

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.

Keywords: 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 11th March, 2020. A total of 2,719,896 laboratory-confirmed cases and 187,705 deaths have been reported as of 25th 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 (Bataller *et al.*, 2000; Campbell-Boswell and Robertson, 1981; Hiruma *et al.*, 1997; Ray *et al.*, 1991), and maintains the hydro-salinity 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; Iwata *et al.*, 2005; Santos *et al.*, 2004) 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 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 (Barreta *et al.*, 2015; Tonello dos Santos *et al.*, 2012). 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 (Hayashi *et al.*, 2003; Shuttleworth *et al.*, 2002), facilitates follicle development (Ferreira *et al.*, 2011; Shuttleworth *et al.*, 2002) and oocyte maturation (Giometti *et al.*, 2005; Stefanello *et al.*, 2006; Yoshimura *et al.*, 1992), contributes to follicular atresia (Kotani *et al.*, 1999;

Obermuller *et al.*, 2004; Tanaka *et al.*, 1995), influences ovulation (Acosta *et al.*, 2000; Ferreira *et al.*, 2007; Guo *et al.*, 2012; Kuji *et al.*, 1996; Kuo *et al.*, 1991; Miyabayashi *et al.*, 2005; Pellicer *et al.*, 1988; Xu *et al.*, 2005; Xu and Stouffer, 2005; Yoshimura *et al.*, 1992; Yoshimura *et al.*, 1993) 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; Tonello dos Santos *et al.*, 2012; Viana *et al.*, 2011) 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 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.*, 2015; Shan *et al.*, 2014). 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 (Delforce *et al.*, 2017; Shibata *et al.*, 2005; Watanabe *et al.*, 2003), 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 (Ghadhanfar *et al.*, 2017; Neves *et al.*, 2008). 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 hours after birth (Dong *et al.*, 2020). Given that the identification of 2019-nCoV in human airway epithelial cells requires at least 96 hours

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 1 of 3 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 (Anton *et al.*, 2009; Anton *et al.*, 2008; Brosnihan *et al.*, 2004; Merrill *et al.*, 2002; 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 (Brosnihan *et al.*, 2004). High expression of Ang II in the placental villus during pre-eclampsia causes a decreased blood flow and nutrition supply in fetuses (Anton *et al.*, 2009; Anton *et al.*, 2008; Shibata *et al.*, 2006). 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 (Chen *et al.*, 2014). Additionally, it has been shown that the up-regulation 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 (Bessa *et al.*, 2019), 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; Chen *et al.*, 2020b; 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; Li *et al.*, 2020d; Zhang *et al.*, 2020a). Pacciarini *et al.* (2008) found that SARS-CoV infects human tubular kidney cells (Pacciarini *et al.*, 2008). 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., W.H., C.H., L.Y., G.Y. prepared the references.

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Conflict of interest

None declared.

