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# Metabolic Imprinting of Obesity

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## Abstract

Increasing evidence indicates that early metabolic programming contributes to escalating obesity rates in children and adults. Metabolic imprinting is involved in the establishment of set points for physiologic and metabolic responses in adulthood. Evidence from epidemiological studies and animal models indicate that maternal health and nutritional status during gestation and lactation have long-term effects on central and peripheral systems that regulate energy balance in the developing offspring. Perinatal nutrition also impacts susceptibility to developing metabolic disorders and plays a role in programming body weight set points. The states of maternal energy status and health that are implicated in predisposing offspring to increased risk of developing obesity include maternal overnutrition, diabetes, and undernutrition. This chapter discusses the evidence from epidemiologic studies and animal models that each of these states of maternal energy status results in metabolic imprinting of obesity in offspring. Also, the potential molecular mediators of metabolic imprinting of obesity by maternal energy status including glucose, insulin, leptin, inflammatory cytokines and epigenetic mechanisms will be discussed.

## INTRODUCTION

### Obesity epidemic

The increasing prevalence of obesity has large implications for the health of the human population as obesity increases the risk of developing a number of serious diseases (1). The escalating incidence of obesity is due not only to environmental changes such as increased availability of high density food and decreased need for physical exertion, but mounting evidence in humans and animal models indicate that early programming events play an important role. Maternal health and nutritional status during gestation and lactation have long-term effects on central and peripheral systems that regulate energy balance in offspring.

### Metabolic Imprinting

Individuals best suited to their environment are most likely to reproduce and pass on their genes. A critical factor impacting survival is the type and availability of food sources. Survival is optimized if energy balance regulation is programmed to most efficiently use available metabolic fuels. Metabolic imprinting is the process by which a stimulus or insult occurring during a critical period of development has a long-term effect on the physiologic and metabolic responses of the offspring. During development, mammals are exposed to two environments: the *in utero* environment and the postnatal environment. Maternal diet, body composition, and energy stores have major influences on both environments. Perinatal nutrition also has long lasting effects on energy balance regulation, influences susceptibility to developing metabolic disorders (2, 3) and plays a role in programming body weight set

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points (4, 5). The states of maternal energy status and health implicated in predisposing offspring to obesity include maternal overnutrition, diabetes, and undernutrition. The current research on each of these states will be discussed in the preceding sections. It is not within the scope of this chapter to cover all of the literature, thus seminal pieces of work that represent the field will be highlighted.

## MATERNAL UNDERNUTRITION

### Evidence from Epidemiological Studies

The consequences of maternal undernutrition on offspring energy balance regulation were first examined in humans that experienced the Dutch famine during gestation. Investigating this population Ravelli et al. discovered that famine during different period of gestation led to differential risks of various metabolic disorders (6, 7). The idea that undernourishment during gestation affects later risk for obesity and metabolic disorders is supported by the findings of David Barker and colleagues who found an association between low birth weight, an indirect measure of the fetal environment, and increased risk of developing cardiovascular disease (8), stroke, hypertension, and diabetes mellitus (9). These findings lead to the development of the “Fetal Origins hypothesis” which postulates that the body’s structure, physiology and metabolism are programmed during embryonic and fetal life and the ‘thrifty phenotype hypothesis” which suggests that undernourishment during development causes an adaptive response that programs offspring to prioritize organ growth and increases metabolic efficiency in preparation for an environment with sparse resources. Programming becomes detrimental when postnatal nutrition is more plentiful than prenatal nutrition as offspring exhibit rapid catch up growth and obesity (10).

