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REVIEW

Potential influence of COVID-19/ACE2 on the female reproductive system

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ABSTRACT: The 2019 novel coronavirus (2019-nCoV) appeared in December 2019 and then spread throughout the world rapidly. The virus invades the target cell by binding to angiotensin-converting enzyme (ACE) 2 and modulates the expression of ACE2 in host cells. ACE2, a pivotal component of the renin-angiotensin system, exerts its physiological functions by modulating the levels of angiotensin II (Ang II) and Ang-(1-7). We reviewed the literature that reported the distribution and function of ACE2 in the female reproductive system, hoping to clarify the potential harm of 2019-nCoV to female fertility. The available evidence suggests that ACE2 is widely expressed in the ovary, uterus, vagina and placenta. Therefore, we believe that apart from droplets and contact transmission, the possibility of mother-to-child and sexual transmission also exists. Ang II, ACE2 and Ang-(1-7) regulate follicle development and ovulation, modulate luteal angiogenesis and degeneration, and also influence the regular changes in endometrial tissue and embryo development. Taking these functions into account, 2019-nCoV may disturb the female reproductive functions through regulating ACE2.

Key words: 2019-nCoV / COVID-19 / angiotensin-converting enzyme 2 / angiotensin II / Ang-(1-7) / female reproductive system / breastfeeding / pregnancy / coronavirus

Introduction

Corona virus disease 2019 (COVID-19) is an emerging acute communicable disease that was identified in patients with pneumonia in December 2019, which was declared a pandemic by the World Health Organization on 11 March 2020. A total of 2 719 896 laboratory-confirmed cases and 187 705 deaths have been reported as of 25 April 2020 (World Health Organization, 2020). Epidemiologically, the genome of the 2019 novel coronavirus (2019-nCoV) is composed of 29 891 nucleotides, with an 89% identity to bat SARS-like-CoVZXC21 and 82% to human SARS-CoV (Chan *et al.*, 2020). 2019-nCoV infects the target cell by binding to angiotensin-converting enzyme (ACE) 2 through its surface spike protein (Lu *et al.*, 2020; Zhou *et al.*, 2020), modulates the expression of ACE2 and causes severe injuries, similar to SARS-CoV (Kuba *et al.*, 2005; Wang and Cheng, 2020).

ACE2 is a zinc metalloprotease which shares homology with ACE in its catalytic domain (Donoghue *et al.*, 2000), and is composed of 805 amino acids including a 17-amino acid N-terminal signal sequence and a C-terminal membrane binding domain (Tipnis *et al.*, 2000). ACE2 contains a single HEXXH zinc-binding motif and is able to hydrolyze angiotensin I (Ang I) to produce angiotensin-(1-9) and also has a high affinity for angiotensin II (Ang II) to generate Ang-(1-7) (Vickers *et al.*, 2002). Ang II, the major component of the ACE/Ang II/AT1 (angiotensin II type 1) axis, facilitates vasoconstriction, promotes cell proliferation (Campbell-Boswell and Robertson, 1981; Ray *et al.*, 1991; Hiruma *et al.*, 1997; Bataller *et al.*, 2000) and maintains the hydrosalinity balance (Hall *et al.*, 1977; Johnson and Malvin, 1977). As an important modulator of the human renin-angiotensin system, Ang-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas (Santos *et al.*, 2003) and specifically inhibits Ang II by the antagonism of AT1 receptors (Roks *et al.*, 1999). Moreover, Ang-(1-7) enhances vasodilation (Brosnihan *et al.*, 1998; Oliveira *et al.*, 1999), protects the heart (Ferreira *et al.*, 2001; Santos *et al.*, 2004; Iwata *et al.*, 2005) and alleviates metabolic syndrome (Giani *et al.*, 2009; Liu *et al.*, 2012).

Evidence has been accumulating that besides lung injury, 2019-nCoV also damages the human heart (Huang *et al.*, 2020; Wang *et al.*, 2020; Zheng *et al.*, 2020), liver (Chen *et al.*, 2020c; Zhang *et al.*, 2020b), kidney (Chen *et al.*, 2020c; Huang *et al.*, 2020; Wang *et al.*, 2020) and nervous system (Li *et al.*, 2020c; Mao *et al.*, 2020). Recently, cases of COVID-19 during pregnancy have been reported (Chen *et al.*, 2020a; Liu *et al.*, 2020; Zhu *et al.*, 2020), but the influence of 2019-nCoV on the female reproductive system needs further investigation. In this review, we analyzed the distribution and function of ACE2, trying to predict the possible targets and transmission routes, as well as the influence on the female reproductive system, of 2019-nCoV.

