Journal of Developmental Origins of Health and Disease (2012), **3**(2), 70–72.

doi:10.1017/S2040174411000705

EDITORIAL

Metabolic programming of obesity *in utero*: is there sufficient evidence to explain increased obesity rates?

Introduction

As the childhood obesity epidemic continues unabated, research underlying its cause is necessary to curtail its progression. The rate of obesity in middle-class preschool-age children has substantially increased over the past 22 years.[1] Recent longitudinal studies indicate that once children of preschool age are obese, the risk of remaining obese in adulthood is doubled.[2] Accordingly, researchers have theorized that intervention to prevent obesity must occur early in life.[3,4] Such an intervention requires identifying infants at risk for obesity before these children become overweight. This presents the question of how to identify early predictors of obesity and infants 'at risk.'

Birth weight has been extensively studied to determine its relationship with obesity risk. Both low birth weight and high birth weight neonates appear to have increased risk of obesity, possibly with similar underlying mechanisms. However, as demonstrated in epidemiologic studies in several countries, most obese children had a normal birth weight.[5,6] Other factors during the perinatal period that have been associated with increased childhood obesity risk include: gestational diabetes mellitus,[7,8] maternal pre-pregnancy obesity[9–11] and excessive gestational weight gain (GWG).[12–15] This active area of research, termed as metabolic programming, is based on the hypothesis that obesity may have its origins *in utero*. However, to date, definitive evidence for metabolic programming as a cause for the increase in obesity rates is lacking.

Low birth weight and obesity risk

Barker's[16] developmental origins of health and disease hypothesis was based on observations in England that death due to cardiovascular disease was inversely related to birth weight. Barker postulated that in poor socioeconomic areas where the infant mortality rate had previously been high, as conditions improved, low birth weight infants survived but had increased rates of cardiovascular disease. This novel theory led others to speculate a 'thrifty phenotype' in which babies born with a low birth weight because of poor nutrition during pregnancy are programmed to stockpile nutrients.[17] Retrospective studies of males exposed to the Dutch famine between 1944 and 1945 during early fetal development had increased weight at age 18, whereas males exposed to the famine in later pregnancy or in the neonatal period were not overweight at age 18.[18] The timing of exposure to nutritional deprivation appears to be critical to metabolic programming. Development in an undernourished uterine environment may program fetuses for an environment of 'thrift'. However, once placed in a postnatal environment with increased food availability, these children have a propensity to develop obesity and coronary artery disease. Further research conducted in poor areas of India extends the developmental origins hypothesis to fetal programming for the development of type 2 diabetes.[19] However, in more developed countries, babies with low birth weight represent just a small proportion of those children who go on to develop obesity and its metabolic sequelae.

High birth weight and obesity risk

At the other end of the spectrum are babies born large for gestational age, typically defined by birth weights greater than the 90th percentile for gestational age. As reviewed by Whitaker and Dietz,[20] multiple studies have demonstrated that large babies have increased rates of obesity. Evidence that metabolic programming occurs in a uterine environment of 'overnutrition' is provided by studies of mothers with gestational diabetes mellitus. More than half a century ago, Pedersen[21] observed that the excess glucose produced by mothers with diabetes crossed the placenta and acted as a growth factor to induce higher birth weight in these neonates. Freinkel[22] further expanded Pedersen's observations and developed the theory of fuel-mediated teratogenesis in which other fuels such as free fatty acids, ketone bodies and amino acids, in addition to insulin, lead to excess fetal growth. Long-term follow-up studies of offspring of women with pre-gestational and gestational diabetes have demonstrated these children to have increased rates of obesity,[8,23] despite a normal birth weight. These studies indicate that large birth weight is neither necessary nor sufficient to predict later obesity. The increased risk for obesity in babies of diabetic mothers is thought to be due to hyperinsulinism and excessive adiposity at birth. However, because of difficulties in obtaining accurate body composition measurements, little data exist on the relationship between newborn adiposity and childhood adiposity.

Contribution of maternal factors to offspring obesity risk

Maternal obesity is clearly linked to offspring obesity,[24] and it is one of the most important risk factors for childhood obesity. However, the influence of intrauterine environment of maternal obesity *v.* the postnatal environment of diet quality and quantity, as well as which influences predominate has not been resolved. Although risk of obesity is highly familial,

*Address for correspondence: Dr J. Josefson, MD, Assistant Professor of Pediatrics, Division of Endocrinology, Children's Memorial Hospital/ Division of Endocrinology, Northwestern University Feinberg School of Medicine, 2300 Children's Plaza, Box 54, Chicago, Illinois, USA.
(Email J-Josefson@northwestern.edu)

genetics alone cannot account for the substantial increases in obesity rates over the span of 30 years. Metabolic programming from maternal obesity is evidenced by studies of sibling pairs. Kral *et al.*[25] showed that offspring born to formerly obese women who had lost substantial weight following gastric bypass surgery exhibited significantly lower rates of obesity compared with older siblings born before their mother's surgery and weight loss. Studies of PIMA Indian sibling pairs showed higher childhood obesity rates among children who were born to mothers with diabetes than their older siblings whose mothers did not have diabetes during those earlier pregnancies.[26] In addition to diabetes, maternal hyperglycemia, with glucose levels below the diagnostic threshold for gestational diabetes, is associated with increased birth weight[27] and increased newborn adiposity.[28] These increased risks for obesity are likely cumulative, in addition to the home environment, as children tend to eat what their mothers eat.

Pregnancy influences

Excessive GWG is also associated with increased risk of offspring obesity.[12–15] The Institute of Medicine (IOM) published guidelines for GWG in 1990 to address the concern that insufficient pregnancy weight gain was contributing to fetal growth restriction. However, in recent years, an estimated 50% of women have exceeded these weight gain guidelines, especially among women who were overweight and obese before pregnancy.[29] In 2009, the IOM updated its GWG guidelines to address the obesity epidemic; however, it became clear that the evidence base for this determination was lacking comprehensive data.

Conclusion

Understanding the causes for increased childhood obesity rates worldwide is necessary to slow down the obesity epidemic. Genetics alone is not sufficient to explain increased rates of obesity. Obesity risk is likely multifactorial and metabolic programming of pregnancy may be one component of this risk. In summary, evidence exists from human studies that metabolic programming *in utero* may increase the risk for offspring obesity in specific populations, that is, those exposed to poor nutrition, diabetes or maternal hyperglycemia. However, as most obese children were not exposed to these adverse uterine environments, further research is necessary to understand the mechanisms by which maternal obesity and excessive GWG contribute to increased offspring obesity risk.

J. Josefson, MD
Assistant Professor
Department of Pediatrics
Division of Endocrinology
Children's Memorial Hospital/Division of Endocrinology
Northwestern University Feinberg School of Medicine
Chicago, Illinois, USA

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