Intrauterine Growth Retardation and Puberty in Girls

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Some, albeit not all studies on the relationship between intrauterine growth retardation (IUGR) and female pubertal development have found an earlier and rapidly progressing puberty as well as concomitant disorders of related functional systems such as polycystic ovary syndrome and short stature. These pubertal changes are part of a growing list of IUGR-related diseases, which includes non-insulin dependent diabetes mellitus and coronary heart disease. A pulsatile release of gonadotropin releasing hormone is thought to be a conditio-sin-ne-qua-non for the initiation of puberty. In the absence of prospective studies on gonadotropin releasing hormone pulse patterns in IUGR-children other markers of pubertal development such as age at menarche have been deployed. From these studies it is not clear, however, whether the findings of an earlier onset of puberty in IUGR-girls merely reflect a more rapid progression of puberty. Both the role for IUGR and the mechanisms behind the onset of puberty are still elusive. Assuming a connection between IUGR and pubertal development, parallels can be drawn between hypotheses on the long-term consequences of IUGR and hypotheses on the initiation of puberty. For example, the somatometer concept proposes a role for fat mass in the initiation of puberty, which is compatible with the hypothesis on non-skeletal catch-up growth after IUGR. The debate on the origins of puberty and the role of IUGR mainly focuses on nature and nurture. Judgmentally, studies in mono- and dizygotic twins discordant for birth weight may be of particular help.

The scope of this article is to provide an overview of changes in pubertal development and associated health problems in relation to intrauterine growth retardation (IUGR) in girls. Aspects of compatibility of hypotheses on pubertal development and hypotheses on the general role of IUGR in long term diseases will be discussed.

Much attention has been going out to short term consequences of IUGR in a neonatal care setting and in early childhood (Ellison et al., 1992; Gortner et al., 1999). The past decade, associations between IUGR and long term diseases with substantial morbidity and mortality have been identified by large cross-sectional epidemiological studies. For example, subjects born small for gestational age (SGA, a crude marker for IUGR) have a six fold increased risk for developing type II diabetes mellitus (NIDDM) and a twofold increased risk for developing coronary heart disease (CHD) (Barker, 1998; Phillips, 1998). These associations have been confirmed in both human (e.g. the Dutch Famine) and animal studies (e.g. protein restriction in pregnant rats; Roseboom et al., 2000; Ozanne & Hales, 1999).

The abundance of data on the short- and long-term diseases associated with IUGR contrasts with the scarcity of data on the transitional period which includes puberty. IUGR-associated differences in pubertal development are, however, of particular interest. After fetal life, puberty is another important period associated with dramatic changes in physiology and structure. It is a well-known principle that developing systems have an increased susceptibility for pathological derangements. Indeed, IUGR, as measured by birth weight, has been shown to be associated with changes in all hallmarks of pubertal development as well as derangements related to systems that evolve during puberty. Changes in pubertal development and related diseases thus add to the growing list of diseases with fetal origins. Nevertheless, both the role of IUGR and the origins of pubertal development are still elusive.

The Onset and Progression of Puberty in IUGR Girls

The initiation of puberty is complex and many factors have been identified which either directly or indirectly influence gonadotropin releasing hormone (GnRH) production or - secretion. Although the exact mechanisms behind the initiation of puberty have not been fully elucidated, a central regulation of the onset of puberty (Figure 1) is most likely since agonadal children (e.g. children with Turner syndrome) show a normal biphasic pattern of GnRH-secretion from the hypothalamus and a normal pattern of low levels of GnRH in the prepubertal years (Nathwani et al., 1998). In fetal life and early postnatally GnRH-secretion is present and disappears in infancy and childhood. During puberty GnRH-secretion reawakens as nighttime pulsatile patterns, which is the first sign of a narrow definition of puberty (Wennink et al., 1990).

Pubarche (i.e. the appearance of pubic hair) is part of a broader definition of puberty and preceeds GnRH reawakening. Pubarche is, however, more related to adrenarche with increasing activity of adrenal androgens and adrenarche does
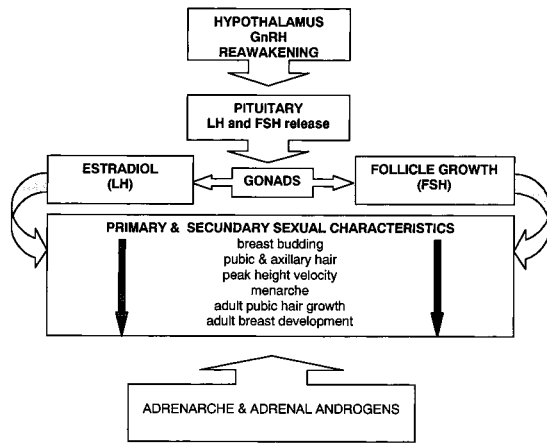
Figure 1

Pubertal development: During fetal life GnRH secretion is present and disappears shortly after birth. Reawakening of GnRH secreting cells in the hypothalamus is thought to initiate puberty. GnRH is transported through the portal veins to the anterior pituitary where it stimulates the production – and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) which in turn have effects on estradiol production and follicle growth respectively. Primary and secondary sexual characteristics develop as a consequence of increasing estradiol levels, and adrenal androgens after adrenarche.