ACE2 in the ovary

ACE2 presents in stroma and granulosa cells as well as oocytes in immature rat ovaries, the expression of which is enhanced in antral and preovulatory follicles subjected to equine CG treatment (Pereira *et al.*, 2009). In bovine theca cells and granulosa cells, *ACE2* also exists (Tonellotto dos Santos *et al.*, 2012; Barreta *et al.*, 2015). Notably, *ACE2* mRNA transcripts were detected in ovaries from reproductive-age women and postmenopausal women (Reis *et al.*, 2011). We analyzed ACE2 data from the GeneCards (https://www.genecards.org/cgi-bin/carddisp.pl?gene=ACE2#protein_expression) database, and found that ACE2 is most abundantly expressed in the ovary. In the meantime, data obtained from Bgee (https://bgee.org/?page=gene&gene_id=ENSG00000130234) showed that the expression level of *ACE2* in oocytes is relatively high. Therefore, the ovary and oocyte might be potential targets of 2019-nCoV.

ACE2 is the key enzyme in the axis that plays a synergistic role in balancing the levels of Ang II and Ang-(1-7). Ang II induces steroid secretion (Shuttleworth *et al.*, 2002; Hayashi *et al.*, 2003), facilitates follicle development (Shuttleworth *et al.*, 2002; Ferreira *et al.*, 2011) and oocyte maturation (Yoshimura *et al.*, 1992; Giometti *et al.*, 2005; Stefanello *et al.*, 2006), contributes to follicular atresia (Tanaka *et al.*, 1995; Kotani *et al.*, 1999; Obermuller *et al.*, 2004), influences ovulation (Pellicer *et al.*, 1988; Kuo *et al.*, 1991; Yoshimura *et al.*, 1992, 1993; Kuji *et al.*, 1996; Acosta *et al.*, 2000; Miyabayashi *et al.*, 2005; Xu and Stouffer, 2005; Xu *et al.*, 2005; Ferreira *et al.*, 2007; Guo *et al.*, 2012) and maintains corpus luteum progression (Sugino *et al.*, 2005). Ang-(1-7) promotes the production of estradiol and progesterone (Costa *et al.*, 2003) and enhances ovulation (Muthalif *et al.*, 1998; Viana *et al.*, 2011; Tonellotto dos Santos *et al.*, 2012) and the resumption of meiosis in the oocyte (Honorato-Sampaio *et al.*, 2012). A recent study showed that the level of Ang-(1-7) is also associated with the maturation of human oocytes (Cavallo *et al.*, 2017).

ACE2 in the uterus and vagina

ACE2 mRNA has been identified in the uterus of human (Vaz-Silva *et al.*, 2009) and rat (Brosnihan *et al.*, 2012). Vaz-Silva *et al.* (2009) claimed that *ACE2* mRNA is more abundant in epithelial cells than in stromal cells, and higher in the secretory phase than in the proliferative phase (Vaz-Silva *et al.*, 2009). Moreover, we confirmed the presence of *ACE2* in uterus and vagina after analyzing the data from the Human Protein Atlas (https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue) and GeneCards. Noteworthy is the report of a high infection rate among sexual partners of 35 2019-nCoV-positive females (Cui *et al.*, 2020), suggesting the possibility of sexual transmission. However, the confirmation of sexual transmission still needs extensive investigation.

Ang II plays a dual role in vascular bed and endometrium regeneration, and initiates menstruation through spiral artery vasoconstriction (Ahmed *et al.*, 1995; Li and Ahmed, 1996a, 1997). The balance between Ang II and Ang-(1-7) could regulate the regeneration of endometrium (Vaz-Silva *et al.*, 2009) and myometrium activity (Deliu *et al.*, 2011; Vaz-Silva *et al.*, 2012). Moreover, Ang II increases the proliferation of uterus epithelial and stroma cells and enhances endometrial fibrosis, an effect that can be inhibited by Ang-(1-7) (Hering *et al.*, 2010; Shan *et al.*, 2014, 2015). Notably, the normal function of Ang II in endometrium is necessary for regular menstrual cycles, and alterations in its distribution and the level of the receptors may be related to dysfunctional uterine bleeding associated with hyperplastic endometria (Li and Ahmed, 1996b). Furthermore, many authors have described in the literature that intense ACE2 and Ang II expression correlates with the metastasis and prognosis of endometrial carcinoma (Watanabe *et al.*, 2003; Shibata *et al.*, 2005; Delforce *et al.*, 2017), and highlighted that the increased ACE2/Ang-(1-7)/MAS/AT2R pathway activity in endometrial cancer can be an important mechanism to counteract the actions of Ang II/AT1R (AbdAlla *et al.*, 2001; Kostenis *et al.*, 2005).

