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EDITORIAL

Placenta-Heart-Brain Connection in Congenital Heart Disease

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Increasing recognition of the critical role of the placenta in the long-term health of the fetus and mother has generated two important and evolving areas of research: the developmental origins of health and disease (DOHaD) and cardiovascular health after maternal placental syndromes (CHAMPS).[1] Yet, the human placenta remains a poorly understood organ. The Human Placenta Project (HPP) was launched by the Eunice Kennedy Shriver National Institute of Child Health and Development in 2014 to address gaps in knowledge about the placenta and has supported >40 studies and >450 publications on placental structure, development, and function across gestation.[2] Concurrently, investigations of placental pathology have identified key features as risk factors for adverse maternal and infant outcomes.[3–5] In accordance with this evolving literature, guidelines for evaluation of clinical placental pathology were recently updated.[6]

See article by Nijman et al.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Nijman et al[7] take a key step in advancing our understanding of the DOHaD by linking placental pathology with altered brain development in neonates with severe congenital heart disease (CHD). Their data are the first to support the widespread hypothesis that placental abnormalities are intricately intertwined with brain development in CHD. The authors adapted a placental pathology scoring system to assess placental function, loss of functional placental parenchyma, and placental impact on neonatal homeostasis. They then measured regional brain volumes using preoperative magnetic resonance imaging in 65 neonates with severe forms of CHD requiring cardiac intervention in the first 6 months of life. Linear regression modeling, adjusting for postmenstrual age at magnetic resonance imaging, demonstrated an association between higher placental pathology severity score and lower brain volumes for cortical gray matter, cerebellum, and total brain. Interestingly, placental pathology was not significantly associated with volume of white matter,[7] a region that is particularly vulnerable in the fetus with CHD.[8] White matter growth peaks in the early third trimester, whereas growth of the cerebral cortex and cerebellum increases exponentially throughout the third trimester of pregnancy.[9] The accelerated complexity of fetal brain development during the third trimester requires increased oxygen and substrate delivery.[10] Taken together, these data suggest that placental dysfunction has the greatest impact on brain regions that are developing the most rapidly in the third trimester, when metabolic requirements are higher than in other periods.

The findings by Nijman et al[7] not only advance our understanding of brain development in CHD but also

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contribute to the growing field of neuroplacentology, which links placental physiology and pathology with fetal brain development.[4] Most clinical investigations in this area have focused on cerebral palsy, neonatal encephalopathy, neonatal stroke, or forms of brain injury common in preterm infants (ie, intraventricular hemorrhage and periventricular leukomalacia). In a systematic review, the placental lesions most commonly associated with adverse neurological outcomes were acute chorioamnionitis with fetal inflammatory response and fetal thrombotic vasculopathy.[5] The relationship between placental pathology and fetal/neonatal neurological abnormalities may occur through a variety of pathophysiologic mechanisms that disrupt typical placental development. Placental growth and function evolve throughout gestation via developmentally regulated angiogenesis, trophoblast differentiation, and syncytium formation, which adapt to the maternal environment and contribute to fetal programming.[11] Optimal placental development and functioning is essential for adequate oxygen and nutrient exchange between the mother and fetus, but is also critical for hormonal regulation, immune modulation, and filtering of toxins and pathogens.[4,11] A number of neuroactive hormones (eg, allopregnanolone), immune molecules (eg, proinflammatory cytokines), and growth factors (eg, placental growth factor and soluble fms-like tyrosine kinase-1) are produced by the placenta and may have detrimental or protective effects on the fetal brain in direct and indirect ways.[4] Disturbances in any of these pathways have the potential to alter the typical developmental trajectory of the fetal brain.

Additional mechanisms may be particularly pertinent to the fetus with CHD. Shared genetic and epigenetic factors may influence development of the placenta, heart, and brain.[12] Vascular endothelial growth factor, placental growth factor, and soluble fms-like tyrosine kinase-1 are critical for formation of the placental vascular network, are dysregulated with preeclampsia and fetal growth restriction (both of which are common with fetal CHD), and are altered in maternal serum, infant cardiac tissue, and fetal brain tissue when a cardiac defect is present in the fetus.[13–15] Evolving preclinical data suggest that placental trophoblast-specific knockouts and defects in syncytiotrophoblasts may cause CHD.[16] Alterations in glucose transporter expression and downregulation of genes and gene pathways related to cell cycle regulation also occur, specifically in hypoplastic left heart syndrome.[17] Finally, Notch and Wnt pathways are important for cardiomyocyte specification, extravillous trophoblast invasion, neural progenitor proliferation, neuronal migration, and cortical neurogenesis.[12,17,18] In addition to these molecular pathways, the cardiac defect may cause hemodynamic changes that result in chronic hypoxia in the fetus with CHD.[12] Chronic hypoxia could activate inflammatory pathways and disrupt angiogenesis, leading to placental and brain maldevelopment.[4] Collectively, these data support that genetic, epigenetic, and hemodynamic disturbances may all contribute to abnormalities of placental, heart, and brain development in the fetus with CHD.

With respect to placental pathologic abnormalities in CHD, decreased placental weight, abnormal umbilical cord insertion, chorangiosis, maternal and fetal vascular malperfusion (including fetal thrombotic vasculopathy), chronic inflammation, and delayed villous maturation have all been reported.[16] The frequency and pattern of abnormalities identified by Nijman et al[7] are consistent with prior literature, although take a slightly different approach to pathology interpretation by using a severity scoring system. While it is clear that gross and histopathologic abnormalities occur with CHD, less is known about the impact on the brain in this population. In one cohort, placental pathologic abnormalities were associated with brain injury in infants with CHD.[19] Another study demonstrated that an impaired maternal-fetal environment (eg, preeclampsia and gestational diabetes) increased the frequency of preoperative white matter injury.[20] Nijman and colleagues[7] did not find an association between placental pathology and brain injury, despite its association with impaired brain growth. One limitation to their study is that the authors did not account for maternal or fetal factors that could be mediators or moderators of this relationship, such as preeclampsia, diabetes, and genetics (an exclusion criterion). A recent study in patients with CHD identified a univariate association between placental pathology and early childhood neurodevelopmental outcome, but this relationship was no longer present after adjusting for clinical factors.[21] Thus, while Nijman et al[7] have laid an important foundation for the placenta-brain connection in CHD, causality is more difficult to discern. A myriad of complex, intersecting factors within the maternal-fetal environment could cause abnormal placental and brain development, thereby predisposing to adverse postnatal neurological and developmental outcomes in CHD.

In their foundational work relating placental pathology to altered brain development in CHD, Nijman et al[7] have set the stage for future mechanistic research. It is still uncertain whether placental abnormalities reflect early maldevelopment from genetic/epigenetic disturbances that also cause fetal cardiac and brain defects, whether the fetal cardiac defect causes placental and fetal brain abnormalities through hemodynamic alterations, or whether additional pathways (eg, placental and brain maldevelopment secondary to maternal stress after a fetal CHD diagnosis) play a role in disrupting typical development across the placenta and brain in CHD. Future investigations that incorporate detailed collection of perinatal risk factors,

placental function and histology, genetic and epigenetic approaches, neuroimaging metrics, and neurodevelopmental outcomes will be key to addressing these critical knowledge gaps. Innovative mechanistic studies and machine learning approaches to elucidate the interrelationships between the placenta, heart, and brain may lead to future maternal-fetal interventions that improve brain structure and neurodevelopmental outcomes in patients with CHD.

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