### Animal Models of Maternal Undernutrition

Prenatal undernutrition has been extensively modeled in rodents by restricting the amount of calories received by the mother during different stages of gestation. Results vary depending on the timing, length and magnitude of the food restriction. Studies by Jones and colleagues which restricted food by 50% during the first two trimesters of pregnancy find that male (but not female) offspring develop hyperphagia and delayed-onset obesity when maintained on either a control or a high fat diet (HFD) (11, 12). Offspring that experience severe dietary restriction (30% of *ad libitum* consumption) throughout gestation exhibit adult-onset obesity, hyperinsulinemia, and hyperleptinemia associated with hyperphagia and hypoactivity (2, 13). However, even a mild 30% food restriction during pregnancy leads to reduced birth weight, catch up growth and hypersensitivity to HFD-induced obesity (5). While the mechanisms leading to long-term reprogramming are poorly understood, leptin has been identified as a key factor. Undernourished offspring exhibit premature onset of the neonatal leptin surge (5) and when the leptin surge was artificially induced prematurely in control offspring they also exhibited hypersensitivity to HFD-induced obesity. Therefore, both the magnitude and timing of the leptin surge appears to be important for the development of metabolic systems. This will be further discussed by Bouret in Chapter 8.

Rodent models have many advantages such as short gestation and the ability to manipulate genetics. However, the critical periods for development of energy balance regulatory systems are different between rodents and humans. In rodents, the neural pathways regulating energy balance are immature at birth and are not fully developed until the third postnatal week (mice) (14). In contrast, in humans, nonhuman primates, pigs, and sheep hypothalamic feeding circuits develop primarily prenatally (15). Thus, models of maternal undernutrition in which the development of energy balance regulation occurs prenatally are particularly relevant. Nathanielsz and colleagues developed a nonhuman primate model of maternal undernutrition in which pregnant females are fed 70% of *ad libitum* consumption

from early to mid gestation (16). In this model, undernourished mothers have fetal offspring with normal body weight, but decreased hip circumference and perturbations in kidney and liver development (16). Future studies examining the phenotype of juvenile and adult offspring are critical to understanding the effects of maternal undernutrition on obesity susceptibility in primates.

## MATERNAL OVERNUTRITION

### Evidence from Epidemiological Studies

As modern man experiences an environment in which food scarcity is rare and energy dense foods are readily available, the most common perturbation of maternal nutritional status in developed countries is maternal obesity and overnutrition. Currently, over one third of pregnant American women are obese (17) and the majority consume an excess amount of food and fat (18). Epidemiological studies show that maternal obesity increases the incidence of obesity and metabolic syndrome in children (19). The effect of maternal obesity on offspring susceptibility to obesity is independent of gestational diabetes as obese women with normal blood glucose have heavier babies with increased adiposity (20). It is clear that higher birth weight and weight gain during early postnatal life greatly increases the risk of becoming an obese adult (19). Several animal models are used to study the effects of overnutrition during gestation and the early postnatal period on the developing offspring.

### Animal Models of Maternal Overnutrition

Promoting obesity by feeding animals a HFD is a common model of maternal overnutrition. Interpretation of these studies is complicated as the duration of exposure (acute vs. chronic) and composition of diets vary across studies. At weaning, pups from rats fed a HFD during pregnancy and lactation are heavier, fatter, hyperglycemic and have increased hepatic lipid content than pups from control mothers (21). In a mouse model of chronic maternal overnutrition offspring are hyperphagic, have reduced locomotion and increased adiposity (22). Another group demonstrated that rats feed a highly palatable processed junk food diet during gestation, lactation and/or post-weaning become heavier and display an increased preference for fatty, sugary and salty foods (23). Although the majority of studies find that offspring from HFD fed mothers are overweight, several studies report that maternal HFD consumption produces lighter offspring, potentially due to impaired lactation in obese mothers (24). Differences in the duration of HFD consumption (i.e. chronically or only during gestation and lactation) and fatty acid composition of the diets are hypothesized to explain differences in offspring phenotype (24).

