Review Article

Interaction of SARS-CoV-2 With RAS / ACE2 in the Female Reproductive System

Farideh Zafari Zangeneh

Vali-e-Asr Reproductive Health Research Center, Tehran University of Medical Sciences, Tehran, Iran

Received February 2021; Revised and accepted July 2021

Abstract

Objective: The purpose of this review was to investigate current knowledge of COVID-19 by highlighting its effect on female reproductive tract.

Materials and methods: In this study, all articles related to the effect of SARS, MERS, and CoV-19 viruses on the female reproductive system from 2003 to 2021 were reviewed.

Results: The coronavirus enters the host cell by binding to the enzyme that is most abundant in the host lung. The corona or spike (S) protein of this virus is the main tool for binding to the receptor in the host cell membrane and facility the entrance of CoV into the target cells. This receptor is the Angiotensin-Converting Enzyme-2 (ACE2), but the high expression of this receptor can be a mystery to increase infection in host cells. The overexpression of ACE2 in different tissues has a close connection to the severity of this viral infection. Infection in the female reproductive system requires more attention because it may affect the generation and future progeny by damaged gametes.

Conclusion: The existing evidence proposes that ACE2 is widely expressed in the reproductive tract includes: ovary, uterus, vagina, and placenta.

Keywords: Reproduction; Gonadal Steroid Hormones; Coronavirus; Renin-Angiotensin System; Angiotensin-Converting Enzyme 2

Introduction

1. Renin-angiotensin system (RAS)

The renin-angiotensin system (RAS) is an important regulator of electrolytes, blood volume, and systemic vascular resistance that plays a vital role in cardiovascular homeostasis. Angiotensinogen is the main protein of this system (RAS) which is synthesized in the liver. RAS consists of different regulatory components with effective peptides that can help dynamically control the vascular system in both healthy and pathological conditions. Although these components may have conflicting functions, they must ultimately provide a coordinated response to the stimulus. Angiotensin-converting enzyme (ACE) metabolizes angiotensin I (Ang-I) to angiotensin II (Ang- II) as the dipeptide carboxypeptidase enzyme and angiotensin-converting enzyme2 (ACE2) converts Ang-II to Ang 1-7 (1). Studies show that the RAS activity in the local tissue can also control the functional proteins Ang-I and Ang-II. Angiotensinogen must be converted into Ang-I by Renin from the renal organ and then Ang-I by the angiotensin-converting enzyme (ACE) becomes Ang-II. In 1988, the human endothelial ACE was first cloned by Soubrier and described as a glycoprotein (170-kDa) with two homologous active sites (2). ACE2 as homologue of ACE is not inhibited

Correspondence:
Dr. Farideh Zafari Zangeneh
Email: zangeneh14@gmail.com

by ACE inhibitors. Angiotensin 1-7 is the main product of ACE2 activity which therefore opposes Ang-II. Therefore, the main function of ACE2 is to act as an equalizer for ACE and the increasing of Ang-II level can up-regulate ACE2 activity. Thus, ACE2 plays a vital role in cardiovascular and cardio-renal functions (3). ACE2 is a suitable target for drugs, and Lowers blood pressure by hydrolysis of Ang-II (a vasoconstrictor peptide) into Ang-1-7 (a vasodilator) (4).

1-1 Local Physiological response of RAS & Female reproductive system: The ovarian renin-angiotensin system (RAS) shows an important physiological role in steroidogenesis, follicular growth, oocyte maturation, ovulation and follicular atresia. Gonadotropins regulate ovarian RAS expression, and RAS is an important regulator in autocrine/paracrine mechanisms at different stages of the female reproductive cycle (5). In humans, all of the RAS family members have been demonstrated at the protein level, but in the ovaries of rat (6), porcine (7), and bovine only single combinations of the RAS have been expressed (8).

1-2 RAS & Ovary function/follicular growth: The presence of RAS compounds appears to be considerably involved in regulating fetal growth. The RAS expression in the porcine ovary can be recognized about 45 days of gestation. It is observed by detection of angiotensin receptors (ATR1 and ATR2) of primordial, primary, and secondary follicles phases in the granulose cells (7). Ang II is a significant modulator for steroidogenesis, and formation of the corpus luteum. It has a stimulator role in the oocyte maturation and ovulation through Ang II- receptors on the granulosa cells, and is a main regulator for follicle atresia stage (5). Therefore, Ang II and its receptors ATR1 and ATR2 play regulatory role on maturation of the oocyte nuclear and ovulation (9). AT2R antagonist can significantly inhibit bovine ovulation (10, 11). In rats, expression AT1R was observed in healthy follicles (12) and expression AT2R was clearly involved in follicular atresia by apoptosis (13). Studies show that there are considerable differences between the species. Of course in physiologic system, irregularities result can be increased the risk of pathologic states. Then disorders in the ovarian RAS can be the result of polycystic ovarian syndrome (PCOS), ovarian hyperstimulation syndrome, ovarian tumors, and ectopic pregnancy. In humans, [ACE2/Ang-(1–7)/MAS1] axis has a significant role in physiologic and pathological stages of follicular growth (Figure 1) (14).