References

- AbdAlla S, Lothar H, Abdel-tawab AM, Quitterer U. The angiotensin II AT2 receptor is an AT1 receptor antagonist. *J Biol Chem* 2001;**276**:39721-39726.
- Acosta TJ, Ozawa T, Kobayashi S, Hayashi K, Ohtani M, Kraetzl WD, Sato K, Schams D, Miyamoto A. Periovulatory changes in the local release of vasoactive peptides, prostaglandin f(2alpha), and steroid hormones from bovine mature follicles in vivo. *Biol Reprod* 2000;**63**:1253-1261.
- Ahmed A, Li XF, Shams M, Gregory J, Rollason T, Barnes NM, Newton JR. Localization of the angiotensin II and its receptor subtype expression in human endometrium and identification of a novel high-affinity angiotensin II binding site. *J Clin Invest* 1995;**96**:848-857.
- Anton L, Merrill DC, Neves LA, Diz DI, Corthorn J, Valdes G, Stovall K, Gallagher PE, Moorefield C, Gruver C *et al.* The uterine placental bed Renin-Angiotensin system in normal and preeclamptic pregnancy. *Endocrinology* 2009;**150**:4316-4325.
- Anton L, Merrill DC, Neves LA, Stovall K, Gallagher PE, Diz DI, Moorefield C, Gruver C, Ferrario CM, Brosnihan KB. Activation of local chorionic villi angiotensin II levels but not angiotensin (1-7) in preeclampsia. *Hypertension* 2008;**51**:1066-1072.
- Barreta MH, Gasperin BG, Ferreira R, Rovani M, Pereira GR, Bohrer RC, de Oliveira JF, Goncalves PB. The components of the angiotensin-(1-7) system are differentially expressed during follicular wave in cattle. *J Renin Angiotensin Aldosterone Syst* 2015;**16**:275-283.
- Bataller R, Gines P, Nicolas JM, Gorbic MN, Garcia-Ramallo E, Gasull X, Bosch J, Arroyo V, Rodes J. Angiotensin II induces contraction and proliferation of human hepatic stellate cells. *Gastroenterology* 2000;**118**:1149-1156.
- Baud D, Giannoni E, Pomar L, Qi X, Nielsen-Saines K, Musso D, Favre G. COVID-19 in pregnant women -Authors' reply. *The Lancet Infectious Diseases* 2020.
- Bessa ASM, Jesus EF, Nunes ADC, Pontes CNR, Lacerda IS, Costa JM, Souza EJ, Lino-Junior RS, Biancardi MF, Dos Santos FCA *et al.* Stimulation of the ACE2/Ang-(1-7)/Mas axis in hypertensive pregnant rats attenuates cardiovascular dysfunction in adult male offspring. *Hypertens Res* 2019;**42**:1883-1893.
- Bharadwaj MS, Strawn WB, Groban L, Yamaleyeva LM, Chappell MC, Horta C, Atkins K, Firmes L, Gurley SB, Brosnihan KB. Angiotensin-converting enzyme 2 deficiency is associated with impaired gestational weight gain and fetal growth restriction. *Hypertension* 2011;**58**:852-858.
- Brosnihan KB, Bharadwaj MS, Yamaleyeva LM, Neves LA. Decidualized pseudopregnant rat uterus shows marked reduction in Ang II and Ang-(1-7) levels. *Placenta* 2012;**33**:17-23.
- Brosnihan KB, Li P, Tallant EA, Ferrario CM. Angiotensin-(1-7): a novel vasodilator of the coronary circulation. *Biol Res* 1998;**31**:227-234.
- Brosnihan KB, Neves LA, Anton L, Joyner J, Valdes G, Merrill DC. Enhanced expression of Ang-(1-7) during pregnancy. *Braz J Med Biol Res* 2004;**37**:1255-1262.

