Fetal Programming of Adult Disease

Implications for Prenatal Care

Christopher Lau, PhD, John M. Rogers, PhD, Mina Desai, MD, and Michael G. Ross, MD, PhD

The obesity epidemic, including a marked increase in the prevalence of obesity among pregnant women, represents a critical public health problem in the United States and throughout the world. Over the past two decades, it has been increasingly recognized that the risk of adult health disorders, particularly metabolic syndrome, can be markedly influenced by prenatal and infant environmental exposures (ie, developmental programming). Low birth weight, together with infant catch-up growth, is associated with a significant risk of adult obesity and cardiovascular disease, as well as adverse effects on pulmonary, renal, and cerebral function. Conversely, exposure to maternal obesity or high birth weight also represents an increased risk for childhood and adult obesity. In addition, fetal exposure to select chemicals (eg, phytoestrogens) or environmental pollutants (eg, tobacco smoke) may affect the predisposition to adult disease. Animal models have confirmed human epidemiologic findings and provided insight into putative programming mechanisms, including altered organ development, cellular signaling responses, and epigenetic modifications (ie, control of gene expression without modification of DNA sequence). Prenatal care is transitioning to incorporate goals of optimizing maternal, fetal, and neonatal health to prevent or reduce adult-onset diseases. Guidelines regarding optimal pregnancy nutrition and weight gain, management of low- and high-fetal-weight pregnancies, use of maternal glucocorticoids, and newborn feeding strategies, among others, have yet to fully integrate long-term consequences on adult health.

(Obstet Gynecol 2011;117:978–85)
DOI: 10.1097/AOG.0b013e318212140e

Formalized prenatal care was established as a program of three pregnancy visits in Boston, Massachusetts, in the early 1900s. As the maternal death rate approached 1% of pregnancies, it is not surprising that care focused on maternal mortality (eg, preeclampsia, infection, and hemorrhage). With the dramatic reductions in maternal mortality, the prenatal care focus in the latter part of the 20th century transitioned to reducing fetal and neonatal morbidity and mortality. As detailed in this review, we are at the precipice of another transition: to optimize fetal and neonatal health to prevent or reduce a diversity of adult-onset diseases.

Obesity has emerged as a preeminent public health problem.[1] In the United States, 66% of adults are overweight (body mass index [BMI, calculated as weight (kg)/[height (m)]^2] 25 to less than 30), half of whom are obese (BMI 30 or more), representing a modern health crisis. Perhaps of even greater concern is the continued increase in prevalence of obesity among pregnant women, which is associated with high-birth-weight newborns and a known risk factor for childhood obesity.[2,3] To further exacerbate this problem, childhood obesity is known to lead to adult obesity.[4] Over the past two decades, it has been increasingly recognized that the risk of adult health disorders, particularly obesity and metabolic syndrome, can be markedly influenced by early life events, such as prenatal and neonatal growth trajectory and environmental exposures. Much of the impetus in this area is attributable to the seminal works of Barker and Hales,[5,6] who in the early 1990s linked nutritional insufficiency during embryonic and fetal development to latent diseases in adulthood. The Barker hypothesis postulates that a number of organ

From the Toxicity Assessment Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina; and the Department of Obstetrics and Gynecology, Geffen School of Medicine at UCLA, Los Angeles, California; Harbor-UCLA Medical Center, Torrance, California.

This document has been reviewed in accordance with the U.S. Environmental Protection Agency policy and approved for publication. Approval does not signify that the contents reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Corresponding author: Michael G. Ross, MD, MPH, Professor and Chairman, Department of Obstetrics and Gynecology, Harbor-UCLA Medical Center, 1000 W. Carson St, Box 3, Torrance, CA 90502; e-mail: mikeross@ucla.edu.

Financial Disclosure
The author did not report any potential conflicts of interest.

ISSN: 0029-7844/11

structures and associated functions will undergo programming during prenatal life, determining the set points of physiological and metabolic responses that continue into adulthood. Alterations in embryonic and fetal nutrition as well as endocrine status during gestation can result in developmental adaptations that produce permanent structural, physiological, metabolic, and epigenetic changes, thereby predisposing an individual to adult cardiovascular, metabolic, and endocrine diseases, particularly metabolic syndrome. This fetal origin hypothesis since has been expanded to include early childhood development and effect on a diversity of adult disorders. This article provides a brief overview of the developmental origins of health and disease concept, recent scientific advances, and implications for future investigation.

