Low birth weight and endocrine dysfunction in postnatal life

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I. Introduction

Small size at birth has long been recognized to increase neonatal morbidity and mortality. As early as 1962 J.V. Neel a population geneticist proposed that changes of in utero environment made to guarantee survival during adverse conditions could become harmful during nutrition abundance [1]. This concept is now well established. Reduced growth in early life is strongly linked with a number of endocrine dysfunctions. Included among the most important alterations are insulin insensitivity, gonadal and somatotropic axis abnormalities and premature adrenarche [2, 3]. These have been associated with an escalating prevalence of Type 2 Diabetes Mellitus (T2DM) [4]. Coronary Heart Disease (CHD) [5], abnormal gonads and genitalia [6]-[9], growth hormone resistance and decreased growth [7][11], as well as early puberty [8]. The usual hypothesis proposed to explain the development of these long term alterations relates to the thrifty phenotype as an adaptive response to in utero malnutrition [9] and modifications thereof; initially termed “Fetal Origins” [10] and updated to “Developmental Origins” which include the additional contributions of the patterns of growth in infancy and childhood [11]. Throughout this chapter we review the current knowledge of the programming of the fetus and infant that lead to endocrine dysfunction in postnatal life.

II. Genetic Factors of Fetal Growth

Fetal growth is a delicate controlled process influenced by hormones, growth factors and the intrauterine milieu. Examples of some variables that affect fetal growth are chromosomal abnormalities, genetic diseases, maternal alterations (TORCH, Hypertension, nutrition, Tobacco, collagen diseases), placental and demographic factors. The mechanisms that participate in the regulation of size
at birth and the later consequences of the intrauterine insult are shown in Figure 1. Insulin trophic actions play a key role in the regulation of fetal growth; this is evidenced by the severe intrauterine growth impairment occurring in congenital mutations of the insulin structure or of the insulin pathway function (1-3) and by the reduced size of the fetus present at birth in infants with specific gene mutations (11-13). The opposite picture develops in diabetic hyperglycemic mothers who give birth to large for gestational age infants, as a result of chronic in utero fetal hyperinsulinism that develops to compensate for maternal glycemic fluxes.

Experimental models that retard fetal growth in rats induce modifications of glucose utilization in several fetal tissues [12],20]. In addition, insulin like growth factors (IGF’s) and their binding proteins (IGFBP’s), are involved in the regulation of fetal growth [13]. In fact the mechanisms of action of IGF’s and insulin are shared at several levels in the cell [14]. Models that attempt to explain the association of low birth weight and postnatal diseases, consider as central, the action of insulin and related peptides [10],[15]. Genetically programmed low energy consumers would present resistance to anabolic hormones such as insulin [16]. However, no mutation has been identified to explain the strong highly prevalent linkage to insulin resistance genes [17].

The candidate genes associated with reduced size at birth are shown in Table 1. These include homozygote or compound heterozygous insulin receptor mutations causing Leprechaunism [18], Insulin promoter factor –I [IPF1] mutation with pancreatic agenesis [19] and heterozygous glucokinase mutation [20]. These mutations may involve alterations in any of the factors that belong to the family of growth receptors with intrinsic tyrosine kinase activity, including the Insulin receptor (IR), Insulin like growth factor (IGF-I), its receptor (IGF-I-R) and the hybrid IR/IGF-I-R [21]. These lead to signaling pathway alterations in insulin action and constitute molecular targets of insulin resistance [22]. The cellular effectors of insulin participate in intermediary metabolism and in cell proliferation, a disruption in action results in insulin resistance [22], 28].
The pattern of insulin secretion per se is able to modify the response of peripheral tissues to this hormone [23]. A relevant factor that determines the pattern of insulin secretion is the short term insulin gene transcription by glucose in the late phase of Beta cell response [24]. In vitro the gene promoter of variable number of tandem repeat (VNTR) alleles of insulin is able to modify its transcriptional activity through the Pur-1 factor [25]. These molecular findings have clear clinical correlations that associate allelic variants of VNTR in the insulin gene with Diabetes Mellitus (DM), as well as reduced size at birth [26], [27]. In Caucasian populations the most frequent allelic VNTR at the insulin gene minisatellite locus (type I) is associated with an increased risk for type 1 DM (T1DM); whereas the type III allelic VNTR is associated with T2DM, obesity and ovarian hyperandrogenism [26], [28]. The type III allele is also associated with increased birth weight [27]. We recently demonstrated a greater insulin secretion after an intravenous glucose infusion (IVGGT) in a cohort of term 1 year old infants who had the type III allelic VNTR [29]. A second candidate gene, the one encoding calpain (CAPN10), was also identified as being responsible for the T2DM association with the 1 locus in chromosome 2 [30]. Other genes that have been proposed to be involved in the association of low birth weight (LBW) and later insulin resistance include IGF-1, IRS-1, Glucokinase, H19, pre-adipocyte factor-1 and growth factor receptor-bound proteins (GRB-10) which constitute a family of structurally related multidomain adapters with diverse cellular functions which have been implicated in the regulation of insulin receptor signaling [20] [31].