- Brosnihan KB, Neves LA, Joyner J, Averill DB, Chappell MC, Sarao R, Penninger J, Ferrario CM. Enhanced renal immunocytochemical expression of ANG-(1-7) and ACE2 during pregnancy. *Hypertension* 2003;**42**:749-753.
- Campbell-Boswell M, Robertson AL, Jr. Effects of angiotensin II and vasopressin on human smooth muscle cells in vitro. *Exp Mol Pathol* 1981;**35**:265-276.
- Cavallo IK, Dela Cruz C, Oliveira ML, Del Puerto HL, Dias JA, Lobach VN, Casalechi M, Camargos MG, Reis AM, Santos RA *et al.* Angiotensin-(1-7) in human follicular fluid correlates with oocyte maturation. *Hum Reprod* 2017;**32**:1318-1324.
- Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, Yuen KY. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect* 2020;**9**:221-236.
- Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q *et al.* Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020a;**395**:809-815.
- Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, Feng L, Xiong G, Sun G, Wang H *et al.* Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. *N Engl J Med* 2020b.
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020c;**395**:507-513.
- Chen YP, Lu YP, Li J, Liu ZW, Chen WJ, Liang XJ, Chen X, Wen WR, Xiao XM, Reichetzedder C *et al.* Fetal and maternal angiotensin (1-7) are associated with preterm birth. *J Hypertens* 2014;**32**:1833-1841.
- Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, Fung KS, Tang HL, Yan WW, Chan HW *et al.* Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int* 2005;**67**:698-705.
- Costa AP, Fagundes-Moura CR, Pereira VM, Silva LF, Vieira MA, Santos RA, Dos Reis AM. Angiotensin-(1-7): a novel peptide in the ovary. *Endocrinology* 2003;**144**:1942-1948.
- Cui P, Chen Z, Wang T, Dai J, Zhang J, Ding T, Jiang J, Liu J, Zhang C, Shan W *et al.* Clinical features and sexual transmission potential of SARS-CoV-2 infected female patients: a descriptive study in Wuhan, China. *medRxiv* 2020:2020.2002.2026.20028225.
- Delforce SJ, Lumbers ER, Corbisier de Meaultsart C, Wang Y, Proietto A, Otton G, Scurry J, Verrills NM, Scott RJ, Pringle KG. Expression of renin-angiotensin system (RAS) components in endometrial cancer. *Endocr Connect* 2017;**6**:9-19.
- Deliu E, Tica AA, Motoc D, Brailoiu GC, Brailoiu E. Intracellular angiotensin II activates rat myometrium. *Am J Physiol Cell Physiol* 2011;**301**:C559-565.
- Dong L, Tian J, He S, Zhu C, Wang J, Liu C, Yang J. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. *JAMA* 2020.
- Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R *et al.* A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res* 2000;**87**:E1-9.
- Fan C, Li K, Ding Y, Lu WL, Wang J. ACE2 Expression in Kidney and Testis May Cause Kidney and Testis Damage After 2019-nCoV Infection. *medRxiv* 2020:2020.2002.2012.20022418.
- Ferrazzi E, Frigerio L, Savasi V, Vergani P, Prefumo F, Barresi S, Bianchi S, Ciriello E, Facchinetti F, Gervasi M *et al.* Mode of Delivery and Clinical Findings in COVID-19 Infected Pregnant Women in Northern Italy. *SSRN Electronic Journal* 2020.
- Ferreira AJ, Santos RA, Almeida AP. Angiotensin-(1-7): cardioprotective effect in myocardial ischemia/reperfusion. *Hypertension* 2001;**38**:665-668.

