*Special Article*

# Early postnatal nutrition and programming of the preterm neonate

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*Early postnatal nutrition is a vital determinant of adult health; this is particularly true for the infant born prematurely and cared for in a hospital setting such as the neonatal intensive care unit. Human and animal studies support the contribution of postnatal dietary composition and the rate of extrauterine growth to long-term metabolic outcomes. One mechanism by which postnatal nutrition affects long-term outcome is via developmental programming. Programming, or the modulation of gene expression to impart a short-term advantage accompanied by a long-term cost, may be achieved by epigenetic modifications to chromatin. This review summarizes the details of postnatal nutritional content and rate of growth on the development of metabolic disease. The role of epigenetics in developmental programming of the preterm infant is also discussed, with an emphasis on animal models of dietary manipulation and directions in which the field must move in order to formulate effective feeding strategies for the preterm infant.*



## INTRODUCTION

The importance of early life events in the development of adult disease has become widely recognized. The "Developmental Origins of Adult Disease Hypothesis" deals with the origin of adult disease in terms of developmental adaptation, also known as "programming." The ability to adapt to environments encountered during development increases the odds of survival; however, the short-term gain appears to be accompanied by a long-term cost. Specifically, adaptations made in the short term are accompanied by changes in tissue character and gene expression profiles, which, in the long term, set the stage for the development of adult morbidities, particularly metabolic disease.[1]

Much of the emphasis on programming has focused on prenatal insults, including premature birth. In 2007, 12.7% of babies born in the United States were preterm. The causes of preterm birth vary according to gestational age as well as genetic and environmental factors.[2] A wealth of epidemiological evidence has connected a suboptimal gestational environment, including nutritional deprivation, to an increase in adult-onset metabolic disease.[3,4] It is now becoming clear that the early postnatal environment, including nutrition, is also a vital determinant of adult health; this is particularly true for the infant born prematurely and cared for in a hospital setting such as the neonatal intensive care unit (NICU).

Effective management of preterm, hospitalized infants is integrally linked to nutrition. It is vital that these infants receive sufficient nutrients to prevent extrauterine growth restriction and promote neurodevelopment while minimizing predisposition to adult metabolic disease. In order to achieve these important goals it is necessary to understand the mechanisms by which postnatal feeding strategies can predispose these infants to adult disease. This will facilitate evidence-based implementation of dietary regimes and assessments of the specific effects of macro- and micronutrients on preterm infants. This review focuses on recent advances in understanding of

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*Key words: epigenetics, obesity, postnatal nutrition, programming, pup-in-the-cup*

doi:10.1111/j.1753-4887.2010.00370.x

the mechanisms by which the postnatal diet can contribute to programming in the preterm, hospitalized infant.

## NUTRITIONAL DILEMMAS FACED BY THE PRETERM INFANT

Recent decades have seen a greater survival rate of infants who are born extremely premature; however, many of these babies experience extrauterine growth delay. While maintaining a postnatal growth trajectory similar to the gestationally equivalent fetus in utero is the standard of care, there is significant controversy over whether this is an appropriate goal. Such a growth trajectory is difficult to achieve, and extrauterine growth restriction is still common among premature infants, even after they achieve the goal growth velocity.[5–7] This may be the result of insufficient provision of protein and energy for the metabolic requirements of these infants. The use of fortified maternal milk, preterm formulas, and specialized amino acid preparations has improved postnatal growth indices and parameters associated with neurodevelopment and brain growth.[8–12] However, the use of these specialized feedings has also been associated with accretion of greater body fat relative to weight at term-corrected age[13] as well as increased deposition of visceral adipose.[14]

A further contribution is limitations in the ability of the preterm infant to absorb nutrients.[15–17] Nutrient absorption for the preterm infant could be decreased because of the preterm infant's underdeveloped gastrointestinal tract and accompanying microflora. The microbiota found in the human gastrointestinal tract is diverse, dynamic, and likely aids in processes that result in the maturation of the innate and adaptive immune systems.[18] The GI tract of the premature infant has a thin layer of immature epithelial cells that overlies a highly immunoreactive submucosa. The premature infant's microbiota formation has been shown to be dependent on the microbes that first colonize the GI tract within the first several days after birth, with a healthy microbiota being critical for normal development. Factors that affect the infant's microbiota include mode of delivery, delayed enteral feeding, being exposed to pathogens within the NICU, and being exposed to a mother's oral and skin microbiota and breast milk.[19–21]

Given the complexity of the neonate's nutritional dilemmas, the difficult question that still remains is how to maximize neurodevelopment and appropriate extrauterine growth in this sensitive population and is the subject of much controversy. Clinical studies in humans and studies in animal models, however, demonstrate that both the dietary composition and the resultant growth trajectory affect long-term outcomes.