III. In utero programming

Several authors have proposed the existence of a prenatal metabolic programming which would promote the development of a “thrifty phenotype” (9). A poor intrauterine nutrition would determine an endocrine adaptation designated to sustain the development of more sensitive organs, such as the central nervous system. This response consist mainly of the inhibition of anabolic factors (insulin and IGFs) in muscle, adipose and connective tissues, during the time of need,
which would persist into adult life [10]. In animal models there are some examples of prenatal adaptations, which persist into postnatal life [32], [33]. However, in humans there is no direct evidence to support this theory.

A) Programming Evidence

Various experimental models have been utilized to study the potential in utero programming mechanisms of a thrifty phenotype. Nutritional restriction of the pregnant animal, in terms of total calories or protein deprivation is a model that has been utilized to test this hypothesis [32]. The human extension of these results has been controversial [34], since LBW due to maternal nutrition deprivation is rare in the occidental world. Another model employed has been the restriction of oxygen delivery to the placental-uterine bed. This model exposes to low oxygen tension in the environment the pregnant animal [35]. This model is clearly a not applicable to humans.

Wigglesworth developed a model in rats, which limits the utero-placental oxygen delivery [36], has also been applied to sheep [37]. In this model partial or total stretching of the uterine artery (s) during the last part of gestation is used. Recent modifications to the technique apply repeated embolization of uterine vessels [38] and systemic use of vasoconstrictor agents such as tromboxan [39]. These maneuvers have been used to better reflect what occurs in intrauterine growth restriction (IUGR) due to placental dysfunction, which is the most common cause of small for gestational age deliveries (SGA)( 50%) [40].

In spite of the differences between the above experimental models, the data have been consistent and provide evidence of the fetal and new born metabolic consequences of the adverse intrauterine environment. Both protein caloric restriction and vascular supply, produce a fetus and new born that develops hypoglycemia, hypoaminoacidemia and hypoinsulinemia, among the most important metabolic consequences [41], [42]. Hypoinsulinemia correlated with the alterations in the development of beta cells in the Langerhans islet [43],[44].
However there was no glucose intolerance and the glucose uptake in peripheral tissues (muscle and adipose) [45], and insulin/glucose ratios in fetuses and newborns, indicated that there was a greater insulin sensitivity compared to control animals [41],[42]. These findings are in agreement with limited human data provided by chordocentesis [46].

These experimental data have led some authors to cast a note of caution about the Barker’s hypothesis, which considers the development of insulin resistance during fetal life [10]. Alternatively, it could also be that the resistance is specific to certain tissues. In fact that is what has been shown when protein restrictive models are used; namely changes of expression in glucose transporter (GLUT) family proteins in adipose, muscle and nervous tissues [47]. The applicability of these findings to humans was demonstrated [48].

**B) Programming Mechanisms**

Insulin sensitivity might be altered during fetal life as a response to endocrine modifications following an adverse intrauterine environment (Figure 2). One such modification could be the increased levels of circulating cortisol, a counter-acting hormone to insulin. In addition the hyperactivity of the hypothalamic-pituitary-adrenal axis as a consequence of fetal stress [49]-[50] may be attributable to a decreased activity of the placental enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) which degrades cortisol and thereby alters the maternal impact of the fetal compartment[51]. The enhancement of cortisol levels would act in several tissues, including the liver which is key in determining insulin sensitivity [52]. TNF-α, is also able to induce insulin resistance in several tissues [53]. In fact a certain polymorphism in the promoter region of the TNF-α gene has been linked to the development of insulin resistance in adults [54]. Elevated TNF levels are present in fetal blood in several fetal stress situations, such as premature delivery and intrauterine infection [55].
The initial associations of LBW with a decrease in insulin sensitivity were established in studies performed in Hertfordshire, England. In the first studies 5654 men born between 1911 and 1948 whose birth weights and subsequent growth until 1 year of age had been registered, were retrospectively analyzed. In this population those with the lowest birth weight had the highest mortality rates due to cardiovascular disease [5]. From the same population 468 men had a fasting glucose determination and 370 had a complete OGTT; 40% of men with birth weights equal or below 2.5 kg had a glycemia at 2 and 4 hours of 140 mg/dl or more compared with only 14% of men born with the highest weights [56]. Subsequently other retrospective studies documented the presence of the other components of the metabolic syndrome; i.e. hypertension, and hypercholesterolemia [57, 58]. These studies confirmed the greater risk of this disease when LBW was present [59, 60].

