

# Early Postnatal Nutritional Programming: The Effect of Early Postnatal Nutrition on Long-term Outcomes

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**Abstract** Epidemiologic studies show a strong relationship between early nutrition and growth and subsequent metabolic problems such as obesity, type 2 diabetes, hypertension and atherosclerosis (the metabolic syndrome). Genetic predispositions and high food intake play significant roles, but epigenetic mechanisms are also likely to be involved. Largely based on studies from animals, we are just beginning to understand the mechanisms of these developmental origins of disease in adulthood. Here we briefly discuss these mechanism and provide suggestions for a rational approach to early nutrition.

**Key words** Metabolic syndrome; Newborn; Nutrition; Obesity; Programming

Obesity related illnesses and the so-called "metabolic syndrome" are quickly becoming the number one health concern throughout the world. The prevalence of overweight adults as determined by body mass index (BMI) in the United States in 2003-2004 was over 60%, and obesity was approximately 30%.<sup>1</sup> The prevalence of obesity is higher in women compared to men and among African and Hispanic Americans compared to whites. Most of the racial disparities in the prevalence of obesity and overweight are related to gender. A higher percentage of African American women are obese compared to white women. However, there are no ethnic or racial differences in the prevalence of obesity among men.

The high prevalence of overweight and obesity is not limited to adults. According to the United States Center for Disease Control, approximately 14% of children and 12% of adolescents are overweight.<sup>1</sup> The prevalence of overweight in children has tripled between 1980 and 2000

and parallels the increase seen in adults over the same period.<sup>2</sup> The growing rate of overweight and obesity in children and adolescents is of particular concern because children and adolescents who are overweight and obese are likely to carry the condition into adulthood, thus foretelling significant personal and social health consequences for many years to come if action is not taken to reverse these trends. Obesity and overweight in children is also not a problem limited to the United States. European and Asian children are rapidly catching up.<sup>3,4</sup>

The greatest blame for this epidemic of overweight and obesity has been placed on poor dietary habits; however heredity plays a significant role. Using a genome scan of DNA samples from the Framingham Heart Study participants to identify a common genetic variant associated with obesity, it was found that an obesity-predisposing genotype is present in 10% of individuals.<sup>5</sup>

In addition to poor dietary habits and heredity, a more Lamarckian concept has been evolving over the past decade. Several epidemiologic studies support the concept that undernutrition during fetal life can lead to metabolic programming during a critical window of development, which causes adaptations toward a metabolically more thrifty phenotype.<sup>6,7</sup> When the individual with such a thrifty phenotype is exposed to high levels of nutrients during later life, these adaptations toward thriftiness can dispose toward obesity, hypertension, and type-II diabetes, which might be able to span for generations.

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*Received January 26, 2007*

*\*Presented at the 16th James Hutchison Memorial Lecture, 2 May, 2006, Hong Kong*

Most of the recent research on the "Early Origins" hypothesis has focused on undernutrition in the fetus with intrauterine growth restriction (IUGR) and its consequences. However, critically ill premature infants frequently undergo a period of undernutrition in the first few weeks of life that lead to delays in growth when compared to the growth they would have undergone had they remained *in utero*.<sup>8</sup> This has been termed extrauterine growth restriction (EUGR). Attempts at rapid catch-up growth in previously critically ill infants with EUGR may result in effects that are often already evidenced during infancy, and manifested as chubby babies who have undergone periods during which they have received high energy nutrients that have been utilised for fat deposition. However, it is becoming apparent that the effects of early catch up growth may be more subtle. Studies showing slower flow mediated brachial artery dilatation in a cohort of 13-16 year old teenagers who were born premature but grew more rapidly in the first 2 weeks of life has raised concerns.<sup>9</sup> Similarly, the concentrations of 32-33 split proinsulin (a marker of Type 2 diabetes) were higher in those teenagers who gained the most weight in the first 2 weeks of life.<sup>10</sup> These studies suggest that slower growth during the first two weeks of life may be associated with less detrimental metabolic consequences than more rapid growth. Of interest, is that the nutritional intake of these infants was not related to these differences, but rather just the differences in growth, which could generate from genetic factors as well as degree of illness in these infants. The latter influence, the degree of illness (or intensity of care required in the neonatal intensive care unit), has been found to correlate to the degree of intra-abdominal visceral fat accumulation when premature infants reach term gestation.<sup>11</sup> The intra-abdominal visceral fat accumulation, in turn, has been found to directly relate to the development of Type 2 diabetes. This increased intra-abdominal fat accumulation has been speculatively linked to greater stress in the most critically ill infants, who in turn have the highest levels of circulating glucocorticoids.<sup>11</sup>

Obvious difficulties in evaluating effects of early nutrition in humans relate to the amount of time required to obtain meaningful results and difficulties in obtaining tissues to evaluate mechanisms. Several animal models of early growth restriction have been utilised. Some of these have relied on manipulation of feeding in the mother to obtain intrauterine or extrauterine growth restriction through a putative change in nutrients obtained by the fetus through the placenta or the mothers' milk. Other studies

have relied on litter manipulation, wherein small litters receive greater quantities of nutrition than large litters. Classic studies using this technique were among the first to show the effects of nutritional programming. Litter expansion to approximately 18 pups per litter during the weaning period when compared to smaller litters, resulted in lower growth in the litter expanded animals and this lower weight persisted throughout the life of the animal, whereas nutritional restriction after the weaning period resulted in only transient growth delay, with rapid return to the growth curve.<sup>12</sup> Thus, the preweaning period in rats is considered a critical window during which early nutritional programming may occur.

