect of the COVID-19 pandemic on male fertility. Clin Exp Reprod Med 2021; 48: 189-193.

[12] Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L and Wang X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 2020; 581: 215-220.

[13] Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H and Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426: 450-454.

[14] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C and Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271-280, e8.

[15] Heurich A, Hofmann-Winkler H, Gierer S, Liepold T, Jahn O and Pöhlmann S. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. J Virol 2014; 88: 1293-1307.

[16] Douglas G, O'Bryan M, Hedger M, Lee D, Yarski M, Smith A and Lew R. The novel angiotensin-converting enzyme (ACE) homologue, ACE2, is selectively expressed by adult Leydig cells of the testis. Endocrinology 2004; 145: 4703-4711.

[17] Moshrefi M, Ghasemi-Esmailabad S, Ali J, Findikli N, Mangoli E and Khalili MA. The probable destructive mechanisms behind COVID-19 on male reproduction system and fertility. J Assist Reprod Genet 2021; 38: 1691-1708.

[18] Liu X, Chen Y, Tang W, Zhang L, Chen W, Yan Z, Yuan P, Yang M, Kong S, Yan L and Qiao J. Single-cell transcriptome analysis of the novel coronavirus (SARS-CoV-2) as sociated gene ACE2 expression in normal and non-obstructive azoospermia (NOA) human male testes. Sci China Life Sci 2020; 63: 1006-1015.

[19] Huang HH, Wang PH, Yang YP, Chou SJ, Chu PW, Wu GJ and Chang CC. A review of severe acute respiratory syndrome coronavirus 2 infection in the reproductive system. J Chin Med Assoc 2020; 83: 895-897.

[20] Reis FM, Bouissou DR, Pereira VM, Camargos AF, dos Reis AM and Santos RA. Angiotensin-(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary. Fertil Steril 2011; 95: 176-181.

[21] Madjunkov M, Dviri M and Librach C. A comprehensive review of the impact of COVID-19 on human reproductive biology, assisted reproduction care and pregnancy: a Canadian perspective. J Ovarian Res 2020; 27: 140.

[22] Barreta MH, Gasperin BG, Ferreira R, Rovani M, Pereira GR, Bohrer RC, de Oliveira JF and Gonçalves PB. The components of the angiotensin-(1-7) system are differentially expressed during follicular wave in cattle. J Renin Angiotensin Aldosterone Syst 2013; 16: 275-283.

[23] Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, Ng PC, Lam PW, Ho LC, To WW, Lai ST, Yan WW and Tan PY. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 2004; 191: 292-297.

[24] Prabhu M, Cagino K, Matthews KC, Friedlander RL, Glynn SM, Kubiak JM, Yang YJ, Zhao Z, Baergen RN, DiPace JI, Razavi AS, Skupski DW, Snyder JR, Singh HK, Kalish RB, Oxford CM and Riley LE. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: a prospective cohort study. BJOG 2020; 127: 1548-1556.

[25] Zheng QL, Duan T and Jin LP. Single-cell RNA expression profiling of ACE2 and AXL in the human maternal-fetal interface. Reprod Dev Med 2020; [Epub ahead of print].

[26] Zhao Y, Shang Y, Ren Y, Bie Y, Qiu Y, Yuan Y, Zhao Y, Zou L, Lin SH and Zhou X. Omics study reveals abnormal alterations of breastmilk pro-

teins and metabolites in puerperant women with COVID-19. Signal Transduct Target Ther 2020; 5: 247.
[27] Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA and Critchley HOD. Pregnancy and COVID-19. Physiol Rev 2021; 101: 303-318.
[28] Salem D, Katranji F and Bakdash T. COVID-19 infection in pregnant women: review of maternal and fetal outcomes. Int J Gynecol Obstet 2021; 152: 291-298.
[29] Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, Peh S and Gu J. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod 2006; 74: 410-416.
[30] Wang Z and Xu X. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, leydig and sertoli cells. Cells 2020; 9: 920.
[31] Vaz-Silva J, Carneiro MM, Ferreira MC, Pinheiro SV, Silva DA, Silva-Filho AL, Witz CA, Reis AM, Santos RA and Reis FM. The vasoactive peptide angiotensin-(1-7), its receptor Mas and the angiotensin-converting enzyme type 2 are expressed in the human endometrium. Reprod Sci 2009; 16: 247-256.
[32] Shen Q, Xiao X, Aierken A, Yue W, Wu X, Liao M and Hua J. The ACE2 expression in sertoli cells and germ cells may cause male reproductive disorder after SARS-CoV-2 infection. J Cell Mol Med 2020; 24: 9472-9477.
[33] Groner M, de Carvalho R, Camillo J, Ferreira P and Fraietta R. Effects of Covid-19 on male reproductive system. Int Braz J Urol 2021; 47: 185-190.
[34] Wang N, Qin L, Ma L and Yan H. Effect of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) on reproductive system. Stem Cell Res 2021; 52: 102189.
[35] Illiano E, Trama F and Costantini E. Could COVID-19 have an impact on male fertility? Andrologia 2020; 52: e13654.
[36] Pan F, Xiao X, Guo J, Song Y, Li H, Patel DP, Spivak AM, Alukal JP, Zhang X, Xiong C, Li PS and Hotaling JM. No evidence of severe acute respiratory syndrome-coronavirus 2 in semen of males recovering from coronavirus disease 2019. Fertil Steril 2020; 113: 1135-1139.
[37] Holtmann N, Edimiris P, Andree M, Doehmen C, Baston-Buest D, Adams O, Kruessel JS and Bielfeld AP. Assessment of SARS-CoV-2 in human semen-a cohort study. Fertil Steril 2020; 114: 233-238.
[38] Haghpanah A, Masjedi F, Alborzi S, Hosseinpour A, Dehghani A, Malekmakan L and Roozbeh J. Potential mechanisms of SARS-CoV-2 action on male gonadal function and fertility: current status and future prospects. Andrologia 2021; 53: e13883.
[39] Tseng JY. Potential implications of SARS-CoV-2 on pregnancy. Taiwan J Obstet Gynecol 2020; 59: 464-465.
[40] Lai YJ, Chang CM, Lin CK, Yang YP, Chien CS, Wang PH and Chang CC. Severe acute respiratory syndrome coronavirus-2 and the deduction effect of angiotensin-converting enzyme 2 in pregnancy. J Chin Med Assoc 2020; 83: 812-816.
[41] Dutta S and Sengupta P. SARS-CoV-2 and male infertility: possible multifaceted pathology. Reprod Sci 2021; 28: 23-26.