CHILDREN BORN WITH INTRA-UTERINE GROWTH RETARDATION (IUGR) OR SMALL FOR GESTATIONAL AGE (SGA): LONG TERM GROWTH AND METABOLIC CONSEQUENCES

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Intra**U**terine **G**rowth **R**etardation (IUGR) refers to insufficient fetal growth diagnosed either by two direct intrauterine growth assessment (ultra-sonography) or when the fetus or newborn length (height) is less than two standard deviations (or third percentile) bellow the mean for gestational age (Niklasson et al. 1991; De Zegler 1997). When the fetus or newborn body size (weight or length) is insufficient for gestational age, that is less than 2 standard deviations bellow the mean (or third percentile) for gestation during the situation is referred to as **S**mall for **G**estational **A**ge (SGA). Since both fetal weight and length (height) gains are closely related, there is much overlap between SGA and IUGR. The proportion of newborn with normal birth weight and overlap between SGA and IUGR, isolated low birt weight, isolate low birth length and combined low birth weight and length is presented in Tab. 1, according to the most recent series reported nb Niklasson (1991).

SGA/IUGR is a public health problem, since 2.5-3.0 % of newborns are affected by definition, and 8-10 % of then do not catch up postnataly, presenting with a persistent severe height deficiency, developmental difficulties and poor outcome (Underwood 1991; Siegel et al, 1991; Albertsson-Wickland et al. 1993; Lakeman et al. 1994)

1. IUGR and syndrome X

Recent data has shown that IUGR is associated with a late life increased prevalence of syndrome X, a condition associating obesity with hypertension and non-insulin dependent diabetes mellitus (NIDDM=type 2 diabetes). Barker was a leader in associating the correlation between birth size and later development in adult life of syndrome X (Barker 1992; Barker et al. 1993). Carrying out an elegant study on more than 20 000 newborns delivered between 1911 and 1930 in Hertfordshire county and finding retrospectively the medical history of more than 8000 of them, he was able to demonstrate that the smaller the birth weight or the weight at one year (which correlated with the birth weight), the greater was the prevalence of syndrome X in adult life. The relative risk of type 2 diabetes, arbitrarily allocated to the value of 1 in general population, was actualy of 1 when the weight at one year was of 27 pound (=13.3 kg) or more and increased to 8.2 when the weight at 1 year was bellow 18 pounds (=8.1 kg). Not less dramatic was his finding, obtained from the same group of children, that a relative risk of syndrome X in adulthood increased from 1 to 18 when the birth weight decreased from more than -4.25 kg to less than 2.4 kg. Finaly, both plasma lipid anomalies corresponding to the atherogenic risk profile and clotting factors anomalies observed in adulthood were as well directly correlated with low birth weight.

In the same line of evidence, the monozygotic twins studies show that the prevalence of type 2 diabetes is higher in the twins with the lower birth weight (De Zegher et al 1998).

These major public health findings showed the link between the fetal growth anomalies and later development of diseases. IUGR and SGA aree associated with an increase risk factor for syndrome X and car-

Table 1
Intrauterine growth retardation and small for gestational age newborns: Definition of clinical conditions at birth secondary to birth length (height) or birth weight according to gestational age

	Birth Length Below -2 SD (IUGR[1] or SGA[2])	Birth Length Normal	Birth Length Greater than +SD
Birth weight greater than +2 SD	overwight IUGR[1] (or SGA[2])	overweight	macrosomic "proportionate" or "symmetrical"
Birth weight normal	IUGR[1] (or SGA[2])	normal eutrophic or proportionate	
Birth weight below -2 SD (SGA[2])	proportionate ("symmetrical")	SGA[1] or hypotrophic	hypotrophic tall newborn SGA[2]

[1] – IUGR (Intra-Uterine Growth Retardation): when birth length is 2 standard deviations or less below the mean for gestational age; IUGR is defined by birth length

[2] – SGA (Small for Gestational Age): when birth weight and or birth length is 2 standard deviations or less below the mean for gestational age; SGA is defined by both birth length or birth weight

diovascular disease. in addition, whatever the birth weight, the ponderal studies in adulthood adds to the risk factor in a given class of birth weight, the greater the ponderal index at adulthood the greater the risk of syndrome X and cardiovascular disease.

2. Pathophysiology of IUGR and syndrome X: is there a link?

The more we learn on the pathophysiology of insufficient fetal growth leading to IUGR or SGA condition, the more we learn on syndrome X pathophysiology, the more it becomes obvious that a possible link does exist between the two conditions.