Some of these observations were replicated in different countries and populations of different backgrounds. In India a study of 517 adults found that the prevalence of CHD was 11% in those with LBW of less than 2500 g whereas in those with a birth weight of 3100 grs or more it was 3%. These associations were independent of other variables associated to CHD such as life style [60], [61]. The association of T2DM and glucose intolerance with CHD and hypertension suggested that insulin resistance could be present in LBW infants.

**IV. Post-natal programming of endocrine dysfunction.**

One of the main limitations of the above mentioned studies is the retrospective analysis where birth weight is related to the metabolic status or complications detected in later life. **These studies did not take** into account early growth and metabolic changes that occurred after birth. Since 1998 a number of authors have proposed that postnatal growth of LBW children, as characterized by the body
mass index (BMI) at 7-8 years of life, might be an independent factor determining insulin sensitivity [62]-[15, 63, 64]. This hypothesis was confirmed in a term cohort of LBW Chilean children [65]. Insulin resistance could be programmed in the early postnatal life during the catch-up growth (CUG) phase shown by SGA infants. During this phase of CUG there is an increase in the levels of several anabolic hormones; such as; insulin and related peptides (IGFs) [66]. Insulin resistance could initially develop in SGA to counteract their tendency to hypoglycemia, and would then persist during their entire life. CUG could also lead to a disproportionate increase of fat compared to lean mass acquisition [67, 68]. Some authors propose that suppressed thermo genesis leads to this unequal distribution of fat and lean mass during the CUG period [67]. This theory has gained more acceptance because of the current epidemiological data of the explosive worldwide increase in T2DM which has specially affected those countries where LBW is more prevalent [69].

Ong. et al in the ALSPAC (Avon longitudinal study of pregnancy and childhood) cohort also showed that early catch up growth predicted increased body fat mass and central fat distribution at 5 years of age [70]. We demonstrated that at one, two and three years of age, insulin secretion and sensitivity were related to the patterns of catch-up growth. Fasting insulin sensitivity was more closely related to weight catch-up growth and current BMI, whereas insulin secretion appeared to be directly related to length catch-up growth [65]. These data were in accordance with previous studies that showed that at later stages of life those born SGA with early CUG have a greater risk of Syndrome X [71]. Recently a prospective study of the ALSPAC cohort which included term newborns with a large variation of normal birth size confirmed these observations. At 8 years of age, those who were lighter and grew faster in early life were the most insulin resistant among the cohort [72]. Erikson et al analyzed the influence of early catch up growth and birth weight in CHD deaths [63]. Greater mortality rates were present among those subjects who were lighter at birth, but had a normal or increased BMI at of 7 years of age.
In a pioneering pediatric study by Hoffman et al. insulin sensitivity was studied through a long IV glucose tolerance test in prepubertal short stature children, either born SGA or appropriate for gestational age (AGA) [73]. This method allowed the detection of a significant difference in insulin sensitivity; those born SGA had an increased acute phase of insulin release (445 vs. 174 ug/ml). Early changes in insulin sensitivity, secretion, and lipid metabolism were associated with being born SGA at term [81]. During the first 48 hrs of life SGA infants displayed increased insulin sensitivity with respect to glucose disposal, but showed suppression of lipolysis, ketogenesis, and hepatic production of IGFBP-3 as compared with AGA children.