## POSTNATAL DIETARY COMPOSITION

Postnatal dietary undernutrition and concurrent extrauterine growth restriction are associated with adverse consequences, the most notable of which is long-term neurodevelopmental deficits.[22–25] Improved cognitive performance at 18 months and at 7–8 years has been demonstrated in children who were born preterm and received a nutrient-enriched preterm formula compared to those receiving standard infant formula.[26] However, postnatal over-nutrition, and rapid catch-up growth, also appears to place the preterm infant at risk.[27,28] High non-protein energy feeding of low-birth-weight infants results in an increase in weight due to body fat rather than a gain in lean body mass.[29] High-protein diets, while known to be associated with increased growth and neurodevelopment,[9] may also pose a potential problem for increased adipose formation and later obesity.

The hypothesis that increased protein received by formula-fed infants may contribute to obesity is being tested by the European Childhood obesity and protein in infant nutrition (CHOPIN) study (http://clinicaltrials.gov/ct2/show/NCT00338689). In this randomized double-blind intervention trial, formula-fed infants receive either a higher or a lower protein formula during the first year of life. Follow-up at 2 years of age has demonstrated that lower protein formula results in a growth trajectory that mimics that of a breastfed infant and thus may be associated with lower rates of obesity.[30] Although the focus of this review is prematurity, it is important to note in the context of postnatal dietary compositions that breast milk appears to have a protective effect against the development of metabolic disease in term infants. Evidence suggests that breastfed infants have lower blood pressure, lower total cholesterol, and a lower prevalence of overweight and obesity.[31–33] The apparent dichotomy surrounding postnatal nutrient balance presents a challenging problem in the clinical arena and a robust evaluation of the long-term effects of postnatal nutrition is necessary to formulate effective feeding strategies for the preterm infant.

## RATE OF POSTNATAL GROWTH

While the effect of dietary composition is important, the associated rate of postnatal growth is also a vital determinant and, possibly, a marker of future health. A slower rate of postnatal growth has been associated with decreased cognitive scores[34] and adverse neurodevelopmental outcome.[8] Interestingly, it has also been observed that rapid postnatal weight gain over the first 4 months, after intrauterine growth restriction, predicts both increased body weight and decreased cognitive scores at 7 years of age; however, those infants with slower growth

scored much lower on the cognition test (15.5 compared with 2.4 points less with the rapid weight gain group).[34] Increased postnatal weight gain may be associated with adult-onset metabolic disease, and rapid "catch-up" growth and has been shown to correlate with the development of metabolic disease, including visceral adiposity,[35] type 2 diabetes,[36] and cardiovascular disease.[37] In addition, preterm male infants gain weight more rapidly than female infants and thus may be at higher risk.[38]

Animal studies have also been helpful in understanding the effects of the rate of postnatal growth on adult metabolic disease. In a mouse model of low-birth-weight and accelerated postnatal catch-up growth, adipose tissue lipogenic gene expression is increased in the context of enlarged adipocytes.[39] In rats, catch-up growth following fetal growth restriction results in increased weight, percent body fat, and circulating leptin[40] as well as gender-specific changes in metabolic parameters in response to a high-fat diet.[41] Male adolescent rats, following intrauterine growth restriction, also display increased visceral adipose deposition, even before the onset of obesity.[42] In other studies, overfeeding of rats in the immediate postnatal period induces early-onset obesity and accelerated maturation of the hypothalamic-pituitary-adrenal axis, which is important for the regulation of food intake and energy expenditure. An important consideration is that, in adulthood, these rats have increased mRNA levels of glucocorticoid receptor (GR) and 11β hydroxysteroid dehydrogenase type-1 in the visceral adipose tissue.[43] These studies demonstrate that increased postnatal growth results in adipose dysfunction and molecular changes that set the stage for the development of metabolic disease.