ACE2 in pregnancy

ACE2 is widely expressed in human placenta (Valdes *et al.*, 2006). In placental villi, ACE2 is mainly expressed in the syncytiotrophoblast, cytotrophoblast, endothelium and vascular smooth muscle of primary and secondary villi. In the maternal stroma, ACE2 is expressed in the invading and intravascular trophoblast and in decidual cells. ACE2 is also found in arterial and venous endothelium and smooth muscle of the umbilical cord (Valdes *et al.*, 2006). Of note, *ACE2* reaches the highest level in early gestation (Pringle *et al.*, 2011). During early gestation, ACE2 is expressed in the primary and secondary decidual zone, and in luminal and glandular epithelial cells. During late gestation, ACE2 staining is visualized in the labyrinth placenta, and amniotic and yolk sac epithelium (Neves *et al.*, 2008; Ghadhanfar *et al.*, 2017). Moreover, *Ace2* in placenta of rat begins to increase from mid-gestation (Vaswani *et al.*, 2015). According to the GeneCards, the expression of ACE2 in the placenta is greater than that detected in the lung, suggesting a possibility of viral infection of the placenta. Recently, early-onset 2019-nCoV infection was identified in infants whose nasopharyngeal and anal swabs were positive on Day 2 and 4 of life (Zeng *et al.*, 2020), and a neonate born to a mother with COVID-19 had elevated IgM antibodies at 2 h after birth (Dong *et al.*, 2020). Given that the identification of 2019-nCoV in human airway epithelial cells requires at least 96 h of culture (National Health Commission of the People's Republic of China, 2020), we speculate that intrauterine infection with 2019-nCoV may appear and the fetuses may be infected during gestation.

Additionally, the Human Protein Atlas and GeneCards database showed the presence of *ACE2* in female breasts. Wu *et al.* (2020) claimed that one of three samples of breast milk was positive for 2019-nCoV in nucleic acid testing (Wu, 2020), indicating the chance of transmission through breastfeeding. Even if there is no virus in milk, contact transmission during breastfeeding should be taken into account. Given the weaker immune system of newborns, we advise that pregnant patients who are confirmed as positive for 2019-nCoV should carry out artificial feeding instead, or start breastfeeding after a 14-day isolation following recovery and discharge. Concurrently, considering its benefits in decreasing respiratory tract and gastrointestinal tract infections, sudden infant death syndrome and diabetes of the infants (Section on Breastfeeding, 2012), breastfeeding might not be completely forbidden. Nevertheless, Ferrazzi *et al.* (2020) reported that when breastfed by two postpartum women diagnosed with COVID-19 and wearing no masks, the newborns tested positive (Ferrazzi *et al.*, 2020). We strongly support that all possible precautions should be taken to avoid spreading the virus to the infant, including washing hands before touching the infant and wearing a face mask

during breastfeeding (Baud *et al.*, 2020). However, these precautions may not be strictly adhered to, hence increasing the risk of infection in the infants. Therefore, mothers who intend to breastfeed are encouraged to use a dedicated breast pump, and after each pumping session, the breast pump should be appropriately disinfected.