Rodents genetically predisposed to obesity are also used to examine the effects of maternal obesity. In studies using the obese agouti mouse, wild-type offspring of agouti dams bred to wild-type males were heavier than offspring from wild-type crosses. However, no difference in adult weight was found (25). The heterozygous leptin receptor-deficient mouse (db/+) is used to model maternal obesity as they overeat and have increased weight gain during pregnancy. Offspring from db/+ females are heavier than controls regardless of genotype (26). However, this model is complicated by the fact that the mothers also develop spontaneous gestational diabetes. Barry Levin's group derived substrains of Sprague Dawley rats bred to be either resistant or sensitive to diet-induced obesity. This model examines the interaction between genetics and maternal overnutrition. Diet sensitive rats that consume a high energy diet, prior to and during pregnancy and lactation, have offspring with increased adiposity and hyperglycemia when maintained on a control diet and increased weight gain and leptin levels when consuming a high energy diet as compared to offspring from diet sensitive mothers that consumed the control diet. In contrast, maternal diet did not affect weight gain in offspring from diet resistant mothers (27). Indicating that maternal obesity

enhances obesity susceptibility in offspring with a genetic predisposition for diet-induced obesity (27).

The consequences of maternal obesity and HFD consumption on offspring energy balance regulation are being examined in a nonhuman primate model by our group. Surprisingly, fetal offspring from HFD fed mothers, whether obese with severe insulin resistance or lean with normal insulin sensitivity display signs of severe lipotoxicity. Juvenile offspring (6 months of age) from HFD fed mothers were heavier and have increased adiposity, leptin levels and show signs of fatty liver disease (28). Suggesting that in primates, as in rodent models, maternal overnutrition predisposes offspring to early onset obesity and metabolic disorders.

The effects of early postnatal overnutrition have been examined in a variety of animal models. The nutritional state of infant baboons was manipulated by feeding them formula of varying calorie density. Young adult female baboons overfed as infants were heavier and had increased adiposity than control fed females. In male baboons, overfeeding prior to weaning increased adiposity, but did not affect body weight (29). Postnatal overfeeding is examined in rodents by adjusting the number of pups per litter to create a group of mothers with small litters where pups receive increased nutrition and a group with large litters where pups receive reduced nutrition. This paradigm has lead to a number of interesting findings. Overfeeding during suckling has long-term effects on energy balance regulation as adult rats raised in small litters have increased body weight, adiposity (30), leptin resistance (31) and abnormalities in the sensitivity of hypothalamic neurons to several neuropeptide and nutrient signals (32). Our group has shown that overfed offspring are hypersensitive to a HFD in adulthood leading to accelerated weight gain and metabolic disorders. This appears to be at least partially due to long-term defects in hypothalamic leptin sensitivity [Glavas et al. 2009].

## Maternal Diabetes

The insulin and leptin resistance associated with pregnancy increase women's susceptibility to developing gestational diabetes. Thus, 3-14% of pregnancies are complicated by gestational diabetes (15). Clinical studies indicate that mothers with diabetes have babies with increased birth weight, and risk of developing childhood obesity and diabetes mellitus (33). The type and severity of maternal diabetes influences the offspring's outcome. Obesity and impaired glucose tolerance are 2-3 times more frequent in offspring from mothers with diabetes mellitus than offspring from mothers who developed gestational diabetes (34). Maternal diabetes also affects offspring during the postnatal period as diabetic mothers have breast milk with increased insulin levels. Plagemann and colleagues found that infants breast fed by diabetic mothers had a greater risk of developing obesity and impaired glucose metabolism than infants from diabetic mothers fed breast milk from non-diabetic women (35). This finding has important clinical implications and needs to be examined further so that diabetic mothers can be advised on the optimal source of nutrition for their infants.

## Animal Models of Maternal Diabetes

Animal models of maternal diabetes provide strong evidence that maternal diabetes increases susceptibility to obesity and diabetes (26, 36). Female rats made diabetic during pregnancy by continuous glucose infusion produce female offspring with glucose intolerance and impaired insulin secretion (37). Also, hyperglycemia induced by the pancreas islet toxin streptozotocin during early pregnancy produces offspring that are macrosomic at birth and have elevated weight gain during the first ten weeks of life (38). Studies using genetic models of spontaneous diabetes such as the heterozygous leptin

receptor-deficient mouse find that female offspring of mothers with gestational diabetes have increased adiposity and insulin resistance (26).