Animal models of postnatal nutritional manipulation also provide an effective means of probing the long-term effects of postnatal diet. The rat "pup-in-the-cup" model allows evaluation of postnatal dietary composition in the context of maternal separation.[44,45] In this model, a gastrostomy tube is placed in a neonatal rat pup and feeding is accomplished via a pump. This allows detailed and controlled manipulation of the macro- and micronutrient content of the diet. Further, since the rat is developmentally immature at birth, the effect of various dietary regimens on organ development can be evaluated. This model also allows for evaluation of long-term effects, as the pups can then be weaned onto regular rat chow and studied in adulthood. Rat pups receiving high-protein diets via gastrostomy display enhanced short-term weight gain, insulin resistance, and modified expression of adipocyte GLUT4 and liver GLUT2.[44] Changes in adult metabolism, along with obesity, have been observed in rats receiving high-carbohydrate diets via the pup-in-the-cup model. These rats display changes in insulin secretory capacity, increased hexokinase activity, and an increase in insulin biosynthesis. The high-carbohydrate rats have increased numbers of pancreatic islets as well as increased expression of pancreatic duodenal homeobox factor-1 (Pdx-1), protein kinase 2, and phosphatidylinositol 3-kinase.[46–53] A common theme found in animal models of postnatal nutritional modulation is a persistent alteration in gene expression, suggesting that epigenetics may contribute to programming of the preterm infant.

## EPIGENETICS AS A MECHANISM FOR POSTNATAL NUTRITIONAL PROGRAMMING

One means of regulating gene expression over the long term is epigenetics. Epigenetics refers to heritable changes in gene transcription caused by mechanisms other than changes in the underlying DNA sequence. Another way to think of epigenetics is as a means of selectively utilizing the large array of information contained within the genome, particularly in the context of tissue specificity and developmental timing. Epigenetic modifications to chromatin, the functional unit of DNA and protein, affect gene transcription by altering chromatin's three-dimensional structure and associations with the transcription machinery. Epigenetic modifications include DNA methylation, which affects transcription factor binding, and modifications to histones. Modification to the histone proteins occur largely, but not exclusively, in the N-terminal tail region and include acetylation and methylation (see review by Kouzarides[54]) (Figure 1). The effects of individual histone modifications on transcription are not straightforward and provide a complex means of regulating transcription. Generalities such as methylation of histone H3 lysine 9 (K9) contributing to gene inactivation, and methylation of histone H3 lysine 4 (K4) increasing gene expression, are complicated by the compound effect of multiple modifications.

Epigenetic modulation of gene transcription, that is, adjusting the level of expression of genes already being transcribed, can elicit subtle changes to phenotype and provide the "plasticity" necessary to respond to variations in environment. The last decade has seen much interest in the effect of prenatal events on the epigenetic characteristics of the developing fetus. This is true of early embryogenesis and assisted reproduction,[55] late gestational insults such as maternal hypertensive disorders,[56] and gestation-wide insults related to dietary and environmental exposures.[57,58] Based on the notion that the developing fetus is susceptible to epigenetic changes, it is reasonable to assume that the preterm infant is also susceptible. Prolonged changes in gene expression in response to differing postnatal diets are also consistent with epigenetic modifications.

Early-life nutrition has the capacity to alter chromatin structure and gene expression and to modulate health

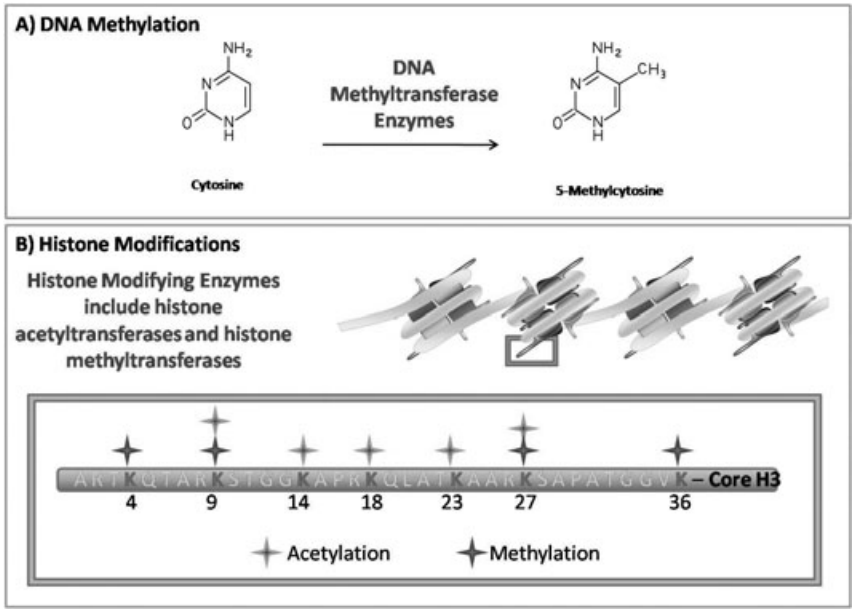


*Figure 1* **Epigenetic modifications to chromatin regulate gene transcription by affecting the interaction of DNA with the transcription machinery. A**) DNA methylation: DNA is modified by the addition of a methyl group to the 5′ position of cytosine by DNA methyltransferase enzymes. **B**) Histone modifications: Histone proteins, around which DNA is wrapped, can be modified by chromatin-modifying enzymes. Lysine (K) acetylation and methylation sites of the N-terminal tail of Histone (H3) is shown as an example (insert).

