Published in final edited form as:

Semin Perinatol. 2008 June ; 32(3): 213–218. doi:10.1053/j.semperi.2007.11.005.

Adult Sequelae of Intrauterine Growth Restriction

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Abstract

Fetal intrauterine growth restriction has been associated with adult disease in both human epidemiologic studies and in animal models. In some cases, intrauterine deprivation programs the fetus to develop increased appetite and obesity, hypertension and diabetes as an adult. Although the mechanisms responsible for fetal programming remain poorly understood, both anatomic and functional (cell signaling) changes have been described in affected individuals. In some animal models, aspects of fetal programming can be reversed postnatally, however at the present time the best strategy for avoiding the adult consequences of fetal growth restriction is prevention.

Fetal intrauterine growth restriction (IUGR) occurs in humans as a consequence of poor maternal nutrition, placental insufficiency and diminished fetal oxygenation, or exposure to teratogens, among other causes. In animals, and in some cases in humans, IUGR from these causes has been associated with the development of adult diseases; this phenomenon is called “fetal programming”. The association of maladaptive programming with adult disease has been termed the “Barker hypothesis”. In general, the Barker hypothesis¹ contends that the malnourished fetus is programmed to exhibit a “thrifty phenotype” with increased food intake and fat deposition and possibly decreased energy output. Faced with ample available calories, such individuals develop obesity and other manifestations of the metabolic syndrome as adults due to alterations in homeostatic regulatory mechanisms.^{2–4}

The issue of fetal programming is not merely of intellectual interest. Currently, 65% of adults in the United States are overweight and almost one in three are obese (BMI>30 kg/m²), representing a modern health crisis.⁵ Obesity and its related diseases are the leading cause of death in Western society, with associated risks of hypertension, coronary heart disease, stroke, diabetes, and breast, prostate and colon cancer. Evidence indicates a striking 25 to 63% of adult diabetes, hypertension and coronary heart disease can be attributed to the effects of low birthweight with accelerated newborn-to-adolescent weight gain.² therefore gestational programming of low birth weight/ IUGR has contributed importantly to the population shift towards obesity. In Western societies, the incidence of low birth weight infants has increased since the mid-twentieth century. Low birth weight infants are now being born to women with chronic diseases who would previously have had limited survival and reproductive capacity, while assisted reproductive technologies and increasing numbers of multiple gestations have resulted in both preterm and low birth weight offspring. When combined with improved

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neonatal survival and exposure to Western diet, this results in an increased number of programmed offspring predisposed to adult obesity. These obese mothers may ultimately give birth to macrosomic newborns, perpetuating obesity in the population.

Evidence for fetal programming

Several lines of evidence suggest that human IUGR is associated with adult obesity. Epidemiological studies of individuals born during the Dutch “hunger winter” of 1944–45 revealed that maternal starvation was associated with a reduced infant birth weight and an increased incidence of obesity, insulin resistance, hypertension and coronary artery disease in adulthood.^{6–10} Work by Barker and colleagues on a cohort of men and women born in Herfordshire, England between 1911 and 1930,¹¹ revealed that low weight at birth and 1 year of age are associated with an increased risk of death from cardiovascular disease and stroke. Additional supporting evidence came from a study of Swedish males army conscripts in which increased diastolic blood pressure was associated with low birth weight.¹²

A large number of manipulations have been used to induce offspring IUGR in animal models, including maternal calorie¹³ and protein¹⁴ restriction, fetal hypoxia from uterine artery ligation¹⁵ and passive maternal smoking,¹⁶ and maternal alcohol administration¹⁷ and hyperthermia.¹⁸ The association of IUGR with adult disease has been demonstrated in many animal species (for review see ¹⁹). In our laboratory, we have developed a rat model of IUGR caused by 50% maternal food restriction (MFR) during the second half of pregnancy. Newborn pups from MFR mothers have lower body weights with decreased plasma leptin levels. IUGR offspring nursed by ad libitum fed dams demonstrate rapid catch-up growth at 3 weeks and continued accelerated growth, resulting in increased weight, percent body fat, and plasma leptin levels as adults. These animals have been utilized in our studies described below.