Borelli et al. (1985) and De Chiara et al. (1990) conducted remarkable experimental studies in mice by invalidating the genes of insulin, IGF-I and IGF-II as well as the genes of their specific receptors. They showed that KO mice for these genes present with severe alteration of fetal growth and, when the survival is present, lack of postnatal catch up and or aggravation of growth failure postnatally. They also showed convincing evidence that insulin and IGF are key factors controlling the fetal growth, making a likely hypothesis that both IUGR and SGA conditions may be the consequence of altered insulin and IGF action during the fetal life. In the human an abnormal IGF-I gene due to an inactivating point mutation has been shown to drive to both IUGR and postnatal severe growth ailure (Poulsen et al. 1997).

Postnatal lack of catch up in IUGR is associsted with insulin resistance (Woods et al. 1996). Indirect evidence points to a possible partial IGF-I resistance in short IUGR postnataly. Syndrome X and type 2 diabetes are the conditions where insulin resistance is documented and is believed to play a key role in their pathophysiology. It is therefore possible to postulate that the association between IUGR and later development of syndrome X is driven by a common mechanism, a possible insulin and/or IGF-I receptor dysfunction.

3. GH treatment of IUGR with persistent postnatal short stature

Growth hormone treatment aiming at inducing catch up growth for short stature in children born with IUGR and remainng short postnataly (due to lack of spontaneous catch up) has been developed through clinical trial in many countries, and approved by the French authorities since 1997 (Chatelain et

al. 1994; De Zegher et al. 1997, 1998). the benefit over the risk ratio is positive in IUGR treated by GH, tolerance to treatment comparing so far to other recognized indications and being good. GH treatment induces a dose dependent catch up and may normalize height during the prepubertal period. Data on final height are still insufficiently documented but due to the degree of catch up induced, it seems likely that, as for other GH treated conditions (such as GH deficiency and Turner syndrome), the sensitivity to GH in short prepubertal IUGR is less than in GH deficiency, but better than in Turner syndroome (Chatelain et al. 1994; De Zegher et al. 1998).

GH and GH dependent growth factors (IGF-I and IGF-II) actively contribute to postnatal growth and possibly to the spontaneous postnatal catch up processes (Cornblath et al 1965; Gluckman 1986; Deiber et al. 1989; De Zegher et al. 1990; Gluckman et al. 1992; Massa et al. 1992). IGF abnormalities may lead to IUGR/SGA newborn and fetal growth failure (Borelli et al. 1988; De Chiara et al. 1990; Baker et al. 1993). apart from its growth promoting effect mediated by IGFs, the growth hormone acts also on fat mass and is lipolytic, as a metabolic hormone.

Taken together, these facts point to the need to improve our knowledge on body composition in IUGR (Lapillonne et al. 1997) and it evolution under exogenous GH treatment, in order to try to answer several questions that are somehow linked together. With respects to GH treatment several questions deserve strong consideration, e.g.: 1. how does long term GH treatemnt (i.e. more that 2 or 3 years) influence the glucose homeostais and insulin sensitivity in short IUGR; 2. whether GH treatment tends to normalize the body composition when this is altered, 3. whether GH treatment may alter the risk of syndrome X in short IUGR either positively or negatively. until we will have more insight in these issues, long-term GH treatment in short IUGR should be considered a part of clinical research.

4. The pediatrician, IUGR and syndrome X

We should keep in mind that we are dealing with two facts, e.g. the increased risk of syndrome X in IUGR on one hand and the increased prevalence of obesity in the general population worldwide on the other. If one takes in consideration these two circumstances, there appear major implications for IUGR: 1. The parents should be informed on these facts; 2. A careful follow up of the weight, height and BMI during the growth and adolescence appear to be of special importance in IUGR/SGA patients, since their endogenous risk factor for syndrome Xx expose them further to its development in an environment of increased prevalence of obesity; 3. clinical experience strongly suggests that the prevention or early intervetion on obesity is easier and more efficaceous than any attempt of treatment once it has occured.

Conclusions

Major advances have been accomplished in fetal growth understanding which brought considerable benefit to IUGR and SGA conditions. Epidemiological studies pointed out to the link between being born too light or too short and the later risk of developing the association of obesity, hypertension and non-insulin diabetes mellitus in the adulthood. Such association raises further concerns among specialists, since we do not have to deal with a progresssively sustained increased prevalence of obesity.

These facts point to a need for pediatricians for careful follow-up these children born with IUGR or SGA with the objectives of documenting postnatal catch up, possibly treating those with persisting severe short stature, and in all cases preventing the development of excessive wieght gain and compaigning for a normal and well balanced quality of food.

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