

6-1-2014

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Bonita Falkner

Department of Medicine and Pediatrics, Thomas Jefferson University

Julie Ingelfinger

Pediatric Nephrology Unit, MassGeneral Hospital for Children at Massachusetts General for Children

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Recommended Citation

Falkner, Bonita and Ingelfinger, Julie, "Understanding the power of perinatal events and metabolic status in childhood." (2014). *Department of Medicine Faculty Papers*. Paper 120.

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Understanding the Power of Perinatal Events and Metabolic Status in Childhood

Bonita Falkner, Julie Ingelfinger

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Over the past 25 years, the concept that perinatal events influence an individual's later health and susceptibility to disease has gained traction. After original observations by Barker et al,¹ epidemiological studies have identified a link between markers such as lower birth weight and placental weight with later cardiovascular, metabolic, and other diseases. The theory of fetal programming in response to the intrauterine environment has been supported by a body of elegant experimental investigations in animals. However, findings from clinical investigations in humans have not always been consistent, and other factors such as weight gain trajectories and various environmental exposures, such as diet, stress, and lifestyle behaviors, also influence later health. Moreover, prospective studies in humans that begin in the neonatal or even perinatal period are limited. Ethical limitations in the conduct of clinical research in newborn infants and young children are obvious, and creative approaches are needed to prospectively investigate the birth weight hypothesis. In this issue of *Hypertension*, Lurbe et al² report on a study that provides new insights on childhood origins of chronic disease.

The authors enrolled a sample of healthy newborn infants. All enrolled infants were born at term after uncomplicated pregnancies. The investigators stratified infants according to birth weight (small [SGA], appropriate [AGA], or large for gestational age [LGA]). Blood pressure (BP) was measured at 2 days of age. The infants were then re-examined at 6 months, 2 years, and 5 years. At each study visit, BP and growth parameters were obtained. At age 5 years, a blood sample was obtained for measurement of metabolic parameters.

Despite the relatively small sample size (n=139) of the study, the results are very interesting. At birth, birth weight and BP are positively related. Each birth weight group gained similar amount of weight in each examination interval; the SGA infants remained the smallest and the LGA infants remained the largest at each subsequent examination. Weight gain within the first 6 months of life was similar in each birth

weight group and was not related to BP or subsequent metabolic parameters. After 6 months, both current weight and weight gain were significantly and positively associated with birth weight; birth weight was not significantly associated with the BP level. Most interesting were the metabolic findings. As depicted by the authors in Figure 1, fasting insulin levels are higher in SGA infants who became heavy at age 5 years compared with AGA and LGA infants who become heavy at age 5 years. Most striking are the homeostatic model assessment index estimates of insulin resistance. As shown in the figure, SGA infants are insulin-resistant relative to AGA and LGA infants, regardless of their weight status at age 5 years. These findings, in a sample of healthy infants, indicate that one or a combination of factors related to lower birth weight set the stage for relative insulin resistance that is enduring and seems not to be driven only by excess weight gain.

Earlier epidemiological studies reported a significant inverse relationship between birth weight and subsequent BP, with hypertension considered to be a major mediating link between low birth weight and subsequent cardiovascular disease. Data in the current report by Lurbe et al² suggest that metabolic variation may be a seminal mediating link as well. Regardless of weight gain, by age 5 years the SGA group was insulin-resistant with lower high-density lipoprotein-cholesterol and higher uric acid levels, compared with the other birth weight groups. Together, these relative metabolic differences suggest that features of the metabolic syndrome are present early, with the risk that high BP could possibly evolve as a consequence of later adiposity.

Based on epidemiological associations between greater body weight at 1 year of age and lower risk of later cardiovascular disease,³ nutritional augmentation to promote growth was considered beneficial for SGA infants. Subsequent studies to test this idea reported that overnutrition in early infancy was associated with later metabolic abnormalities^{4,5} and suggested that overnutrition with accelerated weight gain in the first months of life contributed to adverse metabolic changes. However, metabolic assessments in these studies were obtained in later childhood⁴ or adolescence.⁵ Contrary to these reports, Lurbe et al² found that weight gain within the first 6 months had no effect on metabolic variations measured at age 5 years in SGA infants. Based on a systematic review of published evidence on the association of birth weight with type 2 diabetes mellitus in adults, Whincup et al⁶ reported that in most populations birth weight was inversely related to type 2 diabetes mellitus. The report by Lurbe et al² in this issue adds novel findings on the low birth weight pathway to chronic disease with data demonstrating relative insulin resistance at age 5 years in SGA infants. Recently, in a cross-sectional study

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Medicine and Pediatrics, Thomas Jefferson University, Philadelphia, PA (B.F.); and Pediatric Nephrology Unit, MassGeneral Hospital for Children at Massachusetts General for Children, Boston, MA (J.I.).