- Ferreira R, Gasperin B, Rovani M, Santos J, Barreta M, Bohrer R, Price C, Goncalves PB. Angiotensin II signaling promotes follicle growth and dominance in cattle. *Endocrinology* 2011;**152**:4957-4965.
- Ferreira R, Oliveira JF, Fernandes R, Moraes JF, Goncalves PB. The role of angiotensin II in the early stages of bovine ovulation. *Reproduction* 2007;**134**:713-719.
- 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.
- Giani JF, Mayer MA, Munoz MC, Silberman EA, Hocht C, Taira CA, Gironacci MM, Turyn D, Dominici FP. Chronic infusion of angiotensin-(1-7) improves insulin resistance and hypertension induced by a high-fructose diet in rats. *Am J Physiol Endocrinol Metab* 2009;**296**:E262-271.
- Giometti IC, Bertagnolli AC, Ornes RC, da Costa LF, Carambula SF, Reis AM, de Oliveira JF, Emanuelli IP, Goncalves PB. Angiotensin II reverses the inhibitory action produced by theca cells on bovine oocyte nuclear maturation. *Theriogenology* 2005;**63**:1014-1025.
- Guo B, Zhang XM, Li SJ, Tian XC, Wang ST, Li DD, Liu DF, Yue ZP. Expression and regulation of Ang-2 in murine ovaries during sexual maturation and development of corpus luteum. *Mol Biol (Mosk)* 2012;**46**:900-906.
- Hall JE, Guyton AC, Trippodo NC, Lohmeier TE, McCaa RE, Cowley AW, Jr. Intrarenal control of electrolyte excretion by angiotensin II. *Am J Physiol* 1977;**232**:F538-544.
- Hayashi KG, Acosta TJ, Tetsuka M, Berisha B, Matsui M, Schams D, Ohtani M, Miyamoto A. Involvement of angiotensin II system in bovine follicular development and atresia: messenger RNA expression in theca interna and effect on steroid secretion. *Biol Reprod* 2003;**69**:2078-2084.
- Hering L, Herse F, Geusens N, Verlohren S, Wenzel K, Staff AC, Brosnihan KB, Huppertz B, Luft FC, Muller DN *et al.* Effects of circulating and local uteroplacental angiotensin II in rat pregnancy. *Hypertension* 2010;**56**:311-318.
- Hiruma Y, Inoue A, Hirose S, Hagiwara H. Angiotensin II stimulates the proliferation of osteoblast-rich populations of cells from rat calvariae. *Biochem Biophys Res Commun* 1997;**230**:176-178.
- Honorato-Sampaio K, Pereira VM, Santos RA, Reis AM. Evidence that angiotensin-(1-7) is an intermediate of gonadotrophin-induced oocyte maturation in the rat preovulatory follicle. *Exp Physiol* 2012;**97**:642-650.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**:497-506.
- Irving RJ, Belton NR, Elton RA, Walker BR. Adult cardiovascular risk factors in premature babies. *Lancet* 2000;**355**:2135-2136.
- Iwata M, Cowling RT, Gurantz D, Moore C, Zhang S, Yuan JX, Greenberg BH. Angiotensin-(1-7) binds to specific receptors on cardiac fibroblasts to initiate antifibrotic and antitrophic effects. *Am J Physiol Heart Circ Physiol* 2005;**289**:H2356-2363.
- Johnson MD, Malvin RL. Stimulation of renal sodium reabsorption by angiotensin II. *Am J Physiol* 1977;**232**:F298-306.
- Kostenis E, Milligan G, Christopoulos A, Sanchez-Ferrer CF, Heringer-Walther S, Sexton PM, Gembardt F, Kellett E, Martini L, Vanderheyden P *et al.* G-Protein-Coupled Receptor Mas Is a Physiological Antagonist of the Angiotensin II Type 1 Receptor. *Circulation* 2005;**111**:1806-1813.
- Kotani E, Sugimoto M, Kamata H, Fujii N, Saitoh M, Usuki S, Kubo T, Song K, Miyazaki M, Murakami K *et al.* Biological roles of angiotensin II via its type 2 receptor during rat follicle atresia. *Am J Physiol* 1999;**276**:E25-33.
- Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005;**11**:875-879.