not influence the initiation of central pubertal development (Ibanez et al., 1992). Nevertheless, an earlier and exaggerated adrenarche and pubarche has been linked with IUGR and pathology as well (Ibanez et al., 1998). Regarding a narrower definition of puberty, there are studies that suggest an earlier onset in IUGR-girls as measured by age at menarche (Bhagarva et al., 1995; Cooper et al., 1996; Ibanez et al., 2000). In contrast, others found barely any differences or even found an earlier onset of puberty in heavier newborns (Albertsson-Wikland & Karlberg, 1994; Powls et al., 1996; Bacallao et al., 1996). In the absence of prospective studies that compare nightly GnRH pulsatile patterns, it is not clear whether or not there is truly an earlier onset of puberty in IUGR-girls. Alternatively, the finding of an earlier puberty in studies using markers of puberty (e.g. breast stage, peak height velocity and age at menarche) can be explained by a rapid progression of pubertal development which has been found as well (Ibanez et al., 2000).

Health Problems Associated With an Early or Rapid Progression of Puberty in IUGR Girls

Reduced Final Height

Although different definitions are in use, catch-up growth (CUG) can be defined as the process whereby a child born with a length or weight under the threshold of two standard deviations (SD) below the mean shows percentile-crossing to any point above this threshold in a given period of time. CUG can be divided into skeletal catch-up growth (sCUG) and non-skeletal catch-up growth (nsCUG i.e. adipose tissue). Shortness in final height has been reported in 10–30% of children born small-for gestational age. In a Swedish, population-based study of 3.650 children, 8% of 198 children

born with a length or weight of more than two SD below the mean still had not shown sCUG on reaching final height (Albertsson-Wikland & Karlberg, 1994). In an extended analysis, puberty did not appear to be a period of major sCUG, contrasting with the first two years of life that seemed to be the most crucial period (Luo et al., 1998). Although in this study there was a slight increase in final height prognosis, most cross-sectional studies show final height is further compromised in puberty despite a decreased bone age during the prepubertal years (Preece, 1997). This could result from a rapid progression of pubertal development (Ibanez et al., 2000).

Increasing nutritional intake does not seem to be a good strategy to increase final height (He & Karlberg, 2001). GH-therapy is widely used to increase final height of IUGR-children with short stature. The use is, however, not limited to those IUGR-children with proven suboptimal GH-secretion, comprising up to 50% of IUGR-children who fail to show sCUG (De Waal et al., 1994). The effects of GH-treatment on final height, have yet to be established. First results on final height of GH-treated IUGR-children are somewhat disappointing, showing a gain in final height of only 2–3 cm. There are reports showing better results, although this can probably be ascribed to prepubertal GH-therapy (Rekers-Mombarg et al., 1999). One explanation for the finding that puberty is not an ideal period for GH-treatment is that GH-secretion is maximal in this period for non-GH-deficient IUGR-children and consequentially there is no additive effect of GH-therapy. However, this does not explain meager results in GH-deficient IUGR-children. Another explanation is that, at least in theory, GH-therapy in IUGR-children paradoxically leads to an increased rate of bone maturation and premature closure of growth plates acting in conjunction with a rapidly progressive pubertal development. In addition, there are studies which demonstrate that GH-therapy results in an earlier puberty in children with idiopathic short stature and, hence, a shorter prepubertal growth trajectory (Rekers-Mombarg et al., 1999). It is conceivable that GH and early (and perhaps exaggerated) rises in adrenal androgens and estrogens may work upon growth plates that have limited capacity due to structural changes ensuing from IUGR. In recent years, a combination of GH-therapy GnRH-agonists to delay pubertal development has been subject of study. Preliminary results show an increase in final height prognosis of about 7 cm for girls in groups with central precocious puberty, giving more credits for the benefits of this expensive treatment (Mul et al., 2000). However, to date there are no reports on the benefits in IUGR-children, with the exception of one submitted manuscript showing similar results (Kamp, 2000).

There is some concern about the long term health risks of GH-therapy in the group of IUGR-children. On the one hand IUGR-children are already more insulin resistant than children who experienced normal intrauterine growth and insulin resistance is well known to be aggravated by administration of GH (Arslanian & Suprasongsin, 1996; Sas et al., 2001). Whereas most smaller studies find insulin sensitivity deteriorates without NIDDM evolving, Cutfield et al., found a surplus of 34.4 cases of NIDDM per 100,000 patient-years of GH-treatment in a large sample of IUGR- and non-IUGR children, which is a six fold

increased incidence of NIDDM (Cutfield, 2000). On the other hand, however, in GH-treated children with Turner syndrome, negative effects of GH on glucose homeostasis seem to ware off after discontinuation of GH-therapy (Sas et al., 2000). Moreover, it has been proposed that a certain degree of insulin resistance during puberty may be a physiological way to promote statural growth, since the hyperinsulinemia during euglycaemic hyperinsulinemic clamps in adolescents was found to increase the bio-availability of insulin-like growth factor I (IGF-I) by suppressing circulating levels of its binding proteins IGF-BP 1 and –2 (Caprio, 1999). Supporting this view is the finding that normal puberty decreases insulin sensitivity, which at the end of puberty reaches near-prepubertal values (Johannsson et al., 1999; Moran et al., 1999). It is clear more research is needed on the long term effects of GH-therapy in IUGR-children.

Adipose Tissue

Links are suggested between adiposity and pubertal timing. There is