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Fetal Ultrasound: Shedding Light or Casting Shadows on the Fetal Origins of Airway Disease

The fetal origins of chronic disease hypothesis proposes that fetal undernutrition in middle to late gestation leads to disproportionate fetal growth and induces permanent changes in body structure, physiology, and metabolism that program the later development of coronary heart disease and related diseases (1).

Although the fetal origins hypothesis did not encompass respiratory outcomes, there is evidence to support the principle of fetal origins of obstructive airway disease. First, reduced birth weight has been linked to reduced FEV_1 and increased asthma in children and adults (2). Second, accelerated postnatal growth is associated with increased asthma, wheeze and reduced FEV_1 in children (3, 4). Third, the prevalence of obstructive airway disease was increased in adults exposed to the Dutch famine midgestation, although such overt maternal/fetal malnutrition is now rarely observed in affluent countries (5). From these observations, it might be inferred that for whatever reason, attenuation of fetal somatic and respiratory growth midgestation resulting in reduced birth weight and accelerated postnatal "catch-up" growth is associated with an increased likelihood of asthma and reduced ventilatory function. Further plausibility for there being a fetal origins component to obstructive airway disease is evidenced by embryology; airway branching is completed by midpregnancy, so an insult in early pregnancy to midpregnancy might adversely affect airway development, leading to obstruction. Until recently, the fetal origins of airway disease has not been directly tested in humans; instead, investigators have used birth and/or postnatal anthropometric measurements and speculated on preceding fetal development.

In the last 2 years, four centers have linked antenatal fetal ultrasound measurements to respiratory outcomes in childhood. These centers are (in alphabetical order) Aberdeen (UK) (6, 7), Perth (Australia) (8), Rotterdam (Netherlands) (9), and Southampton (UK) (3). No center is yet able to directly measure fetal respiratory function or lung size, but researchers have assumed that measurements of fetal size reflect lung size (not an unreasonable assumption given the relationship between height and spirometry). In this issue of the *Journal* (pp. 731–737), Sonnenschein-van der Voort and colleagues in Rotterdam relate antenatal and postnatal growth trajectories to respiratory outcomes in 5,125 four-year-olds nested within the Generation R cohort (9). This is the largest study to date to have related fetal ultrasound measurements to childhood respiratory outcomes and along with the Southampton Women's Survey has fetal and postnatal anthropometric data. This cohort recruited women in early pregnancy living in Rotterdam, The Netherlands and is specifically designed to test the fetal origins hypothesis.

The results from the Generation R Study indicate that fetal measurements and growth trajectory are not relevant to respiratory outcomes, but early (0–3 mo) postnatal weight gain is important, regardless of antenatal growth, being associated with increased likelihood of wheezing, shortness of breath, and persistent phlegm in a longitudinal modeling of data over the first 4 years of life (9). The combination of normal fetal growth and early postnatal accelerated weight gain was most strongly associated with these respiratory outcomes.

That fetal measurements and growth trajectories in Generation R were not associated with childhood respiratory outcomes contradicts the three previous studies of fetal measurements. In Aberdeen, reduced first-trimester (10 wk) crown–rump length was associated with increased likelihood of wheeze and asthma and reduced FEV_1 at 5 and/or 10 years, whereas persistently low first- and second-trimester (20 wk) measurements were associated with increased wheeze and asthma and reduced FEV_1 at 5 and/or 10 years (6, 7). In Southampton, reduced head circumference growth in early pregnancy (11–19 wk) was associated with nonatopic wheeze at age 3 years, whereas reduced growth in abdominal circumference in later (19–34 wk) pregnancy was associated with atopic wheeze (3). Analogous to Generation R, Southampton reported increased infant weight and adiposity gain between 0–6 and 6–12 months to be associated with increased atopic and nonatopic wheeze at age 3 years. Preliminary results (based only on fetal measurements) published in abstract form from the Raine cohort in Perth, Australia are consistent with the findings in Aberdeen (8).

As with many new areas of research, there are some inconsistencies in the early literature. One major inconsistency is that in Generation R, there is no evidence of association between fetal size and/or growth and symptoms up to the age of 4 years, whereas other groups do find evidence of such an association. One possible explanation for this inconsistency might be differences in ascertaining fetal gestational age. For studies of fetal origins, gestational age is crucial to interpreting fetal measurements to differentiate between a normal fetus, a large younger fetus, and a small older fetus. Although obstetric research has established that embryos/fetuses have virtually identical growth velocities during early gestation with first-trimester crown–rump length being the recommended method to ascertain gestational age, it is clear that fetuses do differ in size and trajectories (10). While this individual variation does not impact obstetric practice, it is likely to be critically important for studies attempting to relate fetal size and growth trajectory to postnatal outcomes. It is notable that in Generation R, gestational age was ascertained by fetal ultrasound measurements in the second and third trimesters and seemingly also in the first trimester (9). In contrast, in Aberdeen, Southampton, and Perth, gestational age was ascertained using an algorithm combining scan measurements and reported date of last menstrual period (3, 6–8). In Generation R, the reliance on fetal measurement alone to ascertain gestational age may have diminished between-subject variation, with fetuses of a similar size being allocated the same gestational age irrespective of whether they were normal fetuses, large younger fetuses, or small older fetuses.

In Generation R, it is also reported that the combination of restricted fetal and infant weight gain is protective, being associated with a reduced likelihood of wheeze and breathlessness up to the age of 4 years (9). This finding is somewhat surprising in light of evidence that reduced ventilatory function at birth tracks during childhood and is associated with an increased likelihood of wheezing symptoms and asthma (11, 12). Perhaps the association reported in Generation R is a consequence of healthy fetuses that are large for their actual age being classified as less healthy small older fetuses by the ultrasound measurements.

The Generation R Study reported in this issue of the *Journal* has made a welcome addition to the literature and supports the concept of using fetal measurements to investigate the fetal origins hypothesis. Clearly, however, further studies are required to support or refute the reported findings, and the issue of ascertaining gestational age for such studies needs to be addressed and consensus reached. The genetic, environmental, behavioral, and lifestyle factors driving fetal size and growth remain poorly understood, and the timing of exposures that may alter fetal growth are incompletely known and need to be elucidated. Dietary factors may be acting in early pregnancy and maternal smoking may be acting in the second half of pregnancy (6, 13). Antenatal determinants of respiratory disease have been sought for many years, and studies such as the Generation R cohort have the ability to give important insight into early origins of disease, which will allow studies to be designed to prevent chronic conditions for which at present there are no cure, including obstructive airway disease, coronary artery disease, type II diabetes, and hypertension.

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