- Kuji N, Sueoka K, Miyazaki T, Tanaka M, Oda T, Kobayashi T, Yoshimura Y. Involvement of angiotensin II in the process of gonadotropin-induced ovulation in rabbits. *Biol Reprod* 1996;**55**:984-991.
- Kuo TC, Endo K, Dharmarajan AM, Miyazaki T, Atlas SJ, Wallach EE. Direct effect of angiotensin II on in-vitro perfused rabbit ovary. *J Reprod Fertil* 1991;**92**:469-474.
- Li N, Han L, Peng M, Lv Y, Ouyang Y, Liu K, Yue L, Li Q, Sun G, Chen L *et al.* Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. *Clin Infect Dis* 2020a.
- Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, Shen B, Gong Z. Clinical characteristics of 25 death cases infected with COVID-19 pneumonia: a retrospective review of medical records in a single medical center, Wuhan, China. *medRxiv* 2020b:2020.2002.2019.20025239.
- Li XF, Ahmed A. Dual role of angiotensin II in the human endometrium. *Hum Reprod* 1996a;**11 Suppl 2**:95-108.
- Li XF, Ahmed A. Expression of angiotensin II and its receptor subtypes in endometrial hyperplasia: a possible role in dysfunctional menstruation. *Lab Invest* 1996b;**75**:137-145.
- Li XF, Ahmed A. Compartmentalization and cyclic variation of immunoreactivity of renin and angiotensin converting enzyme in human endometrium throughout the menstrual cycle. *Hum Reprod* 1997;**12**:2804-2809.
- Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020c.
- Li Z, Wu M, Guo J, Yao J, Liao X, Song S, Han M, Li J, Duan G, Zhou Y *et al.* Caution on Kidney Dysfunctions of 2019-nCoV Patients. *medRxiv* 2020d:2020.2002.2008.20021212.
- Liu C, Lv XH, Li HX, Cao X, Zhang F, Wang L, Yu M, Yang JK. Angiotensin-(1-7) suppresses oxidative stress and improves glucose uptake via Mas receptor in adipocytes. *Acta Diabetol* 2012;**49**:291-299.
- Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. *J Infect* 2020.
- Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;**395**:565-574.
- Lumbers ER. Chapter 10 - The Physiological Roles of the Renin-Angiotensin Aldosterone System and Vasopressin in Human Pregnancy. In Kovacs CS, Deal CL (eds) *Maternal-Fetal and Neonatal Endocrinology*. 2020. Academic Press, pp. 129-145.
- Mao L, Wang M, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Li Y, Jin H *et al.* Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. *medRxiv* 2020:2020.2002.2022.20026500.
- Merrill DC, Karoly M, Chen K, Ferrario CM, Brosnihan KB. Angiotensin-(1-7) in normal and preeclamptic pregnancy. *Endocrine* 2002;**18**:239-245.
- Miyabayashi K, Shimizu T, Kawachi C, Sasada H, Sato E. Changes of mRNA expression of vascular endothelial growth factor, angiopoietins and their receptors during the periovulatory period in eCG/hCG-treated immature female rats. *J Exp Zool A Comp Exp Biol* 2005;**303**:590-597.
- Muthalif MM, Benter IF, Uddin MR, Harper JL, Malik KU. Signal transduction mechanisms involved in angiotensin-(1-7)-stimulated arachidonic acid release and prostanoid synthesis in rabbit aortic smooth muscle cells. *J Pharmacol Exp Ther* 1998;**284**:388-398.
- National Health Commission of the People's Republic of China. The notice of launching guideline on diagnosis and treatment of the novel coronavirus pneumonia. (7th edition) Accessed Mar 4, 2020; in Chinese.
- Neves LA, Stovall K, Joyner J, Valdes G, Gallagher PE, Ferrario CM, Merrill DC, Brosnihan KB. ACE2 and ANG-(1-7) in the rat uterus during early and late gestation. *Am J Physiol Regul Integr Comp Physiol* 2008;**294**:R151-161.