Mechanisms of Fetal Programming

IUGR leads to alterations in numerous fetal organs. Obesity is potentiated by alterations in appetite regulation, and by increased adipogenesis. Hypertension is made more likely by alterations in renal and blood vessel development, while diabetes is associated with alterations in cellular insulin signalling and decreased beta cell function. These programmed alterations in function, together, induce the full metabolic syndrome in the adult. Although the specifics of fetal programming are likely to differ depending on the cause of the IUGR, this issue has not been well studied, and the discussion below does not attempt to differentiate the various maternal manipulations leading to offspring IUGR.

Obesity

That MFR induces IUGR and subsequent offspring obesity in association with an increased appetite is well documented.^{20–23} Leptin, a primary satiety factor, normally reduces food intake, it has been shown to be one of the factors influenced by fetal programming. In growth restricted fetuses, cord blood leptin levels are decreased^{24,25} and preterm or low birth weight human, rat, or calf newborns have reduced plasma leptin levels.^{26–28} These findings are not surprising, given the reduced fat stores in IUGR offspring. At 2 months of age, however, subcutaneous fat leptin mRNA is negatively correlated with birth weight.²⁹ As adults, leptin and insulin levels are related to birth weight, independent of adult obesity.²⁴ In normal sheep^{30–33} and rodents,^{34–39} leptin reduces voluntary food intake. Adult IUGR offspring, however, exhibit resistance to the anorexogenic effects of leptin,⁴⁰ suggesting altered control of appetite as a source of IUGR-associated obesity.

The hypothalamus is an important site for central control of appetite. Hypothalamic leptin resistance may be due to alterations in leptin transporter,^{41–44} hypothalamic leptin receptor

(ObRb),^{41,45} and/or leptin signaling,^{46–48} though it is not known which of these mechanism accounts for gestational programming of leptin resistance and obesity. In our studies, MFR-induced IUGR results in offspring with increased ObRb expression and disruption of intracellular leptin signaling. In summary, IUGR offspring exhibit reduced newborn leptin levels, though increased leptin levels as adults, and a decreased anorexic response to leptin, possibly due to abnormalities in intracellular signaling.

In addition to adult leptin resistance, recent studies provide convincing evidence that leptin promotes the development of hypothalamic neuronal projections, consistent with a role in brain development. Neuronal projections from the arcuate nucleus (ARC) are formed in mice primarily during the second week of postnatal life⁴⁹ (developmentally similar to human third trimester of pregnancy). In leptin deficient (ob/ob) mice, these projection pathways regulating appetite are permanently disrupted, demonstrating axonal densities one third to one fourth that of controls.⁵⁰ In the rodent, the crucial developmental window coincides with a natural postnatal surge in leptin. IUGR in mice is associated with an abnormal leptin surge,⁵¹ and postnatal leptin replacement rescues ARC axonal development.⁵⁰ These findings suggest that, in addition to signaling alterations, IUGR may be associated with permanent anatomic changes in the appetite centers of the brain.

IUGR may also affect the development of adipocytes. Development of obesity is associated with increased adipocyte differentiation, adipocyte hypertrophy and/or upregulation of lipogenic genes. PPAR γ ₂, an adipogenic transcription factor, promotes both adipocyte differentiation and lipid storage.^{52,53} In our rat model, IUGR offspring showed significantly increased expression (mRNA and protein) of PPAR γ both as newborns and as adults. Further, the expression of adipogenic transcription factors regulating PPAR γ was also upregulated in both groups. Therefore, in addition to central dysregulation of appetite, IUGR individuals may demonstrate abnormal activation of adipocytes, contributing to the development of obesity.