Correspondence to Bonita Falkner, MD, Department of Medicine and Pediatrics, Thomas Jefferson University, 833 Chestnut St, Suite 700, Philadelphia, PA 19107. E-mail bonita.falkner@jefferson.edu (*Hypertension*. 2014;63:1166-1167.)

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Hypertension is available at <http://hyper.ahajournals.org>
DOI: 10.1161/HYPERTENSIONAHA.114.03290

in Brazil, Crispim et al⁷ reported findings similar to those of Lurbe et al,² but their study was not prospective.

Other issues of interest in the authors' study cohort include the rather high rates of obesity at age 5 years. Fifty percent of LGA newborns were obese at age 5 years, although this sample was limited to 20 children. The obesity prevalence may reflect the current childhood obesity epidemic but could also augment some of the metabolic parameters that were studied. Absent are data on maternal and perinatal parameters including maternal weight, diet, social economic status, and other exposures, as well as maternal weight postpartum. Such information would permit multivariable analysis that might help control for additional factors that may have influenced the results.

In all, the results of the study by Lurbe et al² suggest that metabolic status in 5-year-old children born at term may be influenced or programmed by perinatal events. A variety of potential mechanisms have been considered to explain the developmental origins of health and disease, such as changes in the microarchitecture of various organs, changes in transporters or hormonal levels, and changes that involve epigenetic alterations. Epigenetic modification is a term that indicates modifications in DNA without changes in the DNA sequence per se. These changes may occur via methylation of cytosine in CpG dinucleotides, by phosphorylation, and ADP ribosylation. Other possible changes include the ubiquitination of histones and acetylation. Additionally, the function and conformation of chromatin can be altered by noncoding RNAs. Epigenetic modification may alter the way by which transcription activators and repressors bind to the DNA. The type of epigenetic change may influence the effects—although histone modifications of DNA have relatively short-term effects, DNA methylation may lead to longer-term changes.

There are evolving theories as to how epigenetic changes might influence programming of cardiovascular disease. Although epigenetic changes may be reversible, some epigenetic modifications may be inherited. In other words, epigenetic changes occur as part of the life cycle, but they also occur in response to stress. Thus, the concept that a stressful perinatal environment would potentially lead to epigenetic alterations in the stressed fetus or newborn is attractive. Some of these potential changes will affect the individual in later life, and some might be passed on to future generations. Most epigenetic data with respect to perinatal programming are experimental,⁸ but some human data support the concept that intrauterine stress leads to epigenetic change. For example, changes in the patterns of DNA methylation of insulin-like growth factor 2 (*IGF2DMR*) have been noted in persons exposed to famine conditions in utero.⁹ Indeed, the *IGF2* and *H19* loci have been thought to influence birth weight and growth, though results are conflicting.¹⁰ Bouwland-Both et al¹¹ recently examined a

prospective birth cohort of SGA children in The Netherlands and compared them to children who were AGA at term. The authors extracted DNA from umbilical cord white blood cells, examined DNA methylation, and observed that decreased DNA methylation of *IGF2DMR* was present among SGA children.

Further epigenetic studies may be helpful to our interpretation of prospective studies such as Lurbe et al's.² One hopes that banking of cord blood samples may allow comparisons of physiological results to both genetic and epigenetic studies. To understand the phenomenon of perinatal programming, it will be necessary to take careful phenotypic observations such as those of the current study and pair them with molecular mechanisms. The molecular ability to do so is increasingly available and has the potential to deepen our understanding on fetal origins of chronic diseases such as hypertension and diabetes mellitus.

Disclosures

None.

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Hypertension. 2014;63:1166-1167; originally published online March 31, 2014;
doi: 10.1161/HYPERTENSIONAHA.114.03290

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:

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