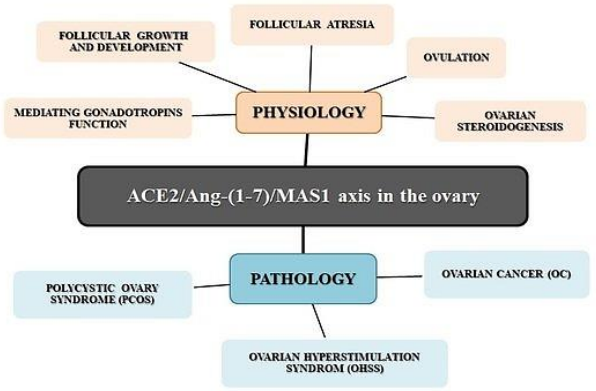

Figure 1: ACE2/Ang-(1–7)/MAS1 axis role in physiologic and pathological stages of follicular growth

1-3 RAS & the other reproductive organs: The effects of RAS on vascular function in the corpus luteum are mediated by Ang-II. It stimulates microvascular endothelial (MVE) function in the corpus luteum. ACE expression of MVE in the corpus luteum by Hayashi et al. in 2000 showed that MVE cells are able to convert Ang-I into Ang-II. The Ang-II production synergistically rises significantly by estradiol stimulation with vascular endothelial growth factor (VEGF) (15).

All localized RAS components are expressed in the fallopian tube and endometrium (16). Of course RAS expression varies during the menstruation cycle (17). Ang-II is augmented in the proliferative phase, and reduced in the secretory phase by AT1/AT2 receptors. Ang-(1–7) and its MAS receptor is existent during the menstrual cycle but rise in the glandular endometrium (18). In pregnancy, RAS family can be identified from 6 weeks of pregnancy until birth. For example mRNA of ACE is elevating in gestation but declines near term. AT1R protein and mRNA are increasing during pregnancy, but their level reaches the highest at the end time (19). There is a direct link between Ang-II and AT1R in the placenta; it has been hypothetical that Ang-II may have a regulator role on the AT1R expression (20). Studies in the past few years show the pathophysiological features of RAS in reproductive tract for example in polycystic ovary syndrome (PCOS) (21), hypertension and preeclampsia (22, 23) ovarian cancer (24) and endometrial cancer (25). In components of the renin-angiotensin system, ACE2 plays a vital role and is a suitable target for drugs.

2- Angiotensin-converting enzyme 2 (ACE2)

In 2000, the novel ACE2 was known as a homolog of ACE, with removal ability of the carboxy-terminal phenylalanine in Ang-II for producing the heptapeptide Ang-(1–7) (26). ACE2 is a critical enzyme at the cell surface that can cut up the long chains of angiotensinogen protein, to enter the cell and then regulate cell functions. ACE2 is a suitable receptor for COVI-19 especially in epithelial cells, which can make defensive barriers. ACE2 inhibitors are the most commonly suggested classes of drugs for cardiology and are choice drugs in hypertension and heart failure treatment. It attaches to the cell membranes of lungs, arteries, heart, kidney, and intestines organs (27). The expression map for ACE shows a widespread distribution in the heart and kidney tissues, and is also high in the lungs and pulmonary blood vessels, intestinal (ileum, jejunum, duodenum, and colon), testes and prostate (28). ACE2 is a zinc metalloprotease enzyme with 805 amino acids. ACE2 has a single HEXXH zinc-binding design with a high affinity for production Ang-(1-7) from Ang-II (29). Ang-(1-7) through the G protein-coupled receptor increases vasodilation and cares the heart function (30), and reduces metabolic syndrome (31). ACE2/Ang-(1–7)/mitochondrial assembly receptor [ACE2/Ang-(1–7)/Mas R] axis is the portion of the RAS. Recently, this axis has been recognized as a critical component of pulmonary endothelial, gastric mucosa, and cancer. This axis can be a possible novel therapeutic strategy for cancer (32). In this review, we investigated the spreading and function of ACE2 as a suitable target for effect on the female reproductive system and coronavirus receptor.