Problems with these techniques include difficulty in knowing the exact quantity and composition of the food the fetus or infant is receiving. Another technique, the rodent gastrostomy feeding model, sometimes termed the "pup in the cup" model,<sup>13</sup> which helps alleviate this difficulty, has been employed by our laboratory as well as a few others.

Using this technique, feeding a very high carbohydrate diet in early life has resulted in a long lasting (after 100 days of life) metabolic effect that includes high insulin concentrations, obesity, elevated hexokinase and glucose intolerance in adult animals treated with high carbohydrate intakes during the preweaning period.<sup>14,15</sup> These effects actually persisted into the next generation, despite the mothers being fed similar diets during pregnancy and lactation and the rats being fed similar diets after the weaning period. The level of carbohydrates used in these experiments was very high. Questions are being raised whether use of higher protein intakes, such as those provided to formula fed infants when compared to breast fed infants may play a role in programming toward metabolic syndrome in adulthood. Furthermore, many premature infants or infants born small for gestational age receiving high density nutrients in order to attain catch up growth may be being programmed for obesity in later life.

Several mechanisms have been proposed for developmental programming.<sup>16</sup> One emerging concept relates to epigenetics. The term epigenetics was first coined by Conrad Waddington in 1942 to refer to the mechanisms by which the genes of the genotype bring about phenotypic effects.<sup>17</sup> Molecular biologists today are probably most familiar with epigenetics as the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence. To this day, molecular mechanisms of epigenetic phenomena remain

poorly understood, but include DNA methylation at (cytidyl phospho guanidine) CpG sites that may silence DNA transcription directly by blocking transcription factors, most commonly at promoter regions, and histone side chain alteration with methyl, acetyl, ubiquitin, or other moieties which act by steric alterations of the histone that allow for interaction of transcription sites on the DNA molecule.

Compelling evidence for nutritional modification of phenotype comes from studies wherein pregnant Agouti mice carrying the A<sup>vy</sup> mutation fed a high versus a low methyl donor and 1 carbon metabolism cofactor (methionine, choline, folic acid, vitamin B<sub>12</sub>, and pyridoxal phosphate) diet had offspring with a pseudoagouti phenotype (dark coat, non obese) versus those in the low methyl donor and cofactor group that had a clear yellow and prone to obesity phenotype.<sup>18</sup>

Recent studies in mice have shown that the risk for metabolic syndrome is amplified if the poor fetal growth is followed by rapid postnatal catch-up growth.<sup>19</sup> Poor fetal growth, resulting from maternal protein restriction, followed by postnatal catch-up growth is associated with reduced average longevity in mice. In addition to reduced average longevity, mice which have been growth restricted *in utero* and then grown rapidly during the lactation period have a reduced maximum longevity. Maximum longevity of these mice was further, reduced when the animals were weaned onto an obesity-inducing cafeteria-style diet. Thus maternal nutrition during critical periods of development has a major impact on quantity as well as quality of life.<sup>20,21</sup>

These studies suggest strategies that can be applied in the prevention of metabolic syndrome. In addition to good dietary habits throughout the life cycle, special attention placed on critical windows of development in the fetus and newborn should be applied. Overreaction to some of the recent studies in neonates that show an increased risk to metabolic problems associated with more rapid weight gain in the first two weeks of life<sup>10</sup> is not warranted. These results were not related directly to early nutrition, but more likely, to the stresses of early neonatal life.<sup>11</sup> Thus this should not be utilised as a basis to restrict nutritional intake. A nutritional strategy for premature infants based on continuation of nutrient delivery that would be received by the fetus remains a rational approach. Thereafter, knowledge of the alterations in dietary requirements based on age related considerations should be utilised. For example, a very premature infant may require between 3-4 grams/kg/d of protein.<sup>22</sup> However, as this infant matures toward term gestational age, the protein requirements will

be considerably less. Knowledge of early exposure to growth restriction may also be used as a basis for more rational nutritional approaches. For example, if it is known that a child was IUGR or EUGR; highly aggressive attempts to attain rapid catch up growth or to overcompensate for early growth delays may place such an individual at greater risk.

In summary, epidemiologic studies show a strong relationship between early nutrition and growth and subsequent metabolic problems such as obesity, type 2 diabetes, hypertension and atherosclerosis (the metabolic syndrome). Largely based on studies from animals, we are just beginning to understand the mechanisms of these developmental origins of disease in adulthood. Additional studies are needed from which we can base preventative and therapeutic strategies.

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