Maternal Nutritional Status and Offspring Cardiovascular Diseases and Metabolic Syndrome

In retrospective studies, Barker et al examined the incidence of coronary heart disease in middle-life and late-life patients and correlated that to body measurements at birth. Using birth weight as a surrogate indicator of intrauterine growth, Osmond et al[7] report a nearly twofold increase in death rates from coronary heart disease among those born at the lower (2.5 kg) compared with the upper (4.3 kg) extremes of weight. Similar results were obtained from another cohort, with recognition that individuals who were small at birth (but born full-term), rather than those born prematurely, were at increased risk for coronary heart disease.[8] Since then, a robust body of epidemiological evidence from various populations supports these findings. Broadly speaking, these investigations reported that lower birth weight, coupled with accelerated weight gain during early childhood, was associated with significantly higher incidence of coronary heart diseases later in life. Typically, this correlation was independent of age, sex, ethnicity, socioeconomic status, and marital status. Besides coronary heart disease, blood pressure in adults also appears to be inversely related to birth weight. These findings are supported by historical studies, recent observations,[9] and meta-analyses of the literature,[10] and they have been captured by recent reviews.[11–14]

In the same retrospective studies in which associations between low birth weight and coronary disease were noted, Hales et al[6] observed impaired glucose tolerance or diabetes, whereas Barker et al[15] found that the prevalence of the metabolic syndrome decreased progressively with increasing birth weight. Based on their findings, these two investigators proposed the "thrifty phenotype" hypothesis, which stated that a malnourished fetus made adaptive changes in glucose–insulin metabolism, including reduced capacity for insulin secretion and insulin resistance, to improve survival under conditions of nutritional deprivation.[16] However, if or when nutrition became adequate or excessive postnatally, physiological conflicts arose as glucose intolerance was triggered by a positive caloric balance. Gluckman and Hanson[17] elaborated a "match–mismatch" thesis of the "predictive–adaptive" response by the fetus (Fig. 1). Fetal metabolism is programmed to respond to environmental cues reflective of what is expected after birth. Accordingly, the fetus will adapt by conserving nutrients if the maternal environment signals harsh conditions and by disposing of nutrients if the conditions are favorable. If the postnatal reality "matches" these predicted conditions, then the offspring is best prepared for the challenges of survival. Conversely, should there be a mismatch when a state of nutrient conservation prenatally (reflected by low birth weight and size) is met with an abundance or excess of nutrients postnatally and the individual's metabolic processes are maladapted, leading to elevated risks of chronic diseases in adulthood. Many studies have con-

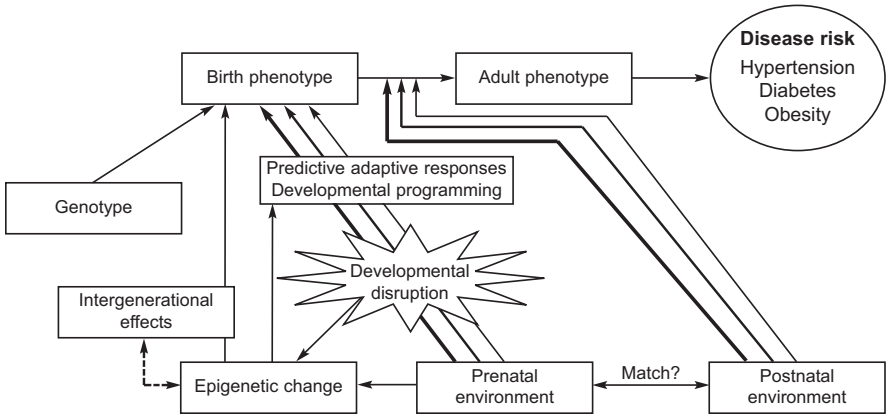

Fig. 1. Effects of epigenetics and environment on birth and adult phenotypes. Modified from Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004;305:1773–6. Reprinted with permission from American Association for the Advancement of Science.

Lau. Programming of Adult Disease. Obstet Gynecol 2011.

firmed an additive effect of fetal growth restriction and subsequent obesity in worsening glucose tolerance and insulin insensitivity.[18] In the thrifty phenotype hypothesis, catch-up growth of newborns who are small for gestational age (SGA) that leads to childhood obesity has been regarded as a key predictor of latent diseases in adulthood[19]; hence, no increase in risk of diabetes for small size at birth was observed in the absence of excessive postnatal weight gain.[20] The associations between birth weight, childhood BMI, and noninsulin-dependent diabetes mellitus are strongly supported by epidemiological studies from different populations[21] and have been summarized in recent reviews.