2-1 ACE2 & female reproductive system/Ovarian function: ACE2-mRNA transcriptions were identified in the ovaries from reproductive-age until postmenopausal women (14). Pereira et al in 2009 showed that ACE2/Ang-(1–7)/Mas axis in the rat ovary increased the ovarian expression of Ang-(1–7), Mas receptor, and ACE2 (8).

In 2012, Honorato-Sampaio et al. reported an animal immunohistochemistry study that showed that LH amplified Ang-(1-7) and ACE2 staining in pre-ovulatory follicles (33). ACE2 is the critical enzyme with a synergistic role that can balance the Ang II and Ang-(1-7) levels for steroid secretion (34), facilitates follicle growth (11), oocyte maturation (35), ovulation (36), follicular atresia (10), and retains corpus luteum development (37). Ang-(1-7) stimulates the production of estradiol and progesterone (13) and improves ovulation (38), and the resumption of meiosis in the oocyte (16). In human, Ang-(1-7) level is related to the maturation of oocytes (39).

2-2 ACE2 & uterus: Many studies confirm the role of angiotensin II in the endometrium which is important for regular menstruation cyclic. An alteration in the distribution of angiotensin II and its receptors is associated with dysfunction of the uterine bleeding by the hyperplastic endometria (40). The pattern of Ang (1–7) localization in the endometrium during menstrual cycle, agreed with the ACE2 mRNA, which is increased in the epithelial than stromal cells (2-fold) and in the secretory phase against proliferative phase (6.6-fold). Mas' receptors were similarly distributed between epithelial and stromal cells and did not alteration through menstrual cycle (41). Can able coronavirus disturb the female reproductive functions via ACE2 or does it adversely affect the mother and fetus during pregnancy?

2-3 ACE2 & pregnancy: In early gestation ACE2 level is highest. During early gestation, ACE2 is expressed in the primary and secondary decidua zone, luminal, and glandular epithelial cells. During late gestation, ACE2 is expressed in the labyrinth placenta, amniotic, and yolk sac epithelium (42), but in rat placenta, ACE2 increases from mid-gestation (43).

In 2006 Valdes et al reported that placental villi are the main sites of immunocytochemical expression of Ang-(1-7)/ACE2. This expression was reported in syncytotuboblast, cytotrophoblast, endothelium and vascular smooth muscle of primary and secondary villi. In the maternal stroma, ACE2 was also expressed in the intravascular trophoblast, decidual cells and was been found in endothelium and smooth muscle of the umbilical cord (44).

Studies show that during pregnancy, Ang II and Ang- (1-7) / ACE2 can principally regulate blood pressure and fetal growth by maintaining the normal physiological function of the uterus through the local autocrine/paracrine system (45) in the early (angiogenesis, apoptosis and growth), and in the late gestation (uteroplacental blood flow) (46). ACE2 as the hydrolyze enzyme converts Ang II into Ang-(1-7), and Ang I into Ang-(1-9), which can rapidly convert to Ang-(1-7) and thus ACE2 control the blood pressure and hydro-salinity equilibrium in the pregnant women (47). The abnormal expression of Ang II and Ang-(1-7)/ACE2 may be led to hypertension of pregnancy, pre-eclampsia and eclampsia (48). Based on the GeneCart, ACE2 expression in the placenta is higher than in the lung.

Most recently, coronavirus infection was been recognized in infants with positive tests in the nasopharyngeal and anal swabs, on the second and fourth day of their birth (49). In a newborn from an infected mother by a coronavirus, has been reported a high level of the IgM antibody in the serum 2 hours after birth (50). Wong et al in 2004 reported the pregnant women infected by CoV are at high risk for adversative consequences include spontaneous abortion, premature labor, and intra-uterine development limitation (51, 52). These findings indicate which; there are expressions of CoV receptors in the human maternal-fetal border.

3- Coronavirus

In the last two decades, after severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), COVID-19 (Corona-virus-disease-2019) as coronavirus disease is the third respiratory infection that was firstly defined in Asia. The first report of COVID-19 was in December 2019 in Wuhan, China. Coronavirus (nCoV) of Wuhan 2020 belongs to the Betacoronavirus.

