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Fetal Growth and Brain Development—One Data Point Is Worth a Thousand Words, But Growth Trajectories Are Worth a Million

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In the article "Patterns of Fetal and Infant Growth and Brain Morphology at Age 10 Years,"[1] Silva and colleagues used a population-based cohort (the Generation R Study), which includes data of 3098 singleton children, to evaluate the long-term associations of fetal and early life growth patterns with brain structure. They found that higher weight gain until the second and third trimester, birth, and ages 6, 12, and 24 months was associated with larger total brain volume, independent of growth during other age windows. Moreover, higher peak weight velocity and body mass index (BMI) reached at adiposity peak were associated with larger brain volumes. Although there are well known associations between neonatal features and childhood brain size, most studies classify newborns into small or appropriate for gestational age according to a cross-sectional evaluation of body weight at birth, and this literature is in general limited by small sample sizes. The authors[1] innovated by providing an advanced analysis of fetal growth trajectories through repeated ultrasonography as well as comprehensive evaluation of infant growth considering the adiposity peak and their association with brain size at age 10 years in a prospective analysis of a large sample. Some of the classifications used in the article are still based on established cutoffs that can be very fragile in defining the infant population at risk of the long-term consequences of poor fetal growth,[2] but additional analysis using conditional regression, peak weight velocity, and BMI at adiposity peak reflect a careful consideration of growth physiology in the study.

Silva et al[1] also found that children with fetal and infant growth deceleration had the smallest total brain volume compared with children with normal fetal and infant growth. However, children with fetal weight deceleration followed by infant catch-up growth had similar brain volumes as children with normal fetal and infant growth rates. This can have important implications for pediatrics and infant nutritional counseling, although caution is advised before a call for change in practice takes place. The association of brain volume with cognitive and behavioral development, specifically in the population of children who experienced growth deceleration, is still not clear. This association may also be different in preterm infants—a group for which there is more data and which is often used as a comparison, although fetal growth deceleration and preterm birth have very different pathophysiologies, causes, and consequences. Contradictory findings in the extent to which catch-up growth improves cognitive and behavioral outcomes in children who experienced growth deceleration exist,[3] and this can be because of the lack of a precise definition of catch-up growth. These limitations are well acknowledged by Silva et al.[1]

Interesting associations of size for gestational age or growth patterns until age 6 months with the size of subcortical structures, such as the amygdala, globus pallidus, thalamus, and putamen, were described. Previous studies have found that altered fetal growth leads to differences in stress responsivity,[4] which is largely associated with the brain amygdala modulation. Altered fetal growth is also related to changes in attention, sensitivity to reward, and impulsivity,[5] behavioral endophenotypes connected to the function of the basal ganglia. Future multilevel studies integrating prospective evaluations of fetal and infant growth developmental trajectories—like that proposed by Silva et al[1]—as well as multiple types of data modalities[6] are warranted for a deeper understanding of these associations.

A frequent argument dismissing the relevance of this line of research focuses on the misconception that poor fetal growth is exclusively linked to maternal undernutrition and hence

infrequent or that it is present only in low-income countries. This is far from the truth. Fetal growth deceleration can happen in several pregnancy conditions that are prevalent in high-income nations, including advanced maternal age, psychosocial stress, and obesity, and it should therefore be better researched. The change in perspective—spotlighting fetal growth trajectory as opposed to classification according to an arbitrary birth weight cutoff—makes the prevalence of small for gestational age births in a given population irrelevant in this context.

It is common knowledge that healthy growth during childhood is essential for brain development. Nonetheless, the long term effects of fetal growth trajectories on brain development have been poorly explored, especially using a repeated and detailed evaluation as done by Silva et al.[1] Fetal malnutrition is associated with increased risk of adult diseases, including type 2 diabetes, atherosclerosis, hypertension, cardiovascular disease, and a wide array of neuropsychiatric conditions.[7] Understanding the association of fetal and infant growth with neurodevelopment is extremely important to inform the elaboration of preventive measures. Although the scenario of preventing adult disease in childhood may seem elusive, advances in several areas of medicine suggest that we are not far from defining more precise and personalized health promotion strategies. Specialties dealing with prevalent adult conditions, such as cardiology and oncology, have used elegant predictive models for many years. For some reason, refined scientific investigations in child growth and development are not as popular. It is time to promote the same level of enthusiasm and sophistication to research that will inform the clinical practice of pediatrics, and we should start by solid investigations. The paper from Silva et al[1] is a good example.

ARTICLE INFORMATION

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