Although considerable attention has been drawn to the developmental origins of cardiovascular disease and metabolic syndrome, the Barker hypothesis has been extended to other adult disease risks as well, including effects on kidney size and function,[22,23] lung function,[24,25] immune function,[26] learning ability,[27] mental health, aging and menopause,[28] polycystic ovaries,[29] and cancer.[30–32] Typically, these recently reported associations tend to be more sporadic, less definitive, and less consistent than those for coronary heart disease and diabetes. Perhaps additional studies on the horizon will lend confirmation and clarity. The predictive–adaptive theory may not be applicable to many of these SGA long-term outcomes. For example, human and animal studies of SGA newborns demonstrate reduced glomerular number, with nephogenesis having been completed at birth in humans. Thus, the process and consequence of reduced intrauterine growth is sufficient to impair renal development, with no evidence to date that a match or mismatch in the postnatal period aids or impedes adult renal function.

Controversies With Interpretation of Birth Weight and Catch-Up Growth

Although birth weight has been used widely as an empirical index to correlate with disease risks in adult life, primarily because the data are readily available, its reliability as a surrogate for the quality of the intrauterine environment has been questioned.[33–35] Low birth weight may reflect genetic differences or adaptations to high altitudes and in itself does not always predict adverse outcomes for the offspring. Other measures such as birth length, ponderal index, or perhaps a measure of muscle and fat mass may provide better indicators of an adverse prenatal environment. Fetal-to-placental weight ratio at birth also has been suggested as a possible predictor of risk of adult diseases.[36] In addition, the window of metabolic programming or plasticity likely extends from fetal life to at least the early infancy period, and sole reliance on birth weight may be misleading. Encouraging postnatal catch-up or accelerated growth also is controversial. As discussed, animal and human studies have provided evidence of health risks (insulin resistance, hypertension, obesity) of such accelerated postnatal growth in newborns born underweight,[37–42] although the findings are not necessarily uniform.[43] Moreover, elevated disease risks also have been associated with poor childhood growth.[44–46] The health benefits and detriments of catch-up growth for undersized newborns remain a subject of debate.[47]

Potential Mechanisms of Developmental Programming

Experiments with laboratory animals have revealed several potential mechanisms of metabolic programming by hormonal signals, epigenetic modifications, and mitochondrial function. A number of studies have focused on resetting of fetal endocrine homeostasis in response to fetal growth impairment. Several hormones known to regulate fetal growth and development also may play a central role in intrauterine programming. These include anabolic hormones such as insulin, insulin-like growth factors (insulin-like growth factor I and insulin-like growth factor II), prolactin, and thyroid hormones, as well as catabolic hormones such as the glucocorticoids. These hormones act as nutritional and maturational cues and adapt fetal development to the prevailing intrauterine conditions, thereby maximizing the chances of survival in utero and after birth. Such endocrine maneuvers may have short-term benefits to the well-being of fetus but also may permanently reset the endocrine system to predispose the adult to aberrant physiological functions and, ultimately, disease.

Epigenetic control of gene expression involves modification of the genome without altering the DNA sequence itself and is typically mediated by changing the DNA methylation pattern or modifications of chromatin packaging via changes in histone acetylation, methylation, or phosphorylation (Fig. 2). The epigenome is re-established at specific stages of development and is largely maintained throughout life, making it a prime candidate as the basis for fetal programming. The seminal work of Waterland and Jirtle[48] demonstrated that dietary supplementation can dramatically alter a heritable phenotype in mice. A number of genes potentially involved in fetal programming have been determined to be under epigenetic regulation, including the glucocorticoid receptor, POMC, 11β-hydroxysteroid dehydrogenase, corticotrophin-releasing factor, leptin, glucose transporter, and