3-1 Coronaviridae Family: The Coronaviridae family is the causative agent of respiratory, intestinal, hepatic, and neurological diseases in humans and animals. Coronaviruses (CoVs) are the largest group of positive-sense RNA viruses with a wide range of natural hosts. The first coronavirus in 1937 was isolated from chicken embryos (53). Coronaviruses have been widely distributed and have been found as a human pathogen since the 1960s. These zoological viruses are common between animals and humans. The name coronavirus is due to the presence of a structure with a crown on its surface (like the sun) under an electron microscope. Coronavirus (CoV) is a member of the Orthocoranavirinae sub-family with four types that was differentiated by their protein classification: Alpha, Beta, Gamma and Deltacoronaviruses (54). The first report of the COVID-19 was from Wuhan, Hubei Province, China, with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). "Symptoms of SARS-Cov-2 infection range from asymptomatic disease to life-threatening acute respiratory distress syndrome (ARDS), severe pneumonia, acute kidney injury, myocarditis, multiple organ failure, and death" (55). Several neurological manifestations, including cerebrovascular events, have been reported in patients with severe infection, even ischemic stroke in the setting of PCR-confirmed SARS-CoV-2 infection (56).

3-2 Coronavirus & S-protein: The single-stranded RNA genome of coronavirus encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein (46). The S-protein is the main vehicle for the virus attachment to receptors on the host cell surface and following to facilitate entrance of viral into the target cell (57). S-protein expression at the cell membrane can be a facilitator for the cell to cell fusion signal, between infected and uninfected cells. S-protein consists of two subunits, S1 and S2. The S1 subunit covers binding to ACE2 in the host cell, while the S2 subunit facilitates the receptor recognition, cell attachment, and fusion during viral infection through making a six-helical bundle by the two-heptad repeat domain (Figure 2) (58).

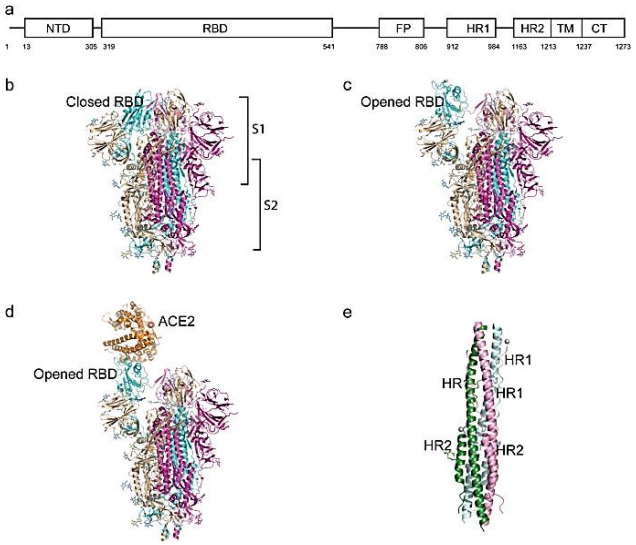

Figure 2: Structure of the SARS-CoV-2 S protein
a Schematic representation of the SARS-CoV-2 spike. b–c The S protein RBD closed and opened status. d The S protein binds to ACE2 with opened RBD in the S1 subunit. e The six-helix structure formed by HR1 and HR2 of the S2 subunit (58).

N-protein (nucleocapsid) is the only coronavirus protein with the function of binding to the CoV-RNA genome, for making nucleocapsid (59). N-protein through the viral genome can involve in the features of the CoV replication cycle and then in the host cellular response against viral infection (60). N-protein localization to the endoplasmic reticulum (ER)-Golgi system can be suggested as the function of assembly and budding processes (61).

The M-protein as the structural protein describes the form of the viral envelope (62). Communication between S with M proteins is essential for maintenance

of S-protein in the ER-Golgi intermediate compartment (ERGIC)/Golgi complex, but is not necessary for the assembly process. The binding between M to N proteins helps to stabilization of the nucleocapsid (N protein-RNA complex), which promotes termination of viral assembly (63).

The E-protein is the smallest structural protein, but it is more of a mystery. In the infected cell during the replication cycle, E-protein initiates to expression, but only a small segment is fused into the virion envelope (64). Golgi intermediate compartment (ERGIC)/Golgi complex is the site of virus assembly and budding processes (65). E-protein has a significant role in virus production and maturation. Recombinant CoV without the E-protein is caused a reduction in the viral titers, crippled viral maturity and products the incompetent progeny (66).

