Pregnancy and breastfeeding during COVID-19 pandemic

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In late 2019 in the Chinese city of Wuhan, a new coronavirus was identified as the cause of a cluster of pneumonia cases designated as COVID-19. The COVID-19 outbreak subsequently spread exponentially to become a global pandemic.[1] The coronavirus that causes COVID-19, referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), binds the host lung epithelial cellular angiotensin-converting enzyme (ACE) 2 receptors to infect the cell, and this is most likely the mechanisms by which human-to-human transmissions of SARS-CoV occur.[2] Binding of the SARS-CoV-2 spike protein to ACE2 results in downregulation of cellular expression of ACE2.[3]

Evidence suggests that ACE2 may play an important role in the response to injury as loss of ACE2 has been associated with increased susceptibility to injury in various organs including heart, lung, and kidney[4] as well as promoting fasting hyperglycemia[5] and inflammation.[6] The mechanisms of ACE2-induced-improved protection against injury include not only the hydrolysis of Ang II, and thus limiting its pathological implications, but also the conversion of Ang II into Ang-(1-7).[4] Evidence suggests that Ang-(1-7) may have several beneficial effects including vasodilation, anti-fibrotic, anti-inflammatory, anti-ischemic, anti-hypertrophic, and anti-proliferative effects.[7]

During normal pregnancy, circulating estrogen causes an increase in hepatic synthesis of angiotensinogen as well as triggering the release of renin by the ovaries and maternal decidua during the first few weeks of pregnancy.[8] Although this leads to increased plasma levels of Ang II, maternal BP remains normal or even decreases, suggesting the presence of a state of relative vascular insensitivity to Ang II during uncomplicated pregnancy.[8] In fact, Assali and colleagues[9] showed that healthy pregnant women, as compared with nonpregnant women, may require twice as much intravenous Ang II infusion to achieve the same vasomotor response. The mechanisms underlying this resistance to the pressor effects of Ang II may include a downregulation of the AT1 receptor, which is the predominant angiotensin receptor responsible for most of the Ang II pathological signaling.[10] In addition, AT1 receptors are monomeric in healthy pregnancies and may be inactivated by reactive oxygen species generated by various insults such as SARS-CoV-2 infection; this may result in further Ang II insensitivity.[11] Interestingly, Merrill and colleagues[12] reported a progressive rise of Ang-(1-7) throughout normal human gestation, reaching peak levels late (at 35 weeks of gestation). High levels of Ang-(1-7) may counterbalance the rise, but most importantly the pathological action attributed to excess Ang II.[12] The observed enhanced ACE2 expression during pregnancy may also contribute to the vasomotor refractoriness to Ang II as this carboxypeptidase has been shown to exhibit high catalytic efficiency to generate Ang-(1-7) while inhibiting the vasoconstrictor counterpart Ang II.[10] Taken together, the above observations suggest that pregnant women may be less vulnerable to developing severe SARS-CoV-2 infection than outside of pregnancy.[13,14] Although pregnancy may be relatively protective, there is still a group of pregnant women, such as women with preeclampsia, who may be at particular risk for severe course of the disease. In preeclampsia, there is heterodimerization of the AT1 receptor, which may increase the responsiveness to Ang II as well as conferring resistance in AT1 receptors to inactivation by reactive oxygen species, which may be generated in individuals infected with SARS-Cov-2 virus.[15–17] Pregnant women with preeclampsia may also have reduced plasma levels of Ang-(1-7), which in the presence of elevated plasma Ang II put them at increased susceptibility to lung and vascular injuries, leaving thus these

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high-risk group population more vulnerable to developing severe disease and less able to cope with SARS-CoV-2 infection. Although there is currently limited data about the impact of elevated blood glucose concentrations on the outcomes of patients infected by SARS-CoV-2 infection, poor glycemic control has been associated with increased risk of complications and death in individuals affected by SARS and influenza H1N1.[18,19] These observations raise the questions of whether pregnant women with poorly controlled gestational diabetes may also be more vulnerable to developing severe disease and less able to cope with SARS-CoV-2 infection.

Recent evidence suggests that SARS-CoV-2 infection can be transmitted from the mother to the fetus.[20] Vivanti and colleagues[21] reported a proven case of transplacental transmission of SARS-CoV-2 from a pregnant woman infected by SARS-CoV-2 during late pregnancy to the fetus. Elevated levels of ACE2 receptors have also been found in fetal placental, suggesting that SARS-CoV-2-infected pregnant women may expose the fetus to SARS-CoV-2 infection.[22] In fact, neonatal cases of SARS-CoV-2 infection have been documented.[23,24] Although neonates are almost never severely affected,[14,17] there is still a small group of newborns who may be at particular risk for severe course of the disease. Changes in the expression of the AT1 and AT2 receptors during pregnancy may be important in the pathophysiology of SARS-CoV-2 infection in pregnancy. AT2 receptors are dominantly expressed in vascular smooth muscle cells in blood vessels of the umbilical cord and placenta during the second and third trimesters. Evidence suggests that AT2 receptors may bind directly to the AT1 receptor, thereby antagonizing important pathological action attributed to excess AT1 receptor activation.[25] As hinted above, there is also a progressive rise of Ang-(1-7) throughout normal human gestation, reaching peak levels late (at 35 weeks of gestation).[12] Taken together, these observations suggest that women infected early during their pregnancy (first trimester) may be more likely to have poor maternal and fetal outcomes compared with those who acquire the infection in late pregnancy.

It is still unknown whether SARS-CoV-2 infection can be transmitted through breastfeeding. Chen and colleagues[23] collected breastmilk samples from pregnant women with laboratory-confirmed SARS-CoV-2 infection after the first lactation and found no virus in the maternal milk. In contrast, Groß and colleagues[26] detected SARS-CoV-2 RNA in milk samples from mothers infected with SARS-CoV-2. Whether this occurred via breastfeeding or through other modes of transmission remains to be clarified. SARS-CoV-2 infection may still be transmitted through close contact during breastfeeding. Thus, breastfeeding women with confirmed or suspected COVID-19 should take precautions to prevent transmission to the infant during breastfeeding. Alternatively, another healthy caregiver can feed expressed breastmilk to the infant until the mother has recovered. Women who choose not to breastfeed should take similar hygiene precautions to prevent transmission through close contact when formula is used.

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