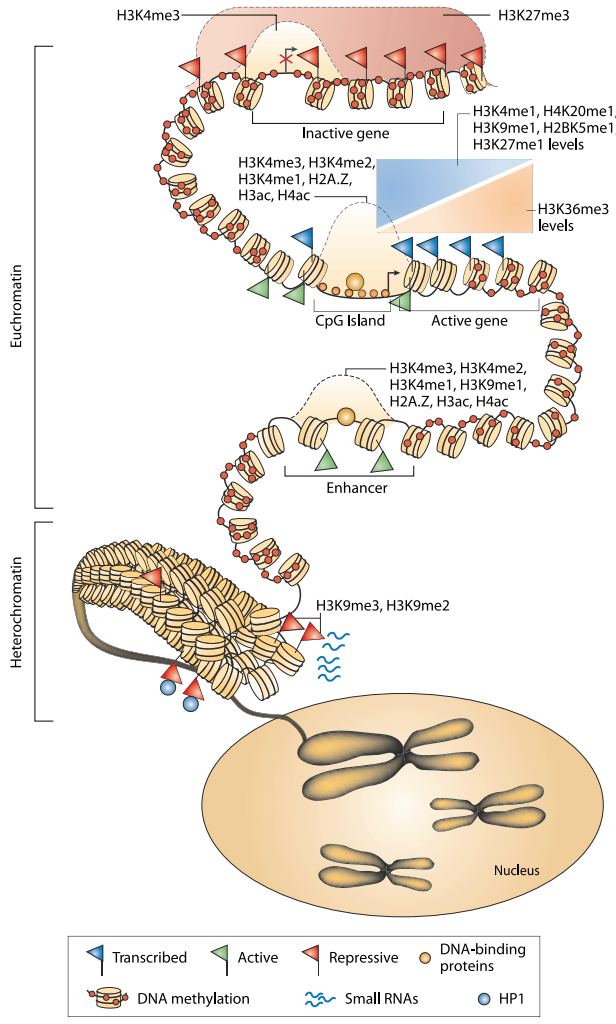

Fig. 2. Characteristics of epigenomes. DNA methylation, histone modifications, nucleosome positioning, and small RNAs interact to regulate gene expression. Reprinted by permission from Macmillan Publishers Ltd (*Nature Reviews Genetics*): Schones DE, Zhao K. Genome-wide approaches to studying chromatin modifications. Nat Rev Genet 2008; 9:179–91, copyright 2008.

Lau. Programming of Adult Disease. Obstet Gynecol 2011.

peroxisome proliferator-activated receptors. Hence, it is reasonable to hypothesize that epigenetic alteration of gene expression attributable to an altered nutrient environment may, at least in part, underlie developmental programming of metabolism.

A Mechanism for Programmed Obesity: Appetite Dysfunction

Appetite and satiety function must develop in utero in precocial species (ie, species in which newborns are relatively mature and mobile at birth) to prepare for newborn life. In the rat and human, although neurons that regulate appetite and satiety are detectable in the fetal hypothalamus early in gestation, the functional neuronal pathways form during the second week of postnatal life in the rat and likely during the third trimester in humans.[49,50] Studies demonstrate a critical neurotrophic role of leptin, the obesity (*ob*) gene product synthesized primarily by adipose tissue and placenta. In the adult, leptin acts as a satiety factor, decreasing appetite. In contrast, in the fetus or newborn, leptin promotes the development of satiety pathways. In leptin-deficient (*ob/ob*) mice, satiety pathways are permanently disrupted, demonstrating axonal densities one-third to one-fourth that of controls,[51] contributing to increased appetite. Treatment of adult *ob/ob* mice with leptin does not restore satiety projections, but leptin treatment of newborn *ob/ob* mice does rescue the neuronal development,[51] indicating the critical role of leptin during the perinatal period. Importantly, SGA fetuses and newborns have significantly decreased plasma leptin because of a lack of adipose tissue,[52] and studies confirm reduced satiety neurons.[53] Mice that lack leptin signaling also show additional brain abnormalities and reduced brain weight, as well as altered expression of neuronal and glial proteins,[54] perhaps explaining the diversity of cognitive and structural abnormalities observed in SGA offspring.

In our laboratory studies,[41] we have utilized a rat model of maternal under-nutrition that results in SGA pups with decreased plasma leptin. SGA offspring nursed by control dams demonstrate significantly increased food intake, with rapid catch-up growth at 3 weeks resulting in adult metabolic syndrome, including obesity, increased percent body fat, and glucose intolerance.[41,55] The obese phenotype is a result of dysfunction at several aspects of the satiety pathway, as evidenced by reduced satiety and cellular signaling responses to leptin.[56,57] Most recently, our studies have demonstrated a hypothalamic up-regulation of the nutrient sensor SIRT1, a factor that epigenetically regulates gene transcription of factors critical to neural development.[58,59] Importantly, we have demonstrated that neuronal stem cells from SGA fetuses and newborns demonstrate reduced growth and impaired differentiation to neurons and glial cells.[58,59] Thus, impaired neuronal development (and ultimately reduced satiety pathways) may be a consequence of a reduction in neural stem cell growth potential and reduced leptin-mediated neurotrophic stimulation during periods of axonal development.

