The Path Forward Is to Look Backward in Time
Fetal Physiology: The New Frontier in Managing Infants With Congenital Heart Defects

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The luxury of studying the cognitive outcomes of survivors of infant heart surgery occurs only as a consequence of the success of the surgeries. The improvement in surgical survival over the last 2 decades has allowed us to focus our attention beyond survival and cardiac outcomes to a more holistic view of the child and his or her academic achievements and prospects for successful independence. Most of what we know about long-term outcomes is from the Boston Circulatory Arrest Study, which began in 1988 and followed the lives of 171 infants with transposition of the great arteries randomized to a surgical strategy that either included hypothermic circulatory arrest or did not. The most recent report on 139 adolescent survivors (age, 16.1±0.5 years) from this study documented significant psychoeducational challenges that were not so severe as they were prevalent. Briefly, grade retention occurred in 17%, special education in 25%, and psychotherapy or counseling in 25%. Most significantly, the report notes the negative finding that surgical strategy failed to identify an increased risk for the outcome measures. To quote the report, “In many respects, the similarities in the outcomes of the 2 groups have been more striking than the differences.” Both groups suffered from poor academic achievement, fine motor function, visual spatial skills, sustained attention, and social cognition.

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Concurrent with this study, investigations of white matter injury (WMI) have been ongoing. In 2002, Dr Mahle and colleagues reported that nearly 20% of infants with mixed types of severe congenital heart defects (CHDs) had evidence of WMI before surgery despite optimal medical management from birth. This number, it appears, is remarkably robust; study after study has shown WMI in ≈1 in 5 infants before surgery.5,6 but increases to 70% after surgery.7 The palliative nature of the first heart surgery corrects the direction of flow in the arch and limits the pulmonary diastolic runoff but does nothing to correct the oxygen content of the blood. Nonetheless, there seems to be a significant benefit in performing the surgery early after birth.7,8

These investigations into the causes of WMI have led to the recognition that preoperative factors and patient-specific factors (heart diagnosis, age at surgery, prenatal diagnosis) rather than surgical or postoperative factors are the major risks. Questions about how alterations in fetal circulation may affect brain growth and maturation first appear with the Miller et al publication in 2007. In that article, the authors used diffusion tensor imaging (magnetic resonance [MR] imaging [MRI]) and MR spectroscopy to demonstrate significant differences in white matter microstructure and biochemistry between newborn infants with CHD and infants without CHD. Soon afterward, our group at the Children’s Hospital of Philadelphia demonstrated, using an MRI-based observational metric called the Total Maturation Scale, that brain maturation in full-term presurgical infants with CHD was equivalent to the expected brain maturation of a 35-week premature infant. Others have since shown that the Total Maturation Scale predicted not only risk for preoperative and postoperative WMI but also neurodevelopmental testing (Bayley scales of infant development) at 2 years.11,12

The landmark study to seal the question about altered brain growth and development in fetuses with CHD came from Dr Limperopoulos and her group in Boston. This group performed brain MRI in fetuses with and without CHD to demonstrate that the brain volumes of infants with CHD diverge from expected normal growth at the beginning of the third trimester. Using fetal MR spectroscopy, Limperopoulos et al also demonstrated that markers of white matter maturation (ratios of N-acetyl aspartate to choline) lagged normal development and were most abnormal in the fetuses with left outflow tract obstruction (hypoplastic left heart syndrome). These findings not only validated the findings of Miller and Licht but also added a time reference as to when during pregnancy the pathological changes were occurring. This wealth of data on normal brain growth and development suggests that, although opportunities for postnatal neuroprotective interventions exist, their yield might be much less than one would hope for.
Novel strategies for fetal intervention and neuroprotection are needed. However, what all the above studies lacked was a clear understanding of the fetal pathophysiology that led to this divergence of brain growth and maturation. Without this knowledge, progression to fetal interventions (medical or surgical) is stalled or at least ununiformed. In this issue of Circulation, Sun and colleagues14 from The Hospital for Sick Children in Toronto publish their results on fetal MRI measurements of cerebral blood flow and cerebral oxygenation in fetuses with and without serious CHD. The significance of this report cannot be overstated, and it goes well beyond the findings they observed in the 60 patients (30 with and 30 without CHD) studied. It is the technical achievement of being able to make noninvasive measurements of vascular and metabolic physiology in a moving fetus that is the most eye-opening. The introduction of metric-optimized gating by coauthor Macgowan has allowed phase-contrast measurements of blood flow and oximetry in fetal vessels.15 There are some assumptions made for the calculations used in this article, but they are equitably applied to the fetuses with CHD and control fetuses. Eventually, numbers like the T2 (T2 of fully oxygenated blood) of fetal blood will be measured, and the absolute quantification of oxygen saturations will be known. For now, these numbers are good, if not perfect, and suffice for comparisons with normal. We must consider that it has only been 7 years since the multislice snapshot technique for measuring fetal brain volumes was published16 and only 5 years since the multislice snapshot technique for measuring these numbers are good, if not perfect, and suffice for comparisons with normal. We must consider that it has only been 7 years since the multislice snapshot technique for measuring fetal brain volumes was published16 and only 5 years since Limperopoulos et al demonstrated discrepant brain growth in fetuses with CHD. These leaps in technology take time.

The main findings in this report by Sun and colleagues highlight the limitations of our perhaps simplistic understanding of how CHD alters fetal physiology. The most striking example of this is the finding that umbilical venous saturations in CHD fetuses were lower than in control fetuses, suggesting that placental pathology may be an important contributor to the central nervous system changes observed in the newborn with CHD. These MRI findings support some preliminary findings by Goff,17 who demonstrated gross differences in placental weights and vascularity. Also unexpected was the finding that cerebral oxygen consumption was significantly lower in fetuses with CHD, and oxygen delivery was not (although trended toward significance).

Both the abnormal cerebral oxygen consumption and placental function raise chicken/egg questions that need to be clarified with the advancement of these MRI techniques. Currently, the major limitation of these MR sequences is certain types of movement and vessel size. Therefore, all measurements are restricted to late-gestation fetuses in which motion is limited and vessels are larger. However, instead of focusing on the limitations, we need to revel in the quantum leap of the advancements the authors bring. Studies in more homogeneous populations (just transposition of the great arteries or hypoplastic left heart syndrome) will follow, as will comparison of fetal and neonatal physiology. Eventually, the refined techniques will allow longitudinal study across the entire gestation. The authors are to be congratulated for such remarkable accomplishments. Implementation of these fetal imaging techniques will improve our understanding of fetal development and will give birth to a new field of fetal medical intervention.

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References


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