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EDITORIAL

Understanding the Maternal-Fetal Environment and the Birth of Prenatal Pediatrics

Catherine Limperopoulos, PhD; David L. Wessel, MD; Adre J. du Plessis, MBChB

In this issue of the *Journal of the American Heart Association (JAHA)*, investigators from the Children's Hospital of Philadelphia, one of the leading centers for fetal medicine, pediatric cardiology, and cardiac surgery, extend their investigation into the factors associated with adverse outcome in children with critical congenital heart disease (CHD).[1] In their article,[2] Savla et al report on a retrospective cohort study that examines the association between prenatal factors in the maternal-fetal environment and mortality after the stage 1 Norwood procedure in children with single-ventricle cardiac lesions. In recent years it has become increasingly recognized that population-based predictors of outcome in these children fail to account for much of the variability in individual patient-based outcomes. This in turn, has triggered a growing interest in factors other than those traditionally considered in risk modeling, such as the anatomic nature of the heart lesion and the specifics of surgical repair and postoperative care. The current study enters into the risk model maternal-placental-fetal factors heretofore rarely considered, such as maternal lifestyle exposures (smoking), maternal illness (diabetes, hypertension), and abnormal placentation (preeclampsia).

See Article by Savla et al.

The outcome of complex CHD is likely a result of complex genetic and environmental factors. Advances in genetic diagnostic techniques have expanded our understanding of the genomic underpinnings of CHD, both syndromic and nonsyndromic, and the role of epigenetic mechanisms that mediate changes in gene expression has helped explain the interaction between the genome and the environment. The pathways to morbidity and mortality for individuals with critical CHD are complex and multifactorial and may include cumulative insults (or multiple "hits"), both iatrogenic (eg, procedural-based treatments) and natural. The advent of neonatal corrective and palliative cardiac surgery, enabled by cardiopulmonary bypass, therapeutic hypothermia, and circulatory arrest, led to a significant decrease in mortality of infants with complex CHD. Although subsequent outcomes for overall CHD have improved, the mortality rates of certain subtypes of CHD have remained stubbornly stable in recent years, including those with a single-ventricle physiology (including hypoplastic left heart syndrome),[3] with one third of affected children dying before age 6 years. Given the extreme physiologic conditions during neonatal cardiac surgery (hypoperfusion, hypothermia), it was logical that earlier research into the outcomes of neonatal CHD repair focused primarily on the surgical and intraoperative support techniques, as well as postoperative care. Around the turn of the millennium reports began to appear implicating preoperative and even prenatal factors in the outcomes, primarily neurodevelopmental,[4–6] of infants with CHD. Around the same time, David Barker and colleagues[7,8] were

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Correspondence to: David L. Wessel, MD, Children's National Hospital, 111 Michigan Ave., NW, Suite W5-108, Washington, DC 20010. E-mail: dwessel@childrensnational.org

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advancing the hypothesis that early life, including prenatal, environmental exposures triggered fetal patterning events that determined subsequent resilience or vulnerability to adversity. The growing recognition of the complexity of the fetal experience and multifactorial influences that play a role in long-term health and disease became known as the "developmental origins of health and disease hypothesis." The fact that the fetal experience is inextricably linked to that of the pregnant mother, during a highly "plastic" period of rapid fetal development, supports the inclusion of maternal-fetal environmental factors in models of risk in CHD.

The role of the placenta in the development of CHD and its outcome has become an area of increasing interest.[9,10] Savla et al[2] included preeclampsia, a complication of impaired placentation, as an environmental variable in their risk model. The rationale for this is several-fold as there are a number of ways in which preeclampsia might be implicated in the causal pathway to adverse outcome in infants with critical CHD. First, disorders of placentation in general, and preeclampsia in particular, are strongly associated with fetal CHD,[10,11] with an increased risk of CHD associated with earlier-onset preeclampsia, suggesting a dose-timing or dose-duration effect.[12] Remodeling of the spiral arteries is a critical element in normal placentation (and impaired in preeclampsia), events that occur in the first trimester concurrent with early development of the heart. Both the heart and placenta are highly vascular organs that develop under the influence of a complex balance of pro-angiogenic and anti-angiogenic vascular growth factors.[13] Reports have described an increase in placental abnormalities (both vascular and villous) in pregnancies complicated by CHD, based on pathology[14] and imaging studies.[15–18] Late gestation fall-off in fetal growth resembling late-onset placental-based fetal growth restriction has been observed in certain (but not all) CHD lesions. More concerning is the third trimester deceleration in fetal volumetric brain growth in the absence of obvious brain injury.[19–21] The causal direction of the association between the placental abnormalities and CHD remains unresolved with evidence to support a primary role for placental abnormality leading to CHD and vice versa (ie, disturbed placental circulation), as well as a bidirectional pathway.