In addition to appetite and satiety dysfunction, our studies indicate that maternal under-nutrition programs enhanced fetal adipose tissue development and function (lipogenesis), a key factor in the development of obesity.[57] Additional organ systems including the kidney

(impaired nephogenesis),[60] lung (reduced alveolar development),[61] placenta (increased apoptosis),[62] and vascular bed (reduced vasculogenesis)[63] likely contribute to the phenotype of adult metabolic syndrome.

Effects of Maternal Obesity and Western Diet

Obesity in pregnancy has adverse effects not only on maternal health and pregnancy outcome but also on the developing fetus. In addition to the effects of low birth weight, epidemiological studies indicate that high birth weights (large for gestational age) or exposure to maternal obesity lead to an increased risk for childhood and adult obesity.[64,65] The 25% to 36% increase in maternal BMI over the past decade has translated to an approximately 25% increase in the incidence of newborns with high birth weight.[66] This is of particular importance, because newborns with high birth weight show increased adipose tissue mass and an increased risk of obesity and diabetes risk in later life.[67] In animal studies, although variable effects of maternal western diets (high fat) on birth weight have been reported, ranging from low to normal to high, the adult offspring consistently exhibit obesity and metabolic abnormalities.[68–70] Studies in our laboratory demonstrate developmental programming of offspring obesity and lipid abnormalities as a result of in utero over-nutrition,[71] a consequence of programming of altered appetite and satiety and adipogenesis.

Thus, epidemiological studies confirm that the relationship between human birth weight and adult obesity, hypertension, or insulin resistance is a "U-shape curve."[42,72–74] Perhaps most importantly, the relation of fetal growth to offspring obesity and metabolic syndrome is a continuum[15] rather than a threshold response. There may well be an optimal newborn weight (potentially specific to an individual mother) at which the programming of obesity potential is minimized. However, within ranges of lower or higher birth weights in comparison to mean values, studies indicate a gradation of propensity to programming sequelae. Thus, changes from "optimal" in utero growth, be it from limited or excess nutrition, increase the relative risk of adult metabolic syndrome.

Implications of Developmental Origins of Health and Disease Findings

The identification of developmental windows of metabolic and epigenetic plasticity heightens awareness of the importance of the intrauterine and early postnatal environment, and it provides a potential window of opportunity for therapeutic intervention. Although a majority of the attention on developmental origins of health and disease thus far has been focused on nutrition, other potential adverse influences on the developmental environment have also emerged. These include maternal cigarette-smoking and alcohol consumption, which have been shown to exert profound effects on growth and development of the fetus and infant.[75,76] Offspring of smoking mothers or mothers exposed to environmental tobacco smoke are born smaller than those born to unexposed mothers and are at increased risk for early-life development of components of the metabolic syndrome including obesity, insulin resistance, and diabetes.[75] Recently, an "environmental obesogen" hypothesis has been advanced to suggest that chemical exposure during perinatal development may alter cellular and molecular signals in adipocytes and other cell types, elevating the risk of obesity. Grun and Blumberg[77] reviewed the literature and provided supporting evidence that developmental exposure to chemicals including diethylstilbestrol, bisphenol A, phytoestrogens, organotins (paint additive), and phthalates (plasticizer) can increase risk of obesity. Dolinoy et al[78,79] reported that maternal exposure to genistein (dietary supplement) conferred protection against development of obesity by modifying the fetal epigenome in mice prone to obesity, and that maternal dietary supplementation with methyl donors counteracted DNA hypomethylation induced by bisphenol A exposure during early development. These findings support the idea that toxicants can influence developmental programming in much the same fashion as nutrition. Clearly, this provocative idea will require substantial scrutiny and additional evidence.[80] The potential for chemicals to influence critical developmental processes leading to altered metabolic programming requires further elucidation but may ultimately give rise to new toxicity testing approaches to detect such latent alterations.

As discussed, we are at the precipice of a transition in prenatal care to incorporate a goal of optimizing fetal and neonatal health to prevent or reduce adult-onset diseases. Simple decisions remain a dilemma to clinicians. What is the optimal nutrition and weight gain for underweight or overweight gravid women? Is it of benefit to deliver SGA fetuses preterm to avoid a prolongation of an "adverse" intrauterine environment? What is the long-term risk-to-benefit ratio of maternal glucocorticoids on developmental programming of adult disease, and does it depend on the gestational age at administration? What is the most effective feeding strategy for preterm infants, and how rapidly should SGA newborns or newborns with low birth weight gain weight? Optimal nutritional programs for such newborns must consider developmental programming effects.

