

Prematurity - A Window of...



Prematurity - A Window of Opportunity? [Editorial]

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Infants born with evidence of restricted fetal growth - those who are small for gestational age - appear to be at increased risk for metabolic disorders (type 2 diabetes mellitus and dyslipidemia), cardiovascular disease (hypertension and coronary heart disease), and even psychiatric disorders later in life. [1,2] Proposed initially by Dr. David Barker and colleagues on the basis of careful epidemiologic studies, these observations have been replicated with variable strength in humans, have been duplicated in some animal models, have spawned an extensive literature, and have provided theories for the developmental origins of some of the most important common chronic illnesses of modern times, including type 2 diabetes mellitus and atherosclerotic heart disease. [1-4] In general, this hypothesis, further amplified as the "thrifty-phenotype hypothesis," [5] posits that survival of the undernourished fetus requires metabolic adaptations that may include shunting of important fuels to the developing brain at the expense of tissues such as muscle and pancreas, resulting in insulin resistance and, possibly, insulin deficiency.

Studies in animals provide support for these concepts. For example, uterine-artery ligation in the pregnant rat leads to intrauterine growth restriction in surviving rat pups that is associated with reduced glucose uptake as well as reduced expression and concentrations of glucose transporter 1 protein in fetal muscle, but not in fetal brain. [6] In addition, when maternal undernutrition during gestation in the rat model is followed by the provision of a high-calorie diet to the pups after birth, the pups become obese, whereas the same postnatal diet does not cause obesity in the pups of mothers that have received adequate nutrition during pregnancy. [7]

Thus, at least two mechanisms are operative. The first involves the concept of "developmental plasticity," by which fetal undernutrition prompts metabolic or genetic adaptations, at least in part, through epigenetic processes such as

imprinting, alternative gene splicing, and ultimately, altered differentiation of tissues and organs, with consequent function that may diverge from normal. [1,4] These permanent adaptive events may explain phenomena such as insulin resistance, demonstrated as early as the first decade of life in children who were small for gestational age at birth. [8] Initially, increased insulin secretion may compensate for such insulin resistance. Genetic or developmental mechanisms that limit insulin secretion will tend to unmask type 2 diabetes mellitus earlier in life, [1,3,4] especially if the antenatal environment of nutrient deficiency is replaced by a postnatal nutrient surfeit, the second of the dual mechanisms required for clinical manifestations of disease. [7-9] Indeed, the epidemic of obesity and type 2 diabetes in children and adolescents over the past decade might well be attributed more to this putative environmental mechanism than to genes, since little genetic change would have occurred in such a short time. [10]

Similar exposure to nutrient excess has been proposed as contributing to the full clinical spectrum of adult cardiovascular disease in persons with intrauterine growth retardation. [11] However, whereas postnatal nutrition is modifiable, any in utero event that acts to produce and program a full-term fetus with intrauterine growth retardation is a fait accompli. But what of the premature infant, whether the birth weight is appropriate for gestational age (at or above the 10th percentile) or low for gestational age (less than the 10th percentile)? Are the adaptive mechanisms associated with fetal intrauterine growth retardation already in place? Or, does the extrauterine environment to which the premature infant is, of necessity, exposed - and which corresponds to the third trimester of a normal pregnancy - influence future functional adaptations?

In this issue of the Journal, Hofman et al. [12] provide data indicating that insulin resistance, as determined by the minimal-model technique, [8] is present in children 4 to 10 years old who were born prematurely, whether their birth weight was low or appropriate for gestational age. The minimal-model technique is an established method for determining insulin sensitivity from an algorithmic analysis of the relationship between glucose and insulin concentrations in serum after sequential intravenous pulses of glucose and tolbutamide. [8] As compared with control children who had been born at term and at a weight that was appropriate for gestational age, children who had been born prematurely had a reduction in insulin sensitivity of

approximately 30 percent, irrespective of whether their birth weight had been appropriate or low for gestational age. At the age of 4 to 10 years, these children who had been born prematurely had an increase in their acute insulin response, which compensated for insulin resistance. [12] Hofman et al. propose that this decrease in insulin sensitivity may predispose premature infants to type 2 diabetes mellitus in adulthood, as already demonstrated among infants born at term who are small for gestational age. Implicit in their findings is the concept that the in utero programming that occurs in term infants who are small for gestational age may also occur ex utero in premature infants during the vulnerable period of adaptive change in the third trimester. However, because this adaptive period occurs ex utero instead of in utero, premature infants may be more amenable to environmental manipulation than are full-term infants with intrauterine growth retardation.