- Obermuller N, Gentili M, Gauer S, Gretz N, Weigel M, Geiger H, Gassler N. Immunohistochemical and mRNA localization of the angiotensin II receptor subtype 2 (AT2) in follicular granulosa cells of the rat ovary. *J Histochem Cytochem* 2004;**52**:545-548.
- Oliveira MA, Fortes ZB, Santos RA, Kosla MC, De Carvalho MH. Synergistic effect of angiotensin-(1-7) on bradykinin arteriolar dilation in vivo. *Peptides* 1999;**20**:1195-1201.
- Pacciarini F, Ghezzi S, Canducci F, Sims A, Sampaolo M, Ferioli E, Clementi M, Poli G, Conaldi PG, Baric R *et al*. Persistent replication of severe acute respiratory syndrome coronavirus in human tubular kidney cells selects for adaptive mutations in the membrane protein. *J Virol* 2008;**82**:5137-5144.
- Pellicer A, Palumbo A, DeCherney AH, Naftolin F. Blockage of ovulation by an angiotensin antagonist. *Science* 1988;**240**:1660-1661.
- Pereira VM, Reis FM, Santos RA, Cassali GD, Santos SH, Honorato-Sampaio K, dos Reis AM. Gonadotropin stimulation increases the expression of angiotensin-(1-7) and MAS receptor in the rat ovary. *Reprod Sci* 2009;**16**:1165-1174.
- 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**:956-962.
- Ray PE, Aguilera G, Kopp JB, Horikoshi S, Klotman PE. Angiotensin II receptor-mediated proliferation of cultured human fetal mesangial cells. *Kidney Int* 1991;**40**:764-771.
- Reis FM, Bouissou DR, Pereira VM, Camargos AF, dos Reis AM, 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.
- Roks AJ, van Geel PP, Pinto YM, Buikema H, Henning RH, de Zeeuw D, van Gilst WH. Angiotensin-(1-7) is a modulator of the human renin-angiotensin system. *Hypertension* 1999;**34**:296-301.
- Santos RA, Ferreira AJ, Nadu AP, Braga AN, de Almeida AP, Campagnole-Santos MJ, Baltatu O, Iliescu R, Reudelhuber TL, Bader M. Expression of an angiotensin-(1-7)-producing fusion protein produces cardioprotective effects in rats. *Physiol Genomics* 2004;**17**:292-299.
- Santos RA, Simoes e Silva AC, Maric C, Silva DM, Machado RP, de Buhr I, Heringer-Walther S, Pinheiro SV, Lopes MT, Bader M *et al*. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proc Natl Acad Sci U S A* 2003;**100**:8258-8263.
- Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics* 2012;**129**(3):e827–e841
- Shan T, Shang W, Zhang L, Zhao C, Chen W, Zhang Y, Li G. Effect of angiotensin-(1-7) and angiotensin II on the proliferation and activation of human endometrial stromal cells in vitro. *Int J Clin Exp Pathol* 2015;**8**:8948-8957.
- Shan T, Zhang L, Zhao C, Chen W, Zhang Y, Li G. Angiotensin-(1-7) and angiotensin induce the transdifferentiation of human endometrial epithelial cells in vitro. *Mol Med Rep* 2014;**9**:2180-2186.
- Shibata E, Powers RW, Rajakumar A, von Versen-Hoyneck F, Gallaher MJ, Lykins DL, Roberts JM, Hubel CA. Angiotensin II decreases system A amino acid transporter activity in human placental villous fragments through AT1 receptor activation. *Am J Physiol Endocrinol Metab* 2006;**291**:E1009-1016.
- Shibata K, Kikkawa F, Mizokami Y, Kajiyama H, Ino K, Nomura S, Mizutani S. Possible involvement of adipocyte-derived leucine aminopeptidase via angiotensin II in endometrial carcinoma. *Tumour Biol* 2005;**26**:9-16.
- Shuttleworth G, Broughton Pipkin F, Hunter MG. In vitro development of pig preantral follicles cultured in a serum-free medium and the effect of angiotensin II. *Reproduction* 2002;**123**:807-818.
- Stefanello JR, Barreta MH, Porciuncula PM, Arruda JN, Oliveira JF, Oliveira MA, Goncalves PB. 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**:2068-2076.

- Sugino N, Suzuki T, Sakata A, Miwa I, Asada H, Taketani T, Yamagata Y, Tamura H. 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**:6141-6148.
- Sykes SD, Pringle KG, Zhou A, Dekker GA, Roberts CT, Lumbers ER, consortium S. 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**:133-139.
- Tanaka M, Ohnishi J, Ozawa Y, Sugimoto M, Usuki S, Naruse M, Murakami K, Miyazaki H. Characterization of angiotensin II receptor type 2 during differentiation and apoptosis of rat ovarian cultured granulosa cells. *Biochem Biophys Res Commun* 1995;**207**:593-598.
- Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J Biol Chem* 2000;**275**:33238-33243.
- Tonello dos Santos J, Ferreira R, Gasperin BG, Siqueira LC, de Oliveira JF, Santos RA, Reis AM, Goncalves PB. 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**:91-98.
- Valdes G, Neves LA, Anton L, Corthorn J, Chacon C, Germain AM, Merrill DC, Ferrario CM, Sarao R, Penninger J *et al*. Distribution of angiotensin-(1-7) and ACE2 in human placentas of normal and pathological pregnancies. *Placenta* 2006;**27**:200-207.
- Vaswani K, Chan HW, Verma P, Dekker Nitert M, Peiris HN, Wood-Bradley RJ, Armitage JA, Rice GE, Mitchell MD. The rat placental renin-angiotensin system - a gestational gene expression study. *Reprod Biol Endocrinol* 2015;**13**:89.
- Vaz-Silva J, Carneiro MM, Ferreira MC, Pinheiro SV, Silva DA, Silva-Filho AL, Witz CA, Reis AM, Santos RA, 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.
- Vaz-Silva J, Tavares RL, Ferreira MC, Honorato-Sampaio K, Cavallo IK, Santos RA, dos Reis AM, Reis FM. Tissue specific localization of angiotensin-(1-7) and its receptor Mas in the uterus of ovariectomized rats. *J Mol Histol* 2012;**43**:597-602.
- Viana GE, Pereira VM, Honorato-Sampaio K, Oliveira CA, Santos RA, Reis AM. Angiotensin-(1-7) induces ovulation and steroidogenesis in perfused rabbit ovaries. *Exp Physiol* 2011;**96**:957-965.
- 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 peptides by human angiotensin-converting enzyme-related carboxypeptidase. *J Biol Chem* 2002;**277**:14838-14843.
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y *et al*. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020.
- Wang P-H, Cheng Y. Increasing Host Cellular Receptor—Angiotensin-Converting Enzyme 2 (ACE2) Expression by Coronavirus may Facilitate 2019-nCoV Infection. *bioRxiv* 2020:2020.2002.2024.963348.
- Watanabe Y, Shibata K, Kikkawa F, Kajiyama H, Ino K, Hattori A, Tsujimoto M, Mizutani S. Adipocyte-derived leucine aminopeptidase suppresses angiogenesis in human endometrial carcinoma via renin-angiotensin system. *Clin Cancer Res* 2003;**9**:6497-6503.
- World Health Organization. Coronavirus disease (COVID-2019) situation reports. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>. 2020