Educating practitioners about the potential secondary effects of developmental programming on

long-term health of offspring will be critical. Clearly, prenatal management decisions will await additional studies exploring mechanisms of developmental programming and consequences and benefits of altered perinatal management. In the interim, we should strive for preconceptional normalization of maternal weight and balanced maternal nutrition during pregnancy. Patient education will be important and pregnancy care providers will increasingly have a role in the optimization of long-term adult health in addition to the acute effects of newborn outcome.

REFERENCES

1. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obes Res 2001;9(Suppl 4):228S–33S.
2. Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. Am J Obstet Gynecol 2004;191:964–8.
3. Obesity in pregnancy. ACOG Committee Opinion No. 315. American College of Obstetricians and Gynecologists. Obstet Gynecol 2005;106:671–5.
4. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. Am J Clin Nutr 2002;76:653–8.
5. Barker DJ. The fetal origins of adult hypertension. J Hypertens 1992;10(Suppl):S39–44.
6. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991;303:1019–22.
7. Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. BMJ 1993;307:1519–24.
8. Barker DJ, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. BMJ 1993;306:422–6.
9. Barker DJ, Osmond C, Kajantie E, Eriksson JG. Growth and chronic disease: findings in the Helsinki Birth Cohort. Ann Hum Biol 2009;36:445–58.
10. Hardy R, Sovio U, King VJ, Skidmore PM, Helmsdal G, Olsen SF, et al. Birthweight and blood pressure in five European birth cohort studies: an investigation of confounding factors. Eur J Public Health 2006;16:21–30.
11. Nuyt AM. Mechanisms underlying developmental programming of elevated blood pressure and vascular dysfunction: evidence from human studies and experimental animal models. Clin Sci (Lond) 2008;114:1–17.
12. Nuyt AM, Alexander BT. Developmental programming and hypertension. Curr Opin Nephrol Hypertens 2009;18:144–52.
13. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, et al. Birth weight and risk of type 2 diabetes: a systematic review. JAMA 2008;300:2886–97.
14. Bruce KD, Hanson MA. The developmental origins, mechanisms, and implications of metabolic syndrome. J Nutr 2010; 140:648–52.
15. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 1993;36:62–7.
16. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992; 35:595–601.
17. Gluckman P, Hanson MA. Mismatch: why our world no longer fits our bodies. New York (NY): Oxford University Press; 2006.
18. Desai M, Crowther NJ, Ozanne SE, Lucas A, Hales CN. Adult glucose and lipid metabolism may be programmed during fetal life. Biochem Soc Trans 1995;23:331–5.
19. Hales CN, Ozanne SE. The dangerous road of catch-up growth. J Physiol 2003;547(Pt 1):5–10.
20. Hypponen E, Power C, Smith GD. Prenatal growth, BMI, and risk of type 2 diabetes by early midlife. Diabetes Care 2003; 26:2512–7.
21. Eriksson JG. Epidemiology, genes and the environment: lessons learned from the Helsinki Birth Cohort Study. J Intern Med 2007;261:418–25.
22. Mackenzie HS, Lawler EV, Brenner BM. Congenital oligonephropathy: The fetal flaw in essential hypertension? Kidney Int 1996;55(Suppl):S30–4.
23. Manalich R, Reyes L, Herrera M, Melendi C, Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int 2000;58:770–3.
24. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ 1991;303:671–5.
25. Stein CE, Kumaran K, Fall CH, Shaheen SO, Osmond C, Barker DJ. Relation of fetal growth to adult lung function in south India. Thorax 1997;52:895–9.
26. McDade TW, Beck MA, Kuzawa CW, Adair LS. Prenatal undernutrition and postnatal growth are associated with adolescent thymic function. J Nutr 2001;131:1225–31.
27. Strang-Karlsson S, Raikkonen K, Pesonen AK, Kajantie E, Paavonen EJ, Lahti J, et al. Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birthweight adults. Am J Psychiatry 2008;165:1345–53.
28. Cresswell JL, Egger P, Fall CH, Osmond C, Fraser RB, Barker DJ. Is the age of menopause determined in-utero? Early Hum Dev 1997;49:143–8.
29. Cresswell JL, Barker DJ, Osmond C, Egger P, Phillips DI, Fraser RB. Fetal growth, length of gestation, and polycystic ovaries in adult life. Lancet 1997;350:1131–5.
30. McCormack VA, dos SS I, De Stavola BL, Mohsen R, Leon DA, Lithell HO. Fetal growth and subsequent risk of breast cancer: results from long term follow up of Swedish cohort. BMJ 2003;326:248.
31. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. N Engl J Med 2004;351:1619–26.
32. Eriksson JG, Thornburg KL, Osmond C, Kajantie E, Barker DJ. The prenatal origins of lung cancer. I. The fetus. Am J Hum Biol 2010;22:508–11.
33. Symonds ME, Budge H, Stephenson T. Limitations of models used to examine the influence of nutrition during pregnancy and adult disease. Arch Dis Child 2000;83:215–9.
34. Wilcox AJ. On the importance–and the unimportance–of birthweight. Int J Epidemiol 2001;30:1233–41.
35. Morley R, Owens J, Blair E, Dwyer T. Is birthweight a good marker for gestational exposures that increase the risk of adult disease? Paediatr Perinat Epidemiol 2002;16:194–9.
36. Godfrey K, Robinson S. Maternal nutrition, placental growth and fetal programming. Proc Nutr Soc 1998;57:105–11.

37. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. Lancet 2001;357:413–9.

38. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089–97.

39. Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? Circulation 2004;109:1108–13.

40. Weaver LT. Rapid growth in infancy: balancing the interests of the child. J Pediatr Gastroenterol Nutr 2006;43:428–32.

41. Desai M, Gayle D, Babu J, Ross MG. Programmed obesity in intrauterine growth-restricted newborns: modulation by newborn nutrition. Am J Physiol Regul Integr Comp Physiol 2005;288:R91–6.

42. Ong KK. Size at birth, postnatal growth and risk of obesity. Horm Res 2006;65(Suppl 3):65–9.

43. Adair LS, Martorell R, Stein AD, Hallal PC, Sachdev HS, Prabhakaran D, et al. Size at birth, weight gain in infancy and childhood, and adult blood pressure in 5 low- and middle-income-country cohorts: when does weight gain matter? Am J Clin Nutr 2009;89:1383–92.

44. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. BMJ 2001;322:949–53.

45. Eriksson JG, Osmond C, Kajantie E, Forsen TJ, Barker DJ. Patterns of growth among children who later develop type 2 diabetes or its risk factors. Diabetologia 2006;49:2853–8.

46. Gaskin PS, Walker SP, Forrester TE, Grantham-McGregor SM. Early linear growth retardation and later blood pressure. Eur J Clin Nutr 2000;54:563–7.

47. Victora CG, Barros FC. Commentary: The catch-up dilemma–relevance of Leitch's 'low-high' pig to child growth in developing countries. Int J Epidemiol 2001;30:217–20.

48. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol 2003;23:5293–300.

49. Bouret SG, Simerly RB. Developmental programming of hypothalamic feeding circuits. Clin Genet 2006;70:295–301.

50. Ahima RS, Prabakaran D, Flier JS. Postnatal leptin surge and regulation of circadian rhythm of leptin by feeding. Implications for energy homeostasis and neuroendocrine function. J Clin Invest 1998;101:1020–7.

51. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. Science 2004;304:108–10.

52. Eckert JE, Gatford KL, Luxford BG, Campbell RG, Owens PC. Leptin expression in offspring is programmed by nutrition in pregnancy. J Endocrinol 2000;165:R1–6.

53. Delahaye F, Breton C, Risold PY, Enache M, Dutriez-Casteloot I, Laborie C, et al. Maternal perinatal undernutrition drastically reduces postnatal leptin surge and affects the development of arcuate nucleus proopiomelanocortin neurons in neonatal male rat pups. Endocrinol 2008;149:470–5.

54. Bouret SG, Simerly RB. Minireview: Leptin and development of hypothalamic feeding circuits. Endocrinol 2004;145:2621–6.

55. Desai M, Gayle D, Babu J, Ross MG. Permanent reduction in heart and kidney organ growth in offspring of undernourished rat dams. Am J Obstet Gynecol 2005;193(Suppl 3):1224–32.

56. Desai M, Gayle D, Han G, Ross MG. Programmed hyperphagia due to reduced anorexigenic mechanisms in intrauterine growth-restricted offspring. Reprod Sci 2007;14:329–37.