in early and later life.[59,60] Much of the current evidence linking early life events to epigenetic modifications stems from animal models of prenatal insult, including rodents subject to maternal malnutrition[61] or uteroplacental insufficiency.[56] Effects of maternal nutrition on epigenetic programming, specifically alterations of histones, during prenatal development can have important implications for disease susceptibility later in life.[62] Maternal diet is important for DNA methylation of genes involved in glucocorticoid metabolism.[63] Upregulation of GR as well as PPARα, in conjunction with a decreased level of the DNA methyltransferase enzyme, DNMT1, is evident in the liver of offspring from mothers undergoing protein restriction during gestation.[64]

Epigenetic effects are also seen in other models of prenatal insult. Uteroplacental insufficiency and resulting intrauterine growth restriction (IUGR), also decreases levels of DMNT1 in the brains of rat offspring, and this is accompanied by global decreases in DNA methylation and increases in histone 3 (H3) acetylation on lysine 9 (K9) and K14.[65] Interestingly, the modifications to chromatin in IUGR rat brains are gender dependent, with a divergence in global acetylation occurring at d21 when female brains continue to be characterized by increased site-specific acetylation, while male brains become characterized by decreased acetylation at K9 and K14 of H3.[65] Liver chromatin modifications are also affected by IUGR, with persistent increases in acetylation of H3K9 and K14[66] as well as reduced hepatic expression of DNMT1.[64] In addition, other epigenetic alterations in IUGR offspring have been observed in skeletal muscle GLUT4 and β-cell Pdx1.[61,67] An important concept is that IUGR affects epigenetics along the entire gene and is associated with fine tuning of transcription, rather than an "on/off" effect traditionally associated with epigenetics. This is exemplified by the effect of IUGR on the epigenetics of hepatic IGF-1, the major source of circulating IGF-1. These epigenetic changes include gender-specific, whole-gene changes in histone modifications and DNA methylation.[68] Importantly, these changes are associated with decreased hepatic IGF-1 mRNA as well as a phenotype characterized by reduced growth and impaired glucose homeostasis (Figure 2).

Epigenetic changes to genes in response to prenatal insults sets the stage for long-term modulation of gene expression and ultimately changes in phenotype. While the role of epigenetics in postnatal programming of the preterm neonate remains to be demonstrated, there appears to be a window in which infants are vulnerable. This window would include the prenatal and postnatal periods. It will be important to establish whether animal models of postnatal dietary manipulation, such as the pup-in-the-cup model, will prove useful in examining the effects of specific macro- and micronutrient manipulations on DNA methylation and histone modifications.

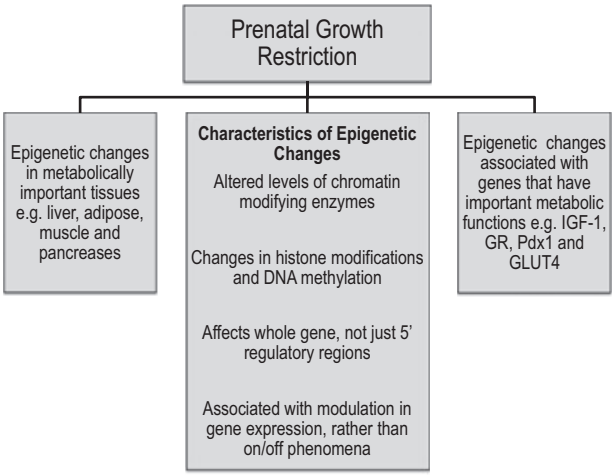


*Figure 2* **Schematic representation of the epigenetic consequences of prenatal growth restriction demonstrated by animal models.**

## CONCLUSION

Nutrition in the postnatal period is an important component of the care of the preterm hospitalized infant. Both under- and overnutrition have negative ramifications for the preterm infant, including long-term programming of metabolic disease. While the details vary depending upon the timing of dietary modification, the dietary macro- and micronutrient contents, and the rate of growth of the infant, one mechanism for programming may be the epigenetic modification of genes critical for metabolic homeostasis. Future epigenetic studies in animal models with postnatal dietary manipulation will be necessary to facilitate identification of dietary and pharmaceutical approaches that can be applied in the postnatal period, with the goal of overcoming some of the challenges faced by these infants.


### Acknowledgments

*Declaration of interest.* The authors have no relevant interests to declare.


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