- Wu YT, Liu C, Dong L, Zhang CJ, Chen Y, Liu J, Zhang C, Duan CC, Zhang HQ, Mol BW *et al*. Viral Shedding of COVID-19 in Pregnant Women. Available at SSRN: <https://ssrncom/abstract=3562059> or <http://dxdoiorg/102139/ssrn3562059> 2020.
- Xu F, Hazzard TM, Evans A, Charnock-Jones S, Smith S, Stouffer RL. Intraovarian actions of anti-angiogenic agents disrupt periovulatory events during the menstrual cycle in monkeys. *Contraception* 2005;**71**:239-248.
- Xu F, Stouffer RL. Local delivery of angiopoietin-2 into the preovulatory follicle terminates the menstrual cycle in rhesus monkeys. *Biol Reprod* 2005;**72**:1352-1358.
- Yamaleyeva LM, Merrill DC, Ebert TJ, Smith TL, Mertz HL, Brosnihan KB. Hemodynamic responses to angiotensin-(1-7) in women in their third trimester of pregnancy. *Hypertens Pregnancy* 2014;**33**:375-388.
- Yamaleyeva LM, Pulgar VM, Lindsey SH, Yamane L, Varagic J, McGee C, daSilva M, Lopes Bonfa P, Gurley SB, Brosnihan KB. Uterine artery dysfunction in pregnant ACE2 knockout mice is associated with placental hypoxia and reduced umbilical blood flow velocity. *Am J Physiol Endocrinol Metab* 2015;**309**:E84-94.
- Yoshimura Y, Karube M, Koyama N, Shiokawa S, Nanno T, Nakamura Y. Angiotensin II directly induces follicle rupture and oocyte maturation in the rabbit. *FEBS Lett* 1992;**307**:305-308.
- Yoshimura Y, Karube M, Oda T, Koyama N, Shiokawa S, Akiba M, Yoshinaga A, Nakamura Y. Locally produced angiotensin II induces ovulation by stimulating prostaglandin production in in vitro perfused rabbit ovaries. *Endocrinology* 1993;**133**:1609-1616.
- Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, Zhou W. Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. *JAMA Pediatrics* 2020.
- Zhang B, Zhou X, Qiu Y, Feng F, Feng J, Jia Y, Zhu H, Hu K, Liu J, Liu Z *et al*. Clinical characteristics of 82 death cases with COVID-19. *medRxiv* 2020a:2020.2002.2026.20028191.
- Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020b.
- Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020.
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020.
- Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, Xia S, Zhou W. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020;**9**:51-60.