EDITORIAL

Growth in Congenital Heart Disease: Outcome or Predictor?

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According to the Greek historian Plutarch, small, deformed, or ill-appearing newborns, deemed by the elders to be unfit for development into strong Spartan warriors, were abandoned in Apothetae. Although we would like to think that our current evaluation of a neonate's fate is not only more humane, but also more nuanced than the methods of the Gerousia of Sparta, the current approach of assessing comorbid risk for infants undergoing congenital heart disease (CHD) surgery remains blunt. Specifically, the risk classification of children with CHD based solely on their birth weight or gestational age ignores the heterogeneity in the pathophysiological characteristics of the in utero environment, early development, and subsequent outcomes within these populations. In the era of personalized medicine, premature and small neonates should not be considered a homogeneous high-risk category. Although prematurity (<37 weeks' gestation) and low birth weight (<2.5 kg) increase risk[1–4] on a population basis, the individual preterm or small infant may actually do well. Extrapolating risk from the outcomes of a diverse cohort to an individual is unreliable and potentially misleading, whether it be for counseling a family or discovering novel interventions to improve outcomes. Better understanding the pathophysiological characteristics underlying earlier birth and lower birth weights in CHD will drive more precise risk assessment for counseling, and will expand our knowledge surrounding the impact of early life events and environment on disease and disease progression. At the crux of our current knowledge gap is whether somatic growth in CHD is the manifestation of a more complicated course and, therefore, should be considered an outcome, or is a reflection of intrinsic genetic, cardiovascular, and placental factors and should, therefore, be considered a predictor of risk.

Considering first birth anthropometry, it is important to recognize that low birth weight, small for gestational age (SGA), and intrauterine growth restriction are distinct entities. Low birth weight refers to a cut point based solely on weight, irrespective of whether that weight is appropriate for gestational age or growth potential. Although SGA takes into account gestational age and sex, it is based on a distribution of a normative population with a distinct cut point at the 10th percentile, and does not account for an individual's or population's growth potential. Intrauterine growth restriction is conceptually straightforward but difficult to delineate clinically because it refers to an in utero environment that leads to a fetus failing to meet its growth potential; the complexity is in assessing "potential." Defining intrauterine growth restriction is even more perplexing in the population with CHD because growth potential may be debated, given the well-described lesion-specific differences in birth weight.[5,6] Steurer and colleagues, in this issue of the *Journal of the American Heart Association* (*JAHA*), provide further evidence that CHD lesions are associated with lower birth weight for gestational age.[7] In their cohort of almost 7000 infants with critical CHD in the state of California, >16% were SGA. Which of those individuals were growth restricted, however, is unknown. Their cohort included multiple Risk Adjustment for Congenital Heart Surgery categories, and it is possible that if they filtered for higher-risk lesions, the SGA percentage would be even greater. In a single institution cohort limited to infants requiring surgery before 60 days of age, the rate of SGA was 23% and was associated with an increased risk of 30-day postoperative mortality.[8] Further narrowing down a cohort to single-ventricle heart disease, a 41% incidence of SGA was reported for patients enrolled in the Pediatric Heart Network SVR (Single Ventricle Reconstruction) Trial.[9] In the California cohort, being born SGA was associated with a higher incidence of oligohydramnios, preeclampsia, and an underweight maternal body mass index, suggesting SGA birth may be the result of a more complex fetal course and, therefore, should be considered an outcome. But if a large percentage of SGA neonates had no maternal comorbidity, it is possible many attained an appropriate, albeit lower, growth potential, thereby making birth anthropometry simply a marker of risk; this possibility is supported by the known

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intrinsic placental pathological characteristics associated with various CHDs.[10–13] Regardless, the pathophysiological characteristics for being SGA are varied, and teasing out which infants are not meeting their growth potential because of environmental insults is nearly impossible on the basis of birth weight and gestational age alone.

The findings from the California cohort add another layer of complexity because the impact of SGA changed depending on the gestational age. The authors report that subtle decreases in weight for gestational age are more important predictors for 1-year mortality in the early-term population than in term and preterm populations. As the authors suggest, one potential explanation is that the risks of preterm birth and SGA are competing and overlapping risks, and the earlier the birth, the more the risk is driven by gestational age, thereby overshadowing the birth weight risk. Another possibility is that the mechanisms leading to growth restriction and preterm birth differ from those leading to growth restriction and early-term birth. Without knowing the fetal growth trajectory or the indication for delivery in this cohort, it is difficult to speculate, but it may be attributable to a difference in the timing of an in utero insult between the 2 groups (or whether there was any insult at all). Along those lines, it would be interesting to know in this and other cohorts how many early-term deliveries were secondary to a sudden change in fetal growth. If a significant amount of early-term deliveries were inductions secondary to an indication of poor fetal growth, it would be important to control for the growth abnormalities in outcomes analyses. With a recent increase in the concern for the impact of early-term delivery on outcomes,[14,15] the findings from this study beg the question of whether the signal for worse survival and poorer neurodevelopmental outcomes in early-term populations would still exist if SGA and/or intrauterine growth restriction was added to the model. It may be even more relevant to control for the insult that led to the growth abnormality. The timing of an in utero insult has been associated with the pattern of growth restriction, with early, more global insults causing symmetric growth restriction and later, more acute insults leading to asymmetric growth restriction.[16] In CHD, however, assessing symmetry in growth as a marker of an in utero insult is again confounded by lesion-specific differences. For example, birth weights of infants with tetralogy of Fallot or coarctation of the aorta appear to be more severely affected than birth weights in infants with transposition of the great arteries.[6] At the same time, infants with transposition or hypoplastic left-sided heart syndrome have proportionally smaller heads for their weight at birth compared with infants with tetralogy of Fallot or coarctation, suggesting the mechanism of fetal growth abnormalities diverges by lesion. Even within a single cardiac lesion, infants with single ventricles, there is a wide distribution of relative head growth, but no clear association of anthropometric asymmetry with outcomes, highlighting again the heterogeneity in development.[17]

Whether growth in CHD is considered an outcome or a risk factor, anthropometry may currently be one of the best clinical markers for teasing out the drivers of heterogeneity in outcomes, particularly those that can be modified or minimized if identified early. Incompletely understood genetic and environmental factors that cause CHD likely affect growth during pregnancy in concert with the impact of blood flow and oxygenation abnormalities. The current article by Steurer and colleagues[7] reminds us that not all SGA newborns with CHD are created equally. Greater understanding of the placental, vascular, and genetic pathological characteristics that drive early development will enhance our assessment of whether growth is an outcome that can be intervened on or simply an indicator of disease severity and predictor of risk. With improved understanding, we may continue to refine the approach of fetal and neonatal assessment so that our wisdom may surpass that of the Gerousia.

Disclosures

None.

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