0031-3998/10/6702-0128
PEDIATRIC RESEARCH

Vol. 67, No. 2, 2010
Printed in U.S.A.

COMMENTARIES

Teasing Out the Effects of Different Fetal Growth Trajectories

Commentary on the article by van Batenburg-Eddes *et al.* on page 132

NEIL MARLOW

Academic Division of Neonatology, Institute for Women's Health, University College London, London WC1E 6HX, United Kingdom

One of the reasons that prematurity is on the increase is the increasing willingness to deliver the fetus early because of poor growth, usually associated with signs of poor fetal health. Classic studies have shown that fetal growth in mid-trimester, particularly in terms of head size, may be related to significantly more developmental problems compared with later onset growth restriction (FGR) (1,2). Premature birth itself is the result of a range of pathologies and measuring infants at birth to determine "normal ranges" is immediately flawed as, compared with fetal growth standards, most preterm children are smaller and lighter than they might have been, which can affect associations between size at birth and, for example, cerebral palsy (3).

Commonly held concepts such as "brain-sparing," where fetal skull growth is less affected compared with somatic growth have been shown to be flawed in that brain growth slows with somatic growth (4) and indeed functional measures of performance in school age children are significantly impaired in the face of a luxuriant cerebral circulation (5), which represents the response of the fetus to impaired fetal brain nutrient supply as opposed to a "protective" mechanism. A randomized trial of deferring preterm delivery in the face of abnormal biophysical measures did not alter fetal, neonatal, or 2 y outcomes (6). This area is complex and using high-risk populations such as those described earlier is not directly relevant to our understanding of broader effects of fetal growth on outcome.

There is some relationship between size at birth and later adverse outcomes, as many studies have shown, leading to a fetal programming hypothesis, (7) which has excited much laboratory and clinical population research. Preterm birth is usually excluded from these claims because, as indicated earlier, it is complicated. It is clear from a multitude of studies that nutritional influences at different stages of pregnancy produce different outcomes (8). So it becomes important for us to study fetal growth in relation to outcomes in a prospective and rigorous fashion.

In this issue of the Journal, the article by van Batenburg-Eddes *et al.* (9) from the Generation R study starts to address some of this issue. Nested within a prospective population cohort study recruited in early pregnancy, they have evaluated fetal growth from two pregnancy observations and birth weight in a whole population sample. For this analysis, the outcome was a neurologic optimality score. These scores have been shown to identify children at risk of later motor impairments, mainly in high-risk populations and using repeated assessments (10). Fetal somatic growth and abdominal/head circumference symmetry were associated with the proportions of children in the "less optimal" tertile for neurologic optimality, implying that less optimal fetal growth is associated with less optimal neurologic profiles at 3 mo of age. We do not know whether this translates into less optimal hard outcomes of meaning to the child and family, but this intriguing observation suggests that we have more interest to come from this study.

Of course, as expected, the rate of preterm birth and birth weight less than the 10th percentile were low in this study, so direct clinical relevance to the investigation of clinically identified fetal growth restriction is not assured. Furthermore, the team is not suggesting that the 33% of children in the less optimal group are abnormal, simply that growth velocity over mid-pregnancy is associated with different motor profiles at 3 mo of age. This may have a range of potential aetiologies and further understanding of the reasons for this growth pattern is required. Interestingly, considering velocity over the last trimester of pregnancy was not useful in identifying these less optimal scores, something we might have predicted from current concepts of "clinical" growth restriction. But this study does provide an opportunity for the investigators to begin to unravel the complex nature-nurture debate in relation to programming of fetal size and the implications thereof.

So, where do we go from here when we recognize a fetus with poor growth? As yet the only intervention we have is delivery and early delivery is associated with potential problems from preterm birth. There are exciting potential therapies

Received November 2, 2009; accepted November 10, 2009.
Correspondence: Neil Marlow, D.M., F.Med.Sci., Institute for Women's Health, University College London, 86-96 Chenies Mews, London WC1E 6HX, United Kingdom; e-mail: n.marlow@ucl.ac.uk

waiting in the wings (11)—until then interpreting the effects of marginal fetal growth velocity in clinical practice remains impossible, and the fetal medicine specialist still needs the Wisdom of Solomon to get it right!

REFERENCES

1. Harvey D, Prince J, Bunton J, Parkinson C, Campbell S 1982 Abilities of children who were small-for-gestational-age babies. Pediatrics 69:296–300
2. Parkinson CE, Wallis S, Harvey D 1981 School achievement and behaviour of children who were small-for-dates at birth. Dev Med Child Neurol 23:41–50
3. Jarvis S, Glinianaia SV, Torrioli MG, Platt MJ, Miceli M, Jouk PS, Johnson A, Hutton J, Hemming K, Hagberg G, Dolk H, Chalmers J 2003 Surveillance of Cerebral Palsy in Europe (SCPE) collaboration of European Cerebral Palsy Registers Cerebral palsy and intrauterine growth in single births: European collaborative study. Lancet 362:1106–1111
4. Duncan KR, Issa B, Moore R, Baker PN, Johnson IR, Gowland PA 2005 A comparison of fetal organ measurements by echo-planar magnetic resonance imaging and ultrasound. BJOG 112:43–49
5. Scherjon S, Briet J, Oosting H, Kok J 2000 The discrepancy between maturation of visual-evoked potentials and cognitive outcome at five years in very preterm infants with and without hemodynamic signs of fetal brain-sparing. Pediatrics 105:385–391
6. Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M 2004 Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet 364:513–520
7. Barker DJ 1990 The fetal and infant origins of adult disease. BMJ 301:1111
8. Symonds ME, Sebert SP, Hyatt MA, Budge H 2009 Nutritional programming of the metabolic syndrome. Nat Rev Endocrinol 5:604–610
9. Van Batenburg-Eddes T, De Groot L, Steegers EAP, Hofman A, Jaddoe VWV, Verhulst FC, Tiemeier H 2010 Fetal programming of infant neuromotor development: the generation R study. Pediatr Res 67:132–137
10. Samsom JF, de Groot L, Bezemer PD, Lafeber HN, Fetter WP 2002 Muscle power development during the first year of life predicts neuromotor behaviour at 7 years in preterm born high-risk infants. Early Hum Dev 68:103–118
11. David AL, Torondel B, Zachary I, Wigley V, Abi-Nader K, Mehta V, Buckley SM, Cook T, Boyd M, Rodeck CH, Martin J, Peebles DM 2008 Local delivery of VEGF adenovirus to the uterine artery increases vasorelaxation and uterine blood flow in the pregnant sheep. Gene Ther 15:1344–1350