Hypertension

Reduced numbers of nephrons are associated with elevations in arterial blood pressure and changes in postnatal renal function. A reduction of nephron number of as little as 11% in sheep⁵⁴ and 13% in the rat⁵⁵ can result in adult hypertension. In the human, there was a strong correlation between low nephron number and hypertension among individuals involved in fatal accidents.⁵⁶ Studies indicate that intrauterine growth restriction correlates with decreased nephron numbers.^{57–61} Work in our laboratory demonstrates a 19% reduction in glomerular number in male rat IUGR offspring at three weeks of age, with the development of adult hypertension.⁶² Many factors are likely to be involved in determining nephron endowment, including all of those responsible for the complex process of nephrogenesis. In our rat model, fetal kidneys demonstrated altered expression of genes in pathways regulating events of nephrogenesis, including UBB and mesenchymal to epithelial transformation (unpublished data). All of this suggests that permanent changes in renal anatomy result from IUGR, with an increased propensity to adult hypertension. Investigation of renal growth in utero suggests that 26–34 weeks of gestation in humans could be the period during which altered renal development may lead to hypertension.⁵⁸

The vascular endothelium is another target for programming. Several studies have shown that endothelial-dependent and -independent vasodilation is impaired and flow-mediated dilation is decreased in low-birthweight individuals at 3 months of age, in later childhood and in early adult life.^{63–65} In rats that were undernourished during the first 18 days of gestation, increased blood pressure at 60 days after birth was noted, and the maximal vasoconstriction response to phenylephrine and norepinephrine was reduced in isolated femoral arteries,⁶⁶ although other maternal nutrient restricted diets^{67,68} showed no effect on vasoconstrictor responses.

A major determinant of blood pressure is arterial compliance, which is a function of the extracellular matrix (ECM).⁶⁹ The ECM, made of collagen, elastin and smooth muscle,⁶⁹ can be altered by diet even in the adult state. Adult rats fed a high salt diet over a course of 8 weeks showed structural changes in the aorta with an increase in wall thickness, a decrease in collagen and an increase in elastin/collagen ratio.⁷⁰ Studies in our laboratory demonstrate marked changes in the ECM composition of vessel wall as a result of MFR.⁷¹

In summary, IUGR is associated with hypertension, particularly in male offspring. Programmed offspring exhibit changes in renal structure, as well as in vascular structure and function that precede and are probably contributory to the development of hypertension. The relative importance of these changes remains to be determined.

Diabetes

Low newborn weight has been associated with an increased risk for type 2 diabetes in human epidemiologic studies⁷² and with abnormal insulin secretion and glucose intolerance in rats and sheep.^{73,74} Several factors may contribute to this phenomenon. First, the IUGR offspring may have a reduced ability to secrete insulin due to reduced numbers of pancreatic islets. Adult humans born IUGR have impaired insulin responses to glucose.⁷ In rats, adult IUGR offspring have a lower beta cell mass and pancreatic insulin content, as well as a reduced insulin response to glucose.⁷⁵ A reduction in the capacity to excrete insulin may be associated in IUGR individuals with an increase in insulin requirement. When the insulin requirement exceeds the capacity of the pancreas, diabetes results.

One reason for an increased insulin requirement in IUGR offspring is increased gluconeogenesis. Hepatic gluconeogenesis is increased in adult IUGR rats,¹⁵ and this increase precedes the development of hyperglycemia and is relatively resistant to the effects of insulin compared to controls. Expression of PPAR γ coactivator-1, a regulator of mRNA expression of glucose-6-phosphatase and other gluconeogenesis enzymes, is increased in the livers of IUGR rat offspring,⁷⁶ suggesting that the alteration in hepatic glucose production may be the result of changes in intracellular signaling.

The development of glucose intolerance in IUGR individuals may also be associated with other alterations in insulin signaling. For example, glucose entry into skeletal muscle occurs via the glucose transporter GLUT4; the process is stimulated by insulin. In the rat, fetal skeletal muscle GLUT4 expression is decreased, but the amount of GLUT4 present on the plasma membrane is increased, with diminished intracellular stores, suggesting a compensatory adaptation to low glucose availability.¹³ In the adult IUGR rat, skeletal muscle GLUT4 continues to be increased on the plasma membrane but there is diminished translocation of additional GLUT4 to the plasma membrane in response to insulin. Adult IUGR human subjects with insulin resistance also demonstrated a failure to upregulate muscle GLUT4 after insulin stimulation.⁷⁷ As skeletal muscle is a primary site for insulin-induced glucose utilization, this unresponsiveness may be associated with glucose intolerance.