One element of the puzzle not previously clarified was whether the decrease in postnatal insulin sensitivity in SGA children was present only when the adverse condition was present in utero or could also develop when adverse postnatal conditions were present, as in the case of an extremely premature birth. It has been suggested that postnatal morbidity during a critical period of rapid growth might contribute to the metabolic modifications observed in LBW children, independently of the adequacy of their birth weight to gestational age. Another question was the effect of prematurity per se, since in most studies the birth weight had been evaluated independently of gestational age or preterm infants were excluded. Therefore the link between LBW and postnatal insulin resistance was assessed regardless of gestational age [63, 74, 75]. The effects of current BMI, birth weight standard deviation score (SDS), postnatal growth rates, and indicators of postnatal morbidity were evaluated in twenty SGA and 40 were AGA very low birth weight (VLBW) children (birth weight between 690-1500 g, gestational age 25-34 weeks). They were evaluated at 5-7 years of age by a short intravenous glucose tolerance test (IVGTT). In this cohort of premature, VLBW children, IUGR rather than LBW was associated with reduced sensitivity to insulin. This link was independent of gestational age and other indicators of postnatal stress. In addition, fasting and first-phase insulin secretion were related to postnatal growth rates, which was in accordance with our previous observations [76]. However an opposite
finding was reported by Hofman et. al. but in their report no comments of the interaction of growth in utero and postnatal growth was described. In addition, the New Zealand cohort was rather small and children had short stature [77].

Several gene polymorphisms involved in the control of intermediary metabolism, such as the insulin gene variable number of tandem repeat (INS VNTR) alleles and Ghrelin C^{247}A(y) leptin C^{-2549}A in peripheral DNA were not related to growth kinetics or to IVGTT response [29]. However, at 1 year class III/III alleles in the INS VNTR locus were associated with increased fasting as well as post-stimulated insulin. These findings were independent of birth weight and postnatal growth kinetics.

One of the important and constant findings regarding the determinants of insulin sensitivity during adulthood is that LBW is not a major determinant of later insulin resistance, except among subjects with the largest current BMI [72]. The factors that determine the transition from relatively low birth weight to childhood overweight are not known, but could be mediated by increased appetite. The regulation of food intake is a complex process involving neural and gut interactions (Chapter____). One of the hormones involved in this interplay is Ghrelin [78] and the specific 7 transmembrane G protein coupled receptor for this hormone present in the hypothalamic arcuate nucleus and pituitary [79]. In animal studies the intracerebrovascular and peripheral administration of Ghrelin induces adiposity and increases appetite and this orexigenic activity appears to be mediated by increases in NPY [80]. In humans, Ghrelin levels are decreased in obesity and increased in anorexia [81].

Since most SGA infants show some degree of postnatal length and weight CUG and since this phenomenon affects postnatal insulin sensitivity independently of birth weight, we postulated that Ghrelin appetite effects could be involved in the CUG. The fasting and post IVGTT circulating Ghrelin levels in SGA and AGA infants aged 1 year were not different [82]. As seen in older children and adults, circulating
Ghrelin concentrations rapidly decreased after IV glucose. Interestingly, post-glucose Ghrelin levels, but not fasting values, correlated positively with current length, current weight, and change in weight. In addition, lower reductions in circulating Ghrelin levels following IV glucose were observed in SGA infants who showed greater weight gain during infancy, suggesting that a sustained orexigenic drive could contribute to postnatal growth.

In the literature only one report addresses the interaction between LBW, postnatal growth and genetic background. Jaquet et al [83] investigated the role of several polymorphisms which modulate insulin sensitivity: Proala12 in PPARγ, G+250C in the β3 adrenergic receptor, G-308A in TNFα. They genotyped 171 adult’s who were born SGA and 233 who were born AGA, submitted to an oral glucose tolerance test (OGTT). The SGA group showed higher serum insulin concentrations at fasting and during stimulation and their fasting glucose-insulin ratios were significantly higher in the TNF/-308,PPAR/ala12 and ADRB3/+250G carriers. Moreover, the effects of these polymorphism on insulin resistance indexes were significantly potentiated by current BMI in the SGA group.[83]. In neither the SGA nor AGA group did the polymorphisms affect glucose tolerance.

**V. Mechanisms of development of Insulin resistance in SGA subjects**

In young adults with a normal BMI and a similar fat mass, glucose oxidation rate and uptake were diminished in those born SGA as compared with those subjects born AGA [84]. In SGA, a decreased expression of glut-4 in muscle and adipose tissues during an euglycemic hyperinsulinemic clamp was detected [48]. Glucose uptake was also reduced during an euglycemic hyperinsulinemic clamp in 8 year old children [73]. These findings reinforce the concept of abnormal glucose transport as an important element in the control of insulin sensitivity. Recently, a study performed in offspring of young, lean patients with T2DM showed an increase in intramyocellular lipid content, concomitant with impairment of
mitochondrial activity in those who were insulin resistant versus insulin sensitive patients [85].