These provocative findings require both reflection and action. Reflection is necessary because epidemiologic studies have not yet indicated that there is an increased incidence of type 2 diabetes mellitus or other manifestations of the fetal-programming hypothesis among long-term survivors of prematurity. The increased survival of premature infants, thanks to neonatal intensive care, is an evolving technological and scientific saga of less than 50 years' duration - too soon to examine its long-term consequences. Few survivors of marked prematurity have reached the age at which atherosclerotic heart disease or type 2 diabetes mellitus is usually manifested. Nor do we know enough about caring for the fragile premature infant in a way that simulates a normal intrauterine environment and avoids neurologic, visual, pulmonary, or other impairments. Simply providing the correct nutrient mix for a premature infant is a challenge. However, oxidative or other types of extrauterine stress may result in insulin resistance without eventuating in type 2 diabetes mellitus. And if type 2 diabetes mellitus does eventually develop, it may do so through entirely different mechanisms, rather than those related to intrauterine growth retardation. Thus, more research is critically needed to identify perinatal adaptations.

Both prematurity and low birth weight are more common among the children of women who lack access to or underuse antenatal health care than among the children of women who receive such care. Action is needed because neonatal outcomes, including the rates of prematurity and low birth weight, are markedly improved by the prenatal provision of adequate health and

nutritional care. [13-15] Thus, the future health of our society may well depend on the care available and provided to pregnant women. This is an area of health care that can be influenced by policy and is not directly dependent on a more complete understanding of underlying mechanisms, which remain to be elucidated by epidemiologic, clinical, and basic research.

REFERENCES

1. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science* 2004;305:1733-6. [Bibliographic Links](#) [\[Context Link\]](#)
2. Mittendorfer-Rutz E, Rasmussen F, Wasserman D. Restricted fetal growth and adverse maternal psychosocial and socioeconomic conditions as risk factors for suicidal behaviour of offspring: a cohort study. *Lancet* 2004;364:1135-40. [Bibliographic Links](#) [\[Context Link\]](#)
3. Cutfield W. Short and sweet: the perinatal origins of type 2 diabetes mellitus. *Pediatr Diabetes* 2004;5:113-6. [\[Context Link\]](#)
4. Kahn IY, Lakasing L, Poston L, Nicolaidis KH. Fetal programming for adult disease: where next? *J Matern Fetal Neonatal Med* 2003;13:292-9. [\[Context Link\]](#)
5. Hales CN, Barker DJP. The thrifty phenotype hypothesis. *Br Med Bull* 2001;60:5-20. [Buy Now Bibliographic Links](#) [\[Context Link\]](#)
6. Simmons RA, Flozak AS, Ogata ES. The effect of insulin and insulin-like growth factor-I on glucose transport in normal and small for gestational age fetal rats. *Endocrinology* 1993;133:1361-8. [Bibliographic Links](#) [\[Context Link\]](#)
7. Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *Am J Physiol Endocrinol Metab* 2000;279:E83-E87. [\[Context Link\]](#)
8. Hofman PL, Cutfield WS, Robinson EM, et al. Insulin resistance in short children with intrauterine growth retardation. *J Clin Endocrinol Metab*

1997;82:402-6. [Bibliographic Links](#) [\[Context Link\]](#)

9. Jackson AA. Nutrients, growth, and the development of programmed metabolic function. *Adv Exp Med Biol* 2000;478:41-55. [\[Context Link\]](#)

10. Miller J, Rosenbloom A, Silverstein J. Childhood obesity. *J Clin Endocrinol Metab* 2004;89:4211-8. [Bibliographic Links](#) [\[Context Link\]](#)

11. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet* 2004;363:1642-5. [\[Context Link\]](#)

12. Hofman PL, Regan F, Jackson WE, et al. Premature birth and later insulin resistance. *N Engl J Med* 2004;351:2179-86. [Ovid Full Text Bibliographic Links](#) [\[Context Link\]](#)

13. Cooke RW. Health, lifestyle, and quality of life for young adults born very preterm. *Arch Dis Child* 2004;89:201-6. [Buy Now Bibliographic Links](#) [\[Context Link\]](#)

14. Lorenz JM. Proactive management of extremely premature infants. *Pediatrics* 2004;114:264. [\[Context Link\]](#)

15. Taylor GB, Katz VL, Moos MK. Racial disparity in pregnancy outcomes: analysis of black and white teenage pregnancies. *J Perinatol* 1995;15:480-3. [\[Context Link\]](#)

Accession Number: 00006024-200411180-00015

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