During pregnancy, Ang II, ACE2 and Ang-(1-7) function mainly through regulating blood pressure and fetus development. Meanwhile, they also interact to maintain normal uterine physiology. Ang II stimulates trophoblast invasion in rat and human cells (Hering *et al.*, 2010). Ang-(1-7) and ACE2 may act as a local autocrine/paracrine regulator in the early (angiogenesis, apoptosis and growth) and late (uteroplacental blood flow) events of pregnancy (Neves *et al.*, 2008). ACE2 hydrolyzes Ang II into Ang-(1-7), and Ang I into Ang-(1-9), which is quickly converted to Ang-(1-7) and thereby controlling the blood pressure and hydro-salinity balance of pregnant women (Pringle *et al.*, 2011). The aberrant expression of Ang II, ACE2 and Ang-(1-7) may be involved in hypertension of pregnancy, pre-eclampsia and eclampsia (Merrill *et al.*, 2002; Brosnihan *et al.*, 2004; Anton *et al.*, 2008, 2009; Sykes *et al.*, 2014; Yamaleyeva *et al.*, 2014). Brosnihan *et al.* (2004) described that pre-eclamptic women presented with suppressed plasma Ang-(1-7) levels when compared with normal pregnancy subjects. High expression of Ang II in the placental villus during pre-eclampsia causes a decreased blood flow and nutrition supply in fetuses (Shibata *et al.*, 2006; Anton *et al.*, 2008, 2009). Meanwhile, low levels of ACE2 and Ang-(1-7) in placenta are associated with intrauterine growth restriction (Ghadhanfar *et al.*, 2017). In gestational *Ace2*$^{-/-}$ mice, plasma Ang-(1-7) decreases and placental Ang II increases, accompanied by abnormal placental functions (including placental hypoxia and uterine artery dysfunction) and ultimately fetal growth retardation (Bharadwaj *et al.*, 2011; Yamaleyeva *et al.*, 2015). Moreover, Chen *et al.* (2014) found that the maternal Ang-(1-7)/Ang II ratio is independently associated with gestational hypertension or pre-eclampsia, factors causing preterm birth. Additionally, it has been shown that the upregulation of ACE2/Ang-(1-7)/Mas prevents premature birth (Lumbers, 2020). It is noteworthy that premature birth and intrauterine growth restriction may predict the cardiovascular disorders that appear in adulthood (Irving *et al.*, 2000). Bessa *et al.* (2019) reported that activation of the ACE2/Ang-(1-7)/Mas axis in hypertensive pregnant rats could attenuate the cardiovascular dysfunction in adult offspring, confirming the engagement of the ACE2 axis in pregnancy.

2019-nCoV infection poses a great threat to pregnant women and fetuses, causing premature birth (20.8%, 25/120), fetal distress (26.7%, 12/45), premature rupture of fetal membranes (13.0%, 10/77) and cesarean section (92.6%, 63/68) (Chen *et al.*, 2020a,b; Ferrazzi *et al.*, 2020; Li *et al.*, 2020a; Liu *et al.*, 2020; Zeng *et al.*, 2020; Zhu *et al.*, 2020). The considerable cesarean section rate is mainly due to the concern about 2019-nCoV and obstetrical indications (Chen *et al.*, 2020b). It is worth mentioning that current data are still insufficient and some reports lack concrete details. Therefore, whether it is 2019-nCoV/ACE2 that causes the placental dysfunction remains elusive and needs further evaluation.

Moreover, just like SARS-CoV patients, patients infected with 2019-nCoV also demonstrate complicated acute renal impairment, renal dysfunction and renal failure (Chu *et al.*, 2005; Fan *et al.*, 2020; Li *et al.*, 2020b,d; Zhang *et al.*, 2020a). Pacciarini *et al.* (2008) found that SARS-CoV infects human tubular kidney cells. Of note is that ACE2 level in the renal tubules of pregnant mice increases by 117% compared to non-pregnant mice, which may contribute to the maintenance of blood pressure (Brosnihan *et al.*, 2003). We suppose that pregnant women with COVID-19 may be susceptible to renal injury.

Conclusion

2019-nCoV may infect the ovary, uterus, vagina and placenta through the ubiquitous expression of ACE2. Moreover, 2019-nCoV/ACE2 may disturb the female reproductive functions, resulting in infertility, menstrual disorder and fetal distress. We suggest a following-up and evaluation of fertility after recovery from 2019-nCoV infection, and delaying becoming pregnant, if possible, especially for young female patients. Moreover, we should persistently pay close attention to the situation of pregnant patients as well as fetuses, and take timely measures. What is more, to decrease the incidence of 2019-nCoV infection, special nursing should be conducted for healthy pregnant women, puerperants and newborn infants.

Authors' roles

C.F. and Y.J. wrote manuscript. L.R.-Q., W.H.-R., C.H.-R., L.Y.-B. and G.Y. prepared the references.

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Conflict of interest

None declared.

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