The adipocyte has been shown to be an active cell that secretes bioactive molecules, termed adipokines [86], [87]. The molecules produced by the adipocyte have autocrine and paracrine actions. These include leptin, tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor type 1 (PAI-1) and adiponectin. Adiponectin is a 244 amino acid protein, product of the most abundant gene transcript-1 (apM1) expressed in human adipose tissue [88]. Recently two adiponectin receptors have been described: adiponectin receptor-1 abundantly expressed in skeletal muscle; and adiponectin receptor-2 predominantly expressed in liver [89]. Several studies have demonstrated that adiponectin modulates glucose tolerance and insulin sensitivity [90-92]. In animal models this protein decreased circulating free fatty acids by increasing oxidation in muscle and decreasing uptake in liver, with subsequent lower plasma triglyceride levels [93]. It also directly activates glucose uptake in adipocytes and muscle through AMP protein kinase. In humans, adiponectin levels predict subsequent changes in insulin resistance, but not lipid profiles or body weight [94, 95]. Adiponectin mRNA is decreased in the adipose tissue of obese and diabetic patients, but is restored to normal levels after weight loss. Increases in adiponectin levels have been described after weight loss in obese and diabetic subjects. In adult Pima Indians, higher plasma adiponectin levels appeared to protect against the development of T2DM [96]. In a small sample of 5 to 10 year old children, hypoadiponectinemia appeared to be the consequence of obesity, but no associations with insulin sensitivity were found [97].

However, it is difficult to assess the effects of weight gain and insulin sensitivity from small cross sectional studies. We therefore determined whether adiponectin levels were related to patterns of postnatal growth and insulin sensitivity in a prospective cohort of infants followed from birth to two years [98]. Serum adiponectin levels at 1 year and 2 years were higher compared with reported
levels in adults and older children and were significantly decreased from 1 to 2 years. At 2 years adiponectin levels were lower in females as compared with males, but no gender differences were seen in leptin and insulin levels. Also no differences existed in adiponectin levels between SGA and AGA infants at 1 year or 2 years. However, in SGA infants the changes in adiponectin levels from year 1 to year 2 were inversely related to weight gain. Adiponectin levels were not related to insulin levels at 1 or 2 years, nor to change in insulin levels. Multiple regression analysis revealed that adiponectin levels were only related to postnatal age. Other determinants of higher adiponectin levels were male gender, lower postnatal body weight, and higher birth weight SDS. In conclusion, changes in serum adiponectin levels during the first 2 years of life were related to patterns of weight gain in SGA infants, but not to early changes in insulin sensitivity [98].

**VI. Gonadal and Adrenal Axis**

The child born small is at increased risk for abnormalities of the gonads and genitalia. Francois et al showed that unexplained, severe hypospadias was related either to restraint of prenatal growth or to complications in early pregnancy [99]. This evidence has been supported by the data of Nordic countries where cryptorchidism as well as hypospadias have been found more frequently in SGA babies [100, 101].

A conclusive support for the concept of non-genetic pseudo-hermaphroditism was presented by De Zegher et al [6]. This report of a pair of monozygotic twins whose gestation was supported by one placenta. The twins were discordant for birth weight and for male differentiation. Detailed studies revealed no evidence for any endocrinopathies. The genitalia of the AGA male were normal, while the SGA had perineal hypospadias and testes in labia-scrotal folds. It is difficult to conceive an experiment whereby a genetic cause of male pseudohermaphroditism could be more convincingly excluded.
Almost half a century ago, Henry Silver noticed that some men who were born small tended to have high urinary gonadotropins levels and to have small testes [102]. This was the first observation indicating that prenatal growth restraint may be followed by reduced Sertoli-cell function and by sub-normal spermatogenesis. More recently Ibañez et al assessed the serum concentrations of inhibin B to determine whether there was a relation between reduced prenatal growth and subsequent Sertoli-cell dysfunction in infancy [109]. SGA boys needed a higher FSH drive to generate the normal feedback level of inhibin B.