3-3 Coronavirus/ACE2 & female reproductive tract: These findings indicate the potential participation of the local RAS as a regulator in the physiological antagonistic pathways in the reproductive tract. Coronavirus after interval and invasion in the host cell, down-regulates the ACE2 expression that leads to an augmented pro-inflammatory response by Ang II (67). Ang II, ACE2 and Ang-(1-7) regulate growth of follicle and its maturation, ovulation (folliculogenesis, steroidogenesis), luteal angiogenesis and atresia processes. It is also a regulator for variations in the endometrial tissue (regeneration) and embryo improvement. ACE2 receptor dispersion in the male reproductive system is higher in the female. For example, Low expression of ACE2 is in the ovary, fallopian tube, vagina, cervix and endometrium (68). In female, a severe acute disease may modify the function of the hypothalamic-pituitary-gonadal (HPG) axis function and leads to reduction of sex hormones. The expression of the estrogen receptors on the lymphocytes, macrophages, and dendritic cells (DC) show that sexual hormones can be a regulator for the immune responses with a protective role against direct antiviral activity in women. Estradiol and progesterone are the important modulators in inflammatory processes, and behavior (69).

Conclusion

This review summarizes the existing literature on RAS local tissue in the reproductive system with respect to physiological and pathological clinical conditions. RAS obviously affects the maturation and quality of oocyte, endometrial coating, hormone production, and therefore RAS is a vital system for the regulation of physiological pathways in the reproductive tract. The activity of RAS is different between men and women, and this gender difference contributes to the rate of coronavirus infection and its resulting mortality, which is more common in men (70).

Reduction in sex hormones is the main in tissue-specific dysfunction because these hormones have a wide range of protective actions. Deficiency in aging is not only associated with loss of reproductive function but is also significant in the brain (neuro-protective) and the cardiovascular system (cardio-protective). Prospective studies show that hormones replacement therapy (HRT) as a promising strategy for delaying and preventing Alzheimer's disease (AD) is not successful. HRT might raise dementia risk by some mechanisms (71), and also large clinical trials have been unsuccessful to establish an advantage from HRT on the risk of dementia (72, 73). But Zhou 2020 in the systematic review reported that HRT can improve cognitive function in women with AD (74). Results of the observational studies suggest that the association of HRT with AD should be related to the timing and type of HRT use. This suggestion can be true of HRT in the treatment of the elderly with coronavirus. Although sex hormones reduce the inflammatory response and modulate ACE2 expression, can they be considered as a supported hypothesis for the treatment of patients with COVID-19?

Acknowledgments

Authors have no conflict of interests.

References

1. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochem J 2004; 383: 45-51.
2. Soubrier F, Alhenc-Gelas F, Hubert C, Allegrini J, John M, Tregear G, et al. Two putative active centers in human angiotensin I-converting enzyme revealed by molecular cloning. Proc Natl Acad Sci USA 1988; 85: 9386-90.
3. Dzau VJ.Angiotensin converting enzyme inhibitors and the cardiovascular system. J Hypertens Suppl 1992; 10: S3–10.
4. Wang W, McKinnie SM, Farhan M, Paul M, McDonald T, McLean B, et al. Angiotensin-Converting Enzyme 2 Metabolizes and Partially Inactivates Pyr-Apelin-13 and