57. Desai M, Casillas E, Han G, Tosh DN, Ross MG. Programmed alteration of hypothalamic leptin and insulin signaling pathways contributes to reduced anorexigenic responses in IUGR offspring. Reprod Sci 2008;15:192A.

58. Desai M, Li T, Ross MG. Programmed impairment of hypothalamic neural stem cell proliferation and differentiation: Mechanism of adult obesity in low birth weight (LBW) offspring. Reprod Sci 2010;17:302A.

59. Desai M, Ti L, Ross MG. Rat embryonic hypothalamic neural stem cells response to trophic factors: selective differentiation responses to leptin and insulin. J Dev Origins Health Dis 2009;(Suppl 1):S78.

60. Abdel-Hakeem AK, Henry TQ, Magee TR, Desai M, Ross MG, Mansano RZ, et al. Mechanisms of impaired nephrogenesis with fetal growth restriction: altered renal transcription and growth factor expression. Am J Obstet Gynecol 2008;199:252–7.

61. Karadag A, Sakurai R, Wang Y, Guo P, Desai M, Ross MG, et al. Effect of maternal food restriction on fetal rat lung lipid differentiation program. Pediatr Pulmonol 2009;44:635–44.

62. Belkacemi L, Chen CH, Ross MG, Desai M. Increased placental apoptosis in maternal food restricted gestations: role of the Fas pathway. Placenta 2009;30:739–51.

63. Khorram O, Khorram N, Momeni M, Han G, Halem J, Desai M, et al. Maternal undernutrition inhibits angiogenesis in the offspring: a potential mechanism of programmed hypertension. Am J Physiol Regul Integr Comp Physiol 2007;293:R745–53.

64. Gluckman PD, Hanson MA, Morton SM, Pinal CS. Life-long echoes–a critical analysis of the developmental origins of adult disease model. Biol Neonate 2005;87:127–39.

65. Harding JE. The nutritional basis of the fetal origins of adult disease. Int J Epidemiol 2001;30:15–23.

66. Surkan PJ, Hsieh CC, Johansson AL, Dickman PW, Cnattingius S. Reasons for increasing trends in large for gestational age births. Obstet Gynecol 2004;104:720–6.

67. Armitage JA, Poston L, Taylor PD. Developmental origins of obesity and the metabolic syndrome: the role of maternal obesity. Front Horm Res 2008;36:73–84.

68. Howie GJ, Sloboda DM, Kamal T, Vickers MH. Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. J Physiol 2009;587(Pt 4):905–15.

69. Ferezou-Viala J, Roy AF, Serougne C, Gripois D, Parquet M, Bailleux V, et al. Long-term consequences of maternal high-fat feeding on hypothalamic leptin sensitivity and diet-induced obesity in the offspring. Am J Physiol Regul Integr Comp Physiol 2007;293:R1056–62.

70. Samuelsson AM, Matthews PA, Argenton M, Christie MR, McConnell JM, Jansen EH, et al. Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming. Hypertension 2008;51:383–92.

71. Desai M, Guang H, Ferelli M, Kallichanda N, Lane RH. Programmed upregulation of adipogenic transcription factors in intrauterine growth-restricted offspring. Reprod Sci 2008;15:785–96.

72. Pettitt DJ, Jovanovic L. Birth weight as a predictor of type 2 diabetes mellitus: the U-shaped curve. Curr Diab Rep 2001;1:78–81.

73. Pettitt DJ, Jovanovic L. Low birth weight as a risk factor for gestational diabetes, diabetes, and impaired glucose tolerance during pregnancy. Diabetes Care 2007;30(Suppl 2):S147–9.

74. Launer LJ, Hofman A, Grobbee DE. Relation between birth weight and blood pressure: longitudinal study of infants and children. BMJ 1993;307:1451–4.

75. Rogers JM. Tobacco and pregnancy: overview of exposures and effects. Birth Defects Res C Embryo Today 2008;84:1–15.

76. Weinberg J, Sliwowska JH, Lan N, Hellemans KG. Prenatal alcohol exposure: foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. J Neuroendocrinol 2008;20:470–88.

77. Grun F, Blumberg B. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. Rev Endocrinol Metab Disord 2007;8:161–71.

78. Dolinoy DC, Weidman JR, Waterland RA, Jirtle RL. Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. Environ Health Perspect 2006;114:567–72.

79. Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci U S A 2007;104:13056–61.

80. Dolinoy DC, Jirtle RL. Environmental epigenomics in human health and disease. Environ Mol Mutagen 2008;49:4–8.