Premature adrenarche, the prepubertal rise in the secretion of adrenal steroids, occurs in association with decreased insulin sensitivity in obese and in girls born SGA [103]. The presence of premature adrenarche in SGA girls was reported in Spain [2] and in a group of Hispanic and African American girls living in New York [104]. A decrease in insulin sensitivity could be the drive to increased adrenal steroidogenesis. Ibañez also postulated that CRH might be the potent adrenal secretagogue in these girls [105]. In addition exaggerated adrenarche appears as a risk marker of ovarian hyperandrogenism [106]. In the northern Spanish girls evaluated by Ibanez et al. the SGA female had smaller ovaries and a smaller uterus in adolescence and also had FSH hypersecretion, first noted during infancy and also present later in adolescence [107],[108]. However, it is important to note that these studies only evaluated girls from an endocrine clinic, with a similar ethnic background. Treatment with the insulin sensitizer mertformin was tried in a the Catalunian cohort of non obese adolescents born SGA with eumenorrheic anovulatory cycles [109]. After only 6 weeks ovulatory cycles resumed and lipid levels improved. A simultaneous decrease in LH, FSH, insulin and androgen levels was noted which suggest that SGA associated anovulation is a result of hyperinsulinism rather than adrenal & ovarian hyperandrogenism. It remains to be elucidated whether these risks are also present in healthy girls born SGA recruited from the community and from other ethnicities, as studies in France [110] and Holland failed to show such an association [111].
VII. Somatotropic axis

The fetal somatotropic axis is characterized by growth hormone resistance in the SGA fetus. A simple way to understand the somatotropic axis of the SGA fetus is to consider such as being in a fasting condition. SGA fetuses display low serum levels of insulin, IGF-1, IGF-2, and IGFBP-3 and high levels of IGFBP-1, whereas the large for gestational age infant shows high insulin and IGF-1 levels and a reverse pattern of IGF binding proteins [7].

After birth, CUG occurs in the vast majority of SGA children [112]. Postnatal CUG begins immediately after birth within a maximum occurring by 6 months of age. By 2 years of age, nearly 90 % of term or preterm SGA infants achieve a height within the normal range. The age of 2 years is an important milestone: in SGA children who were born at term, it is quite rare to observe spontaneous catch-up growth after the age of 2 years. Of the SGA infants who fail to show CUG by 2 years about half remain short even in adulthood. The relative risk for being short at age 18 is 5.2 for children born light and 7.1 for children born short. Failure of CUG could be secondary to altered action of GH, IGF-I or Insulin.

Different series show that there is an increased frequency of growth hormone deficiency (GHD) among SGA with non CUG (35-53%) . Even when GH levels are normal on standard stimulation tests, these children demonstrate abnormalities in the pattern and 24 hour profile of GH, lower IGF-I and IGFBP3 [113] [114] . Cutfield, however in a selected population of short SGA children found normal or elevated IGF-I levels and postulated that hyperinsulinism could play a role [115] . Possible differences among studies could be related to the heterogeneous nature of the SGA condition and some form of IGF-I resistance present in a subset of these children (Chapter___).
During the last decade several investigators studied the effects of therapy with growth hormone for those SGA infants who remained small after 2 years of age. Over the years it has become evident that GH administration improved growth velocity, weight gain, height SDS and final height in SGA children independent of their response to provocative testing. The height gain appears to be related mainly to the total time of GH therapy and the dose employed [116], [117]. During GH therapy weight gain is improved, not due to an excess of fat, but to an increase in lean body mass shown by MRI, and serum leptin [118]. Importantly GH stimulation testing is not a requirement previous to therapy and does not predict growth response during therapy. These test are recommended only if GH deficiency is clinically suspected in an SGA child in view of postnatal growth failure, poor facial development or poor skeletal growth. Bone age is usually delayed and height prediction is unreliable in children with SGA [119].

In July 2001 a consensus with final FDA approval of GH therapy as an indication for non catch up growth SGA children emerged [120]. Recent reports evaluating the final height of SGA children treated with GH, showed that it was significantly improved [121]. The standard dose of GH, however, is less effective in assisting short children born SGA to achieve a sufficient CUG. THE FDA approved dose for SGA is 0.48 mg/K/week. In Europe a lower starting dose of 0.35 mg/K/week is recommended. The main determinants of final height are GH dose, duration of treatment, greater family corrected initial height deficit.

In addition to improvements in height positive metabolic effects such as lower blood pressure and beneficial effects on craniofacial development, body composition, less atherogenic lipid profile and psychological well being have been observed [122].