Apelin-17: Physiological Effects in the Cardiovascular System. Hypertension 2016; 68: 365–77.
5. Yoshimura Y. The Ovarian renin–angiotensin system in reproductive physiology. Front Neuroendocrinol 1997; 18: 247-91.
6. Kobayashi S, Moriya H, Nakabayashi I, Nishiyama J, Fukuda T. Angiotensin II and IGF-I may interact to regulate tubulointerstitial cell kinetics and phenotypic changes in hypertensive rats. Hypertens Res 2002; 25: 257-69.
7. Li YH, Jiao LH, Liu RH, Chen XL, Wang H, Wang WH. Localization of angiotensin II in pig ovary and its effects on oocyte maturation in vitro. Theriogenology 2004; 61: 447–59.
8. Pereira VM, Reis FM, Santos RA, Cassali GD, Santos SH, Honorato-Sampaio K, et al. Gonadotropin stimulation increases the expression of angiotensin-(1–7) and MAS receptor in the rat ovary. Reprod Sci 2009; 16: 1165–74.
9. Yoshimura T, Ito M, Matsui K, Fujisaki S. Effects of highly purified eicosapentaenoic acid on vascular reactivity to angiotensin II and norepinephrine in pregnant rabbits. Prostaglandins 1986; 32: 179-88.
10. Obermuller N, Gentili M, Gauer S, Gretz N, Weigel M, Geiger H, et al. Immuno-histochemical and mRNA localization of the angiotensin II receptor subtype 2 (AT2) in follicular granulosa cells of the rat ovary. J Histochem Cytochem 2004; 52: 545–8.
11. Ferreira R, Gasperin B, Santos J, Rovani M, Santos RA, Gutierrez K, et al. Angiotensin II profile and mRNA encoding RAS proteins during bovine follicular wave. J Renin Angiotensin Aldosterone Syst 2011; 12: 475-82.
12. de Gooyer TE, Skinner SL, Wlodek ME, Kelly DJ, Wilkinson-Berka JL. Angiotensin II influences ovarian follicle development in the transgenic (mRen-2)27 and Sprague-Dawley rat. J Endocrinol 2004; 180: 311–24.
13. Kotani E, Sugimoto M, Kamata H, Fujii N, Saitoh M, Usuki S, et al. Biological roles of angiotensin II via its type 2 receptor during rat follicle atresia. Am J Physiol 1999; 276: E25–33.
14. Domińska K. Involvement of ACE2/Ang-(1-7)/MAS1 Axis in the Regulation of Ovarian Function in Mammals. Int J Mol Sci 2020, 21: 4572.
15. Hayashi K, Miyamoto A, Berisha B, Kosmann MR, Okuda K, Schams D. Regulation of angiotensin II production and angiotensin receptors in microvascular endothelial cells from bovine corpus luteum. Biol Reprod 2000; 62: 162–7.
16. Pawlikowski M, Melen-Mucha G, Mucha S. The involvement of the renin-angiotensin system in the regulation of cell proliferation in the rat endometrium. Cell Mol Life Sci 1999; 55: 506–10.
17. Herr D, Duncan WC, Hack G, Konrad R, Kreienberg R, Wulff C. Regulated expression of the renin-angiotensin-system in human granulosa lutein cells: angiotensin II increases VEGF expression but its synthesis is reduced by hCG. Arch Gynecol Obstet 2010; 281: 409–16.
18. Li XF, Ahmed A. Dual role of angiotensin II in the human endometrium. Hum Reprod 1996; 11Suppl 2: 95-108.
19. Petit A, Geoffroy P, Belisle S. Expression of angiotensin II type-I receptor and phospholipase C-linked G alpha q/11 protein in the human placenta. J Soc Gynecol Investig 1996; 3: 316–21.
20. Kalenga MK, DE Gasparo M, DE Hertogh R, Whitebread S, Vankrieken L, Thomas K. Les récepteurs de l'angiotensine II dans le placenta humain sont de type AT1 .[Angiotensin II receptors in the human placenta are type AT1]. Reprod Nutr Dev 1991; 31: 257–67.
21. Bokal EV, Vrtovec HM, Virant Klun I, Verdenik I. Prolonged HCG action affects angiogenic substances and improves follicular maturation, oocyte quality and fertilization competence in patients with polycystic ovarian syndrome. Hum Reprod 2005; 20: 1562–81.
22. Herse F, Dechend R, Harsem NK, Wallukat G, Janke J, Qadri F, et al. Dysregulation of the circulating and tissue-based renin-angiotensin system in preeclampsia. Hypertension 2007; 49: 604–11.
23. Chappell S, Morgan L. Searching for genetic clues to the causes of pre-eclampsia. Clin Sci (Lond) 2006; 110: 443-58.
24. Suganuma T, Ino K, Shibata K, Kajiyama H, Nagasaka T, Mizutani S, et al. Functional expression of the angiotensin II type 1 receptor in human ovarian carcinoma cells and its blockade therapy resulting in suppression of tumor invasion, angiogenesis, and peritoneal dissemination. Clin Cancer Res 2005; 11: 2686–94.
25. Shibata K, Kikkawa F, Mizokami Y, Kajiyama H, Ino K, Nomura S, et al. Possible involvement of adipocyte-derived leucine aminopeptidase via angiotensin II in endometrial carcinoma. Tumour Biol 2005; 26:9–16.
26. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 2000; 87: E1–9.
27. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J of Pathol