## Molecular Mechanisms Underlying Metabolic Imprinting

It is important to understand the mechanisms by which metabolic imprinting leads to a particular phenotype and influences susceptibility to obesity and metabolic diseases. The mediators and signaling pathways that transmit signals from the mother to program the metabolic phenotype of the developing offspring are not fully elucidated. Hormones such as leptin and insulin, nutrients such as glucose, free fatty acids, and triglycerides and inflammatory cytokines are implicated.

Maternal glucose crosses the placenta and is transfer to the fetus. However, as maternal insulin cannot cross the placenta (19), the fetal pancreas secretes insulin in response to maternal glucose. Maternal overnutrition and diabetes produce maternal hyperglycemia which increases fetal insulin secretion (39). Fetal hyperinsulinemia is hypothesized to be involved in the programming of diabetes and obesity (40). This is supported by studies showing that insulin administration to rats during the third trimester of pregnancy produces obese offspring (3, 12). Also, intrahypothalamic administration of insulin to rat pups during the development of projections from the ARC to the PVH causes increased body weight, hyperinsulinemia, impaired glucose tolerance, and increased susceptibility to diabetes (41). As insulin is a neuronal growth factor (40), fetal hyperinsulinemia may cause perturbations in the development of energy balance regulatory circuitry, increasing susceptibility to obesity and metabolic diseases.

Leptin is also implicated in programming obesity. Studies in mice show that the postnatal leptin plays an important role in the development of hypothalamic neuronal connections (14). In humans, leptin is increased in maternal obesity and diabetes (42, 43) and reduced in babies with intrauterine growth restriction (44). However, evidence indicates that leptin levels do not increase until the end of the third trimester of gestation (44), after hypothalamic development. Studies in nonhuman primates also report that fetal leptin levels are low to undetectable during important developmental stages and do not increase until late in the third trimester (45). Thus, while it is clear that leptin is an important neurotrophic factor in rodents, its role in higher species remains unclear.

Inflammatory cytokines are elevated in obese pregnant women (46) and have been postulated to be a potential mediator of metabolic imprinting. Using a nonhuman primate model, our group found that fetuses from mothers consuming a HFD have elevated circulating and hypothalamic cytokines. As rodent studies show that both AGRP (47) and POMC (48) neurons in the ARC are directly affected by cytokines, it is postulated that fetal exposure to increased cytokines directly impacts the development of neurons regulating energy balance.

A recent area of research is the epigenetic mechanisms of imprinting individual differences in obesity susceptibility. Epigenetics is the study of changes in gene expression not involving changes in DNA sequence such as DNA methylation, covalent histone modifications, packaging of DNA around nucleosomes, folding of chromatin and attachment of chromatin to the nuclear matrix (49). Epigenetic mechanisms are mediated by perinatal nutrition, maternal energy status, maternal endocrine status and oxidative stress (49). For example, maternal calorie restriction is associated with increased methylation of the Hras gene and maternal protein deficiency is associated with alterations in epigenetic regulation of the glucocorticoid receptor and peroxisome proliferator activated receptor alpha. Also, *in utero* exposure to deficiency/excess of various nutrients causes changes in epigenetic modifications (49). This data indicates that it is likely that maternal energy status influences

susceptibility to obesity in the offspring by causing perturbations in epigenetic modifications. However, further research is needed to determine the effects of maternal overnutrition, undernutrition and diabetes on epigenetic modifications and to understand the mechanisms underlying these changes.