In summary, IUGR is associated with both anatomic changes in the pancreatic islets and with changes in intracellular insulin signaling pathways. The end result of these alterations is to decrease the individual's capacity to secrete insulin, while increasing the demand for insulin leading to an increased likelihood of frank glucose intolerance.

Manipulation of Fetal Programming

The many deleterious effects of a programmed "thrifty phenotype" in a setting of postnatal calorie abundance lead to the question as to whether fetal programming can be reversed or

ameliorated. Although no treatments are currently available, there are several promising lines of inquiry.

Immediate postnatal nutrition can affect long-term health in IUGR offspring. Although adults born during the Dutch hunger winter developed hypertension and diabetes as adults, those exposed in utero to starvation in the siege of Leningrad were not diabetic or hypertensive at a rate greater than controls.⁷⁸ One explanation for this is that the siege of Leningrad was of greater duration, and those starved in utero were also likely to have been starved as newborns. Similarly, in our lab⁷⁹ and others,¹³ rats born IUGR who continued to be nutritionally deprived during lactation did not become obese as adults. However, in our studies these postnatally deprived rats did exhibit elevated serum total and LDL cholesterol, and insulin insufficiency.⁷⁹

Treatment of rats with peripheral leptin either to the dam during pregnancy and to the pup during lactation⁸⁰ or to the pup alone during early lactation⁸¹ resulted in adults who were neither obese nor diabetic. These observations suggest that supplementation of leptin to assure a normal plasma leptin surge at rat postnatal day 10–12, may facilitate the development of arcuate axonal projections.^{82,83} In contrast to rats, there is no evidence of a human postnatal leptin surge.⁸⁴ Consequently, it is speculative as to whether leptin administration would be effective in human IUGR.

The interventions above are empiric, and unlikely to be completely effective due to the wide range of effects of IUGR on adult health. Truly reversing the effects of maladaptive fetal programming will likely require an ability to reprogram the changes in gene expression, probably by epigenetic changes to the chromatin.

Epigenetics

There is growing evidence that maternal nutritional status can alter the state of the fetal genome and imprint gene expression. Epigenetic alterations (stable alterations of gene expression through covalent modifications of DNA and core histones) in early embryos may be carried forward to subsequent developmental stages.⁸⁵ Two mechanisms mediating epigenetic effects are DNA methylation and histone modification (acetylation and methylation).⁸⁶ Either of these mechanisms can alter gene expression (is “gene expression” duplicated intentionally?).⁸⁶ Epigenetic changes in IUGR individuals have been demonstrated in relevant genes including those involved in hepatic insulin signaling,⁸⁷ and beta cell development.⁸⁸ Interestingly, folic acid, a methyl donor, has been shown to reverse at least some epigenetic changes associated with IUGR in a rat model, although the folic acid dose used (1mg/kg) far exceeds that used in human clinical practice.⁸⁹

Epigenetic changes may also explain the transgenerational effect of the thrifty phenotype. In support of this hypothesis, offspring of IUGR rat dams demonstrated altered insulin signaling and glucose metabolism, even when gestated by control rats.⁹⁰ Offspring of IUGR dams also had persistence of altered methylation of the promoters for PPAR α and glucocorticoid receptor despite being gestated by dams being fed a regular diet.⁹¹

Conclusion

Growth restriction in utero is associated with the development of obesity, hypertension and diabetes in animal models and in humans when ample calories are provided postnatally, as occurs in most Western societies. The resultant adult obesity has become a significant health risk. The current understanding is that intrauterine deprivation programs the individual for a deprived environment, and that such programming is maladaptive in a non-deprived environment. Programming causes both anatomic changes, such as a decrease in the number

of glomeruli, and functional changes, such as a decrease in GLUT4 induction after insulin treatment. The sum of these changes is an increase in appetite and in adipocyte activity, leading to obesity, a decrease in glomeruli and in vascular compliance, contributing to hypertension, and a reduction in beta cells and insulin signaling, contributing to diabetes. Data suggests that at least some of these programmed effects are subject to postnatal alteration, although there are currently no accepted human manipulations. At present, the best treatment is prevention. Avoiding severe IUGR is therefore of importance not only in improving fetal and neonatal outcomes, but in improving adult health both for the index individual and for their children.

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