2004; 203: 631–7.
28. Paul M, Wagner J, Dzau VJ. Gene expression of the renin-angiotensin system in human tissues. Quantitative analysis by the polymerase chain reaction. J Clin Invest 1993; 91: 2058-64.
29. Vickers C, Hales P, Kaushik V, Dick L, Gavin J, Tang J, Godbout K,Parsons T, Baronas E, Hsieh F,et al. Hydrolysis of biological pepti-des by human angiotensin-converting enzyme-related carboxypep-tidase. J Biol Chem 2002; 277: 14838–43.
30. Iwata M, Cowling RT, Gurantz D, Moore C, Zhang S, Yuan JX, et al. Angiotensin-(1-7) binds to specific receptors on cardiac fibroblasts to initiate anti fibrotic and anti-trophic effects. Am J Physiol Heart Circ Physiol 2005; 289: H2356– 63.
31. Liu C, Lv XH, Li HX, Cao X, Zhang F, Wang L, et al . Angiotensin-(1-7) suppresses oxidative stress and improves glucose uptake via Mas receptor in adipocytes. Acta Diabetol 2012; 49: 291–9.
32. Xu J, Fan J, Wu F, Huang Q, Guo M, Lv Z, et al. The ACE2/Angiotensin-(1–7)/Mas Receptor Axis: Pleiotropic Roles in Cancer. Front Physiol 2017; 8: 276.
33. Honorato-Sampaio K, PereiraVM, Santos RA, Reis AM. Evidence that angiotensin-(1-7) is an intermediate of gonadotrophin-induced oocyte maturation in the rat pre-ovulatory follicle. Exp Physiol 2012; 97: 642-50.
34. Hayashi KG, Acosta TJ, Tetsuka M, Berisha B, Matsui M, Schams D, et al. Involvement of angiopoietin-tie system in bovine follicular development and atresia: messenger RNA expression in theca internal and effect on steroid secretion. Biol Reprod 2003; 69: 2078–84.
35. Stefanello JR, Barreta MH, Porciuncula PM, Arruda JN, Oliveira JF, Oliveira MA, et al. Effect of angiotensin II with follicle cells and insulin-like growth factor-I or insulin on bovine oocyte maturation and embryo development. Theriogenology 2006; 66: 2068–76.
36. Guo B, Zhang XM, Li SJ, Tian XC, Wang ST, Li DD, et al. Expression and regulation of Ang-2 in murine ovaries during sexual maturation and development of corpus luteum. Mol Biol (Mosk) 2012; 46: 900-6.
37. Sugino N, Suzuki T, Sakata A, Miwa I, Asada H, Taketani T, et al. Angiogenesis in the human corpus luteum: changes in expression of angiopoietins in the corpus luteum throughout the menstrual cycle and in early pregnancy. J Clin Endocrinol Metab 2005; 90: 6141–8.
38. Tonellotto dos Santos J, Ferreira R, Gasperin BG, Siqueira LC, de Oliveira JF, Santos RA, et al. Molecular characterization and regulation of the angiotensin-converting enzyme type 2/angiotensin-(1-7)/MAS receptor axis during the ovulation process in cattle. J Renin Angiotensin Aldosterone Syst 2012; 13: 91–8.
39. Cavallo IK, Dela Cruz C, Oliveira ML, Del Puerto HL, Dias JA, Lobach VN, et al. Angiotensin-(1-7) in human follicular fluid correlates with oocyte maturation. Hum Reprod 2017; 32: 1318–24.
40. Li XF, Ahmed A. Expression of angiotensin II and its receptor subtypes in endometrial hyperplasia: a possible role in dysfunctional menstruation. Lab Invest 1996; 75: 137–45.
41. Vaz-Silva J, Carneiro MM, Ferreira Mc, Pinheiro SV, Silva DA, Silva- Filho AL, et al. The Vasoactive Peptide Angiotensin-(1–7), it's Receptor Mas and the Angiotensin-converting Enzyme Type 2 are Expressed in the Human Endometrium. Reprod Sci 2009; 16: 247-56.
42. Ghadhanfar E, Alsalem A, Al-Kandari S, Naser J, Babiker F, Al-Bader M. The role of ACE2, angiotensin-(1-7) and Mas1 receptor axis in glucocorticoid-induced intrauterine growth restriction. Reprod Biol Endocrinol 2017; 15: 97.
43. Vaswani K, Chan HW, Verma P, Dekker Nitert M, Peiris HN, Wood-Bradley RJ, et al. The rat placental renin-angiotensin system- a gestational gene expression study. Reprod Biol Endocrinol 2015; 13: 89.
44. Valdes G, Neves LA, Anton L, Corthorn J, Chacon C, Germain AM, et al. Distribution of angiotensin-(1-7) and ACE2 in human placentas of normal and pathological pregnancies. Placenta 2006; 27: 200–7.
45. Hering L, Herse F, Geusens N, Verlohren S, Wenzel K, Staff AC, et al. Effects of circulating and local uteroplacental angiotensin II in rat pregnancy. Hypertension 2010; 56: 311–8.
46. Neves LA, Stovall K, Joyner J, Valdes G, Gallagher PE, Ferrario CM, et al. ACE2 and ANG-(1-7) in the rat uterus during early and late gestation. Am J Physiol Regul Integr Comp Physiol 2008; 294: R151–61.
47. Pringle KG, Tadros MA, Callister RJ, Lumbers ER. The expression and localization of the human placental prorenin/renin-angiotensin system throughout pregnancy: roles in trophoblast invasion and angiogenesis? Placenta 2011; 32: 956–62.
48. Sykes SD, Pringle KG, Zhou A, Dekker GA, Roberts CT, Lumbers ER, et al. Fetal sex and the circulating renin-angiotensin system during early gestation in women who later develop preeclampsia or gestational hypertension. J Hum Hypertens 2014; 28: 133–9.
49. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr 2020; 174: 722-5.
50. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al.

Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA 2020; 323:1846-8.
51. Wong FS, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al . Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 2004; 191: 292-7.
52. Wong FS, Chow KM, deSwiet M. Severe acute respiratory syndrome and pregnancy.BJOG 2003; 110: 641-2.
53. Beaudette FR, Hudson CB. Cultivation of the virus of infectious bronchitis. Journal of the American Veterinary Medical Association 1937; 90: 51-60.
54. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019; 17:181–92.
55. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al . Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China. Lancet 2020; 395:497–506.
56. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. Brain Behav Immun 2020; 87:115-9.
57. Wang C, Zheng X, Gai W, Zhao Y, Wang H, Wang H, et al. MERS-CoV virus-like particles produced in insect cells induces specific humoral and cellular immunity in rhesus macaques. Oncotarget 2017; 8: 12686–94.
58. Kirchdoerfer RN, Cottrell CA, Wang N, Pallesen J, Yassine HM, Turner HL, et al. Pre-fusion structure of a human coronavirus spike protein. Nature 2016; 531: 118-21.
59. Huang Y, Yang C, Xu Xf, Xu W, Liu Sw. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacologica Sinica 2020; 41:1141–9.
60. de Haan CA, Rottier PJ. Molecular interactions in the assembly of coronaviruses. Adv Virus Res 2005; 64:165–230.
61. McBride R, van Zyl M, Fielding BC. The coronavirus nucleocapsid is a multifunctional protein. Viruses 2014; 6: 2991–3018.
62. Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S, et al. A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol 2011; 174: 11–22.
63. Fehr AR, Perlman S. Coronaviruses: An overview of their replication and pathogenesis. Coronaviruses: Springer; 2015;1282: 1–23.
64. Venkatagopalan P, Daskalova SM, Lopez LA, Dolezal KA, Hogue BG. Coronavirus envelope (E) protein remains at the site of assembly. Virology 2015; 478:75–85.
65. Nieto-Torres JL, DeDiego ML, Álvarez E, Jiménez-Guardeño JM, Regla-Nava JA, Llorente M, et al. Subcellular location and topology of severe acute respiratory syndrome coronavirus envelope protein. Virology 2011; 415: 69–82.
66. Ortego J, Ceriani JE, Patiño C, Plana J, Enjuanes L. Absence of E protein arrests transmissible gastroenteritis coronavirus maturation in the secretory pathway. Virology 2007; 368: 296–308.
67. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med 2010; 2: 247–57.
68. Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. Mol Syst Biol 2020; 16: e9610.
69. Pinna G. Sex and COVID-19: A Protective Role for Reproductive Steroids. Trends Endocrinol Metab 2021; 32:3-6.
70. Kwon JY, Romero R, Mor G. New Insights into the Relationship between Viral Infection and Pregnancy Complications. Am J Reprod Immunol 2014; 71: 387–90.
71. Peckham H, de Gruijter N, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun 2020; 11: 6317.
72. Baum LW. Sex, Hormones, and Alzheimer's disease. J Gerontol A Biol Sci Med Sci 2005; 60: 736–43.
73. Billeci A, Caso V, Paciaroni M, Palmerini F, Agnelli G. Hormone-Replacement therapy dementia and stroke. Womens Health (Lond) 2007; 3:699-710.
74. Zhou C, Wu Q, Wang Z, Wang Q, Liang Y, Liu S. The Effect of hormone replacement therapy on cognitive function in female patients with Alzheimer's disease: A Meta-Analysis. Am J Alzheimers Dis Other Demen 2020; 35: 1533317520938585.

Citation: Zafari Zangeneh F. **Interaction of SARS-CoV-2 With RAS / ACE2 in the Female Reproductive System.** J Family Reprod Health 2022; 16(1): 1-8.