## References


1. Singhal V, Schwenk WF, Kumar S. Evaluation and management of childhood and adolescent obesity. Mayo Clin Proc. 2007; 82(10):1258–64. [PubMed: 17908531]
2. Vickers MH, et al. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. Am J Physiol Endocrinol Metab. 2000; 279(1):E83–7. [PubMed: 10893326]
3. Jones AP, Dayries M. Maternal hormone manipulations and the development of obesity in rats. Physiol Behav. 1990; 47(6):1107–10. [PubMed: 2204072]
4. Vickers MH, et al. Neonatal leptin treatment reverses developmental programming. Endocrinology. 2005; 146(10):4211–6. [PubMed: 16020474]
5. Yura S, et al. Role of premature leptin surge in obesity resulting from intrauterine undernutrition. Cell Metab. 2005; 1(6):371–8. [PubMed: 16054086]
6. Ravelli AC, et al. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr. 1999; 70(5):811–6. [PubMed: 10539740]
7. Roseboom TJ, et al. Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. Mol Cell Endocrinol. 2001; 185(1-2):93–8. [PubMed: 11738798]
8. Barker DJ, et al. Weight in infancy and death from ischaemic heart disease. Lancet. 1989; 2(8663): 577–80. [PubMed: 2570282]
9. Barker DJ. The fetal and infant origins of disease. Eur J Clin Invest. 1995; 25(7):457–63. [PubMed: 7556362]
10. Barker DJ, et al. Fetal origins of adult disease: strength of effects and biological basis. Int J Epidemiol. 2002; 31(6):1235–9. [PubMed: 12540728]
11. Jones AP, Friedman MI. Obesity and adipocyte abnormalities in offspring of rats undernourished during pregnancy. Science. 1982; 215(4539):1518–9. [PubMed: 7063860]
12. Jones AP, et al. Maternal hormonal manipulations in rats cause obesity and increase medial hypothalamic norepinephrine release in male offspring. Brain Res Dev Brain Res. 1995; 88(2): 127–31.
13. Vickers MH, et al. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. Am J Physiol Regul Integr Comp Physiol. 2003; 285(1):R271–3. [PubMed: 12794001]
14. Djiane J, Attig L. Role of leptin during perinatal metabolic programming and obesity. J Physiol Pharmacol. 2008; 59(Suppl 1):55–63. [PubMed: 18802216]
15. Grove KL, et al. Development of metabolic systems. Physiol Behav. 2005; 86(5):646–60. [PubMed: 16289141]
16. Li C, et al. Effects of maternal global nutrient restriction on fetal baboon hepatic IGF system genes and gene products. Endocrinology. 2009
17. King JC. Maternal obesity, metabolism, and pregnancy outcomes. Annu Rev Nutr. 2006; 26:271–91. [PubMed: 16704347]
18. Alberti-Fidanza A, Parizkova J, Fruttini D. Relationship between mothers' and newborns' nutritional and blood lipid variables. Eur J Clin Nutr. 1995; 49(4):289–98. [PubMed: 7796787]
19. Oken E, Gillman MW. Fetal origins of obesity. Obes Res. 2003; 11(4):496–506. [PubMed: 12690076]
20. Sewell MF, et al. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. Am J Obstet Gynecol. 2006
21. Guo F, Jen KL. High-fat feeding during pregnancy and lactation affects offspring metabolism in rats. Physiol Behav. 1995; 57(4):681–6. [PubMed: 7777603]