Diabetes (pre- and gestational) is associated with increased perinatal morbidity and mortality, mediated by inflammatory cytokines, oxidative stress, and epigenetic pathways, among others. These injurious pathways have significant effects on the vascular endothelium of the fetus and placenta, with potential secondary placental failure. Pregestational diabetes is itself associated with increased risk of CHD, including impaired diastolic function or diabetic cardiomyopathy, even in the absence of major structural defects. Together, these widespread injurious influences could reasonably be expected to further increase the mortality risk of infants with critical CHD, as demonstrated by Savla et al.[2]

In recent years maternal mental health disturbances have been identified as the most common complication of pregnancy, affecting more than 20% of women in the prenatal period or first postpartum year. This prevalence is almost doubled in high-risk pregnancies such as those complicated by fetal CHD.[22] Of particular concern is the fact that these conditions are underdiagnosed and undertreated during pregnancy. Furthermore, the prenatal and perinatal risks of maternal toxic stress, anxiety, and depression during pregnancy are increasingly recognized and include spontaneous abortion, prematurity, fetal growth restriction, preeclampsia, placental abruption, and neonatal mortality, as well as impaired brain development and long-term neuropsychological deficits.[23–26] The pathogenetic pathways invoked include activation and abnormal programming of the fetal hypothalamic-pituitary-adrenal axis, as well the effects of elevated circulating cortisol and norepinephrine and inflammatory cytokines. The potential impact of these maternal mental health conditions on the outcome of high-risk populations such as infants with CHD is in urgent need of investigation because in many cases these maternal conditions might be modifiable, even without medications. These findings again demonstrate the complex interaction between the fetal internal and maternal environments and brain development.

Future counseling and formulation of management plans for the high-risk fetus and newborn should incorporate a broader panel of risk factors from the maternal, placental and fetal environments into the assessment than are currently considered. The multitude of potential risk factors add a daunting complexity to the challenge of identifying risks most hazardous to survival and well-being. The approach taken by Savla et al[2] is logical as it starts with associated maternal-placental factors known in general to be the best to start with additional factors that affect fetal well-being. Looking ahead, this important line of inquiry needs to extend beyond survival (as a primary outcome) to elucidate the role of maternal-placental influences on the long-term health and wellness in survivors of CHD across the lifespan. Equally important will be careful consideration of not only the "gene-code" and its relative contribution to outcomes in fetuses with CHD but the increasingly recognized role of the "ZIP code" and socioeconomic and racial disparities that may play a role in altered fetal programming.[27] Studies are needed to further disentangle the social determinants of health in this high-risk population, and the role of stress, adversity, trauma, and resilience, to help guide future

preventative educational strategies and targeted anticipatory prenatal interventions.

The article[2] by Savla et al underscores the need to consider the complex interactions between the maternal, placental, and fetal environments, especially in high-risk fetal conditions, such as critical CHD. Developing precise and personalized care is a major "next frontier" for medicine, in general. As the field advances to more precise and personalized approaches to fetal counseling and formulation of management strategies, it will be increasingly important for greater collaboration between obstetricians and pediatricians. The emerging field of prenatal pediatrics focuses on developing greater expertise and understanding of the prenatal experience of infants arriving into pediatric care at birth. Developing such skills will be critical if pediatric specialists are to anticipate and navigate more successfully the prenatal-postnatal transition of high-risk fetuses, such as those with CHD. Anticipatory personalized care will be critically dependent on the development of more precise diagnostic and surveillance tools with which to interrogate the fetal condition and the intrauterine environment and to assess individual vulnerability and resilience. Rapid advances in genomic techniques, including the ability to better understand the environmental effects on gene expression through epigenetic signals, are likely to play an important role, as will the expanding portfolio of "omics" techniques. Based on the phenomenon of fetal-maternal trafficking, distress signals from the fetus and placenta may become accessible from the maternal circulation, in the form of cell-free fetal DNA, exosomes, and other subcellular elements. Ongoing development and refinement of in vivo fetal imaging techniques that offer composite structural, metabolic, and vascular signatures of maternal-fetal-placental unit health and wellness will further advance the precision with which fetal signals can become accessible and intelligible. This in turn will allow for more informed counseling and the delivery of personalized prenatal care for the maternal-fetal dyad.

The lifespan consequences of events in the fetal and newborn period, particularly in high-risk populations, make a greater understanding of the intrauterine, placental, maternal and external environmental experience during this critical developmental period a major priority. Without such advances the development of precision and personalized prenatal pediatrics will remain elusive. The observations and conclusions by Savla et al[2] further focus the need for pediatric subspecialists across many disciplines to join other perinatal experts and enter the emerging field of prenatal pediatrics. There is an opportunity and obligation to understand the impact of the maternal environment during pregnancy on the well-being of the next generation.

ARTICLE INFORMATION

Affiliations

Division of Diagnostic Imaging and Radiology, Developing Brain Institute, Children's National Hospital, Washington, DC (C.L.); Department of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, DC (C.L., D.L.W., A.J.d.P.); Division of Cardiology (D.L.W.), Division of Critical Care Medicine (D.L.W.) and Division of Fetal and Transitional Medicine, Prenatal Pediatrics Institute (A.J.d.P.), Children's National Hospital, Washington, DC.

Disclosures

None.

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