A number of safety issues have been addressed. So far, the evidence continues to be reassuring for GH therapy in these children. In particular, GH does not seem to increase the risk for precocious puberty or glucose intolerance. Benign cranial hypertension, aggravation of scoliosis, jaw prominence and mild transient hyperglycemia have been reported in recent KIGS data. However, these adverse
events were not different from the short stature population given GH therapy [123-125]

**VIII. Conclusions**

Investigations performed during the last decade have identified the independent association between reduced fetal growth and the later development of endocrine dysfunction primarily manifested by gonadal, adrenal, somatropic, and metabolic abnormalities. Insulin resistance appears to play a critical early role in at least the adrenal and the metabolic alterations associated with frequent diseases producing increased morbidity and mortality among adults. Data suggest that the link between prenatal growth restriction and postnatal insulin sensitivity is already present at 1 year of age. On the other hand, IUGR rather than LBW appears to be associated with reduced sensitivity to insulin. Finally, rapid postnatal catch-up growth appears to contribute actively to insulin sensitivity and secretion, at least during the first years of life. We speculate that accelerated catch-up growth during the postnatal period may lead to the development of a metabolically disadvantaged body composition, with an increase preferentially in body fat independent of birth weight as has been demonstrated for other conditions where CUG occurs [67, 68].

The importance of these data to daily clinical practice is to identify SGA as a risk marker of Insulin resistance, and T2DM.

On the other hand there is a clear need to reconcile the contribution of the “thrifty phenotype” and “thrifty genotype” in the generation of adverse health outcomes after a period of nutritional deprivation in early life. The determination of these respective contributions will also clarify the evolutionary adaptations that improve the likelihood of survival of a developing organism that is under duress, but may carry a consequence for poor adult health outcomes after reproductive senescence. It is clear that there the use of terms such as programming, plasticity and predictive adaptative responses may each be hotly debated, particularly as experimental and epidemiological studies investigate the impact of relative over
nutrition in prenatal life. On the other hand during postnatal life the focus of experimental and epidemiological studies will need to investigate the role of environmental factors that modulate rapid CUG. Until these data are available we are not in a position to recommend the types of intervention required to improve the efficiency of the growth of these infants to minimize the risk of the morbidity and mortality complications prevalent in adults who were born SGA.
ADVERSE INTRAUTERINE ENVIRONMENT  

Prenatal Programming  
INSULIN RESISTANCE

GENES  

INSULIN RESISTANCE

LOW BIRTH WEIGHT

CATCH UP GROWTH

INSULIN RESISTANCE

Increased food /sedentary

INSULIN RESISTANCE

Glucose Intolerance  
Ovarian hyperandrogenism  
Type 2 Diabetes  
Dyslipidemia  
Hypertension

Syndrome X
References


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Table 1

*Genes associated with reduced growth in utero “thrifty genotype”*

Homozygote or compound heterozygous insulin receptor mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Phenotype</th>
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<tr>
<td>IPF1 mutation with pancreatic agenesis</td>
<td>Leprechaunism</td>
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<td>Heterozygous glucokinase mutation</td>
<td>LBW</td>
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<td>Insulin like growth factor (IGF-I)</td>
<td>LBW</td>
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<td>Insulin like growth factor receptor (IGF-I-R)</td>
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<td>Insulin gene: polymorphism of tandem repeat in the promoter gene of insulin (VNTR) I/I</td>
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<td>GRB-10 &amp; H19</td>
<td>Russell Silver (LBW)</td>
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Figure 2

Possible Endocrine modifications following an adverse intrauterine environment

- Fetal growth
- 11β HSD2
- Glucocorticoids
- Growth factors
- Fetus
- Adult disease
- Fetal tissue programming
  (vascular responses, HPA axis activity, insulin-glucose homeostasis, renal structure, set point of GR? PPAR-γ)
- Genes:
  (Obesity, smoking, OH, salt, lack of exercise, stress)
- Adverse maternal environment
  Malnutrition
  Stress
  Smoking
  Alcohol
  Drugs
  Disease
  Diabetes
  Anemia

+ environment
  (diet, NO, hormones, fetal sex steroids)

↑ Glucocorticoids
↓ Growth factors
↓ IGFBP1
↑ IGFI/II
↓ IGF-I/II
↑ Glucocorticoids
↓ Growth factors
↓ IGFBP1
↑ IGFI/II
↓ IGF-I/II