22. Samuelsson AM, 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(2):383–92. [PubMed: 18086952]
23. Bayol SA, Farrington SJ, Stickland NC. A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring. Br J Nutr. 2007; 98(4):843–51. [PubMed: 17697422]
24. Ferezou-Viala J, 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(3):R1056–62. [PubMed: 17553843]
25. Han J, et al. Long-term effect of maternal obesity on pancreatic beta cells of offspring: reduced beta cell adaptation to high glucose and high-fat diet challenges in adult female mouse offspring. Diabetologia. 2005; 48(9):1810–8. [PubMed: 16010523]
26. Yamashita H, et al. Effect of spontaneous gestational diabetes on fetal and postnatal hepatic insulin resistance in Lepr(db/+) mice. Pediatr Res. 2003; 53(3):411–8. [PubMed: 12595588]
27. Levin BE, Govek E. Gestational obesity accentuates obesity in obesity-prone progeny. Am J Physiol. 1998; 275(4 Pt 2):R1374–9. [PubMed: 9756571]
28. McCurdy CE, et al. Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. J Clin Invest. 2009; 119(2):323–35. [PubMed: 19147984]
29. Lewis DS, et al. Preweaning food intake influences the adiposity of young adult baboons. J Clin Invest. 1986; 78(4):899–905. [PubMed: 3760191]
30. Levin BE. Metabolic imprinting: critical impact of the perinatal environment on the regulation of energy homeostasis. Philos Trans R Soc Lond B Biol Sci. 2006; 361(1471):1107–21. [PubMed: 16815795]
31. Schmidt I, et al. Interaction of genetic and environmental programming of the leptin system and of obesity disposition. Physiol Genomics. 2000; 3(2):113–20. [PubMed: 11015606]
32. Bouret SG. Early life origins of obesity: role of hypothalamic programming. J Pediatr Gastroenterol Nutr. 2009; 48(Suppl 1):S31–8. [PubMed: 19214056]
33. Gillman MW, et al. Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics. 2003; 111(3):e221–6. [PubMed: 12612275]
34. Pettitt DJ, et al. Diabetes and obesity in the offspring of Pima Indian women with diabetes during pregnancy. Diabetes Care. 1993; 16(1):310–4. [PubMed: 8422798]
35. Plagemann A, et al. Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. Diabetes Care. 2002; 25(1):16–22. [PubMed: 11772895]
36. Gauguier D, et al. Higher maternal than paternal inheritance of diabetes in GK rats. Diabetes. 1994; 43(2):220–4. [PubMed: 8288046]
37. Gauguier D, et al. Inheritance of diabetes mellitus as consequence of gestational hyperglycemia in rats. Diabetes. 1990; 39(6):734–9. [PubMed: 2189765]
38. Oh W, Gelardi NL, Cha CJ. Maternal hyperglycemia in pregnant rats: its effect on growth and carbohydrate metabolism in the offspring. Metabolism. 1988; 37(12):1146–51. [PubMed: 2973549]
39. Leung TW, Lao TT. Placental size and large-for-gestational-age infants in women with abnormal glucose tolerance in pregnancy. Diabet Med. 2000; 17(1):48–52. [PubMed: 10691159]
40. Simerly RB. Hypothalamic substrates of metabolic imprinting. Physiol Behav. 2008; 94(1):79–89. [PubMed: 18262209]
41. Plagemann A, et al. Lifelong enhanced diabetes susceptibility and obesity after temporary intrahypothalamic hyperinsulinism during brain organization. Exp Clin Endocrinol. 1992; 99(2): 91–5. [PubMed: 1639125]
42. Lepercq J, et al. Fetal macrosomia and maternal weight gain during pregnancy. Diabetes Metab. 2002; 28(4 Pt 1):323–8. [PubMed: 12442070]
43. Hauguel-de Mouzon S, Shafrir E. Carbohydrate and fat metabolism and related hormonal regulation in normal and diabetic placenta. Placenta. 2001; 22(7):619–27. [PubMed: 11504530]
44. Davidowa H, Plagemann A. Decreased inhibition by leptin of hypothalamic arcuate neurons in neonatally overfed young rats. Neuroreport. 2000; 11(12):2795–8. [PubMed: 10976965]

45. Grayson BE, et al. Prenatal development of hypothalamic neuropeptide systems in the nonhuman primate. Neuroscience. 2006; 143(4):975–86. [PubMed: 17029798]

46. Stewart FM, et al. Longitudinal assessment of maternal endothelial function and markers of inflammation and placental function throughout pregnancy in lean and obese mothers. J Clin Endocrinol Metab. 2007; 92(3):969–75. [PubMed: 17192290]

47. Scarlett JM, et al. Regulation of agouti-related protein messenger ribonucleic acid transcription and peptide secretion by acute and chronic inflammation. Endocrinology. 2008; 149(10):4837–45. [PubMed: 18583425]

48. Scarlett JM, et al. Regulation of central melanocortin signaling by interleukin-1 beta. Endocrinology. 2007; 148(9):4217–25. [PubMed: 17525125]

49. Campion J, Milagro FI, Martinez JA. Individuality and epigenetics in obesity. Obes Rev. 2009