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

Yan Jing, Li Run-Qian, Wang Hao-Ran, Chen Hao-Ran, Liu Ya-Bin, Gao Yang, and Chen Fei *

Department of Physiology, Jining Medical University, 272067 Jining, China

* Correspondence address. Department of Physiology, Jining Medical University, 133 Hehua Road, 272067 Jining, China.
Tel: +8605372610652; Fax: +8605372610652; E-mail: chenfei0336@163.com

Submitted on March 21, 2020; resubmitted on April 26, 2020; editorial decision on May 1, 2020

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) have significant influence on the female reproductive system, of 2019-nCoV.

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 type I) 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 hydration 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; Barretta 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 Scouffer, 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 (Muthalf et al., 1998; Viana et al., 2011; Tonellotto dos Santos et al., 2012) and the resumption of meiosis in the oocyte (Honaroto-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, 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.
Coronavirus and female reproduction

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 breastfeeding 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 (Herring 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. Moreover, 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; 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 or that 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., 2020a; 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.

Funding

This work was supported by National Natural Science Foundation of China (No. 31801172).

Conflict of interest

None declared.

References

AbdAlla S, Lother 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 pre eclamptic 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.

Barreto 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, Gorbig 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. Lancet Infect Dis 2020; doi 10.1016/S1473-3099(20)30192-4.

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; doi: 10.1056/NEJMct2009226.

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, Reichetzeder 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 2003;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; doi: 10.1101/2020.02.26.20028225.

Delforce SJ, Lumbers ER, Corbiser de Meautsart 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.

Delu E, Tica AA, Motoc D, Brailoiu GC, Brailoiu E. Intracellular angiotensin II activates rat myometrium. Am J Physiol Cell Physiol 2011;301:C559–C565.

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;323:1846–1848.

Donoghue M, Hsieh F, Baraton B, Godbout K, Gosselin M, Stagliano F, Gervasi M, Bianchi S, Ciriello E, Facchinetti F, Gervasi M. Genomic characterization of the 2019 novel human-pathogenic coronavirus associated with COVID-19. medRxiv 2020; doi: 10.1101/2020.02.12.20022418.

Ferrazzi E, Frigerio L, Savasi V, Vergani P, Prefumo F, Barresi S, Deliu E, Tica AA, Motoc D, Brailoiu GC, Brailoiu E. Intracellular angiotensin II activates rat myometrium. Am J Physiol Cell Physiol 2011;301:C559–C565.

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–E271.

Giometti IC, Bertagnoli AC, Omes RC, da Costa LF, Carambula SF, Reis AM, de Oliveira JP, 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–F544.

Hayashi KG, Acosta TJ, Tetsuka M, Berisha B, Matsui M, Schams D, Ohtani M, Miyamoto A. Involvement of angiotopiin-tie system in bovine follicular development and atresia: messenger RNA expression in theca interna and effect on steroid secretion. *Endocrinology* 2002;143:2804–2809.

Hiruma Y, Inoue A, Hirose S, Hagiwara H. Angiotensin II stimulates oocyte nuclear maturation. *Hum Reprod* 2009;21:642–650.

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, Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Guo F, 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; doi: 10.1093/cid/ciaa352.

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; doi: 10.1101/2020.02.19.20025239.

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;92:552–555.

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; doi: 10.1101/2020.02.08.20021212.

Liu C, Lv XH, LiHX, 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; doi: 10.1016/j.jinf.2020.02.028.

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: CS Kovacs, CL Deal (eds). *Maternal-Fetal and Neonatal Endocrinology*. Academic Press: UK and USA, 2020, 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. *JAMA Neurology* 2020; doi: 10.1001/jamanetworkneurology.2020.1127.

Merrill DC, Karoly M, Chen K, Ferrario CM, Brosnihan KB. Angiotensin-(1-7) in normal and pre eclamptic pregnancy. *Endocrine* 2002;18:239–245.

Miyanobashi K, Shimizu T, Kawuuchi C, Sasada H, Sato E. Changes of mRNA expression of vascular endothelial growth factor, angiopeptins 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. Beijing, China; http://www.nhc.gov.cn/yzwz/202003/46c9294a7dfefe800c07f5912eb1989.shtml (4 March 2020; date last accessed; 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–R161. 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, Sim S, Sampalo 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, Aguiler 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, Reudehuber 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 USA 2003;100:8258–8263. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827–e841.

Shan T, Wang 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-Hoynek F, Gallagher MJ, Lykins DL, Roberts JM, Hubel CA. Angiotensin II decreases system A amino acid transporter activity in human placental villous fragments through ATI receptor activation. Am J Physiol Endocrinol Metab 2006;291:E1009–E1016. Shibata K, Kikikawa 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, Barretha MH, Porciuncula PM, Arnuda 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 pre-eclampsia or gestational hypertension. J Hum Hypertens 2014;28:133–139. Tanaka M, Oshimizu 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. Tonellotto 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. Vasswani 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.
Coronavirus and female reproduction

Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, 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, Cavollo 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 2020a;323:1061–1069.

Wang P-H, Cheng Y. Increasing host cellular receptor—angiotensin-converting enzyme 2 (ACE2) expression by coronavirus may facilitate 2019-nCoV infection. bioRxiv 2020b; doi:10.1101/2020.02.24.963348.

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. 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (25 April 2020, date last accessed).

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://ssrn.com/abstract=3562059 or http://dx.doi.org/10.2139/ssrn.3562059 2020 (25 March 2020, date last accessed).

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 prevulatory 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, Gurlay 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:EB4–E94.

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 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 Pediatr 2020; doi:10.1001/jamapediatrics.2020.0878.

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; doi: 10.1101/2020.02.26.20028191.

Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020b;5:428–430.

Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259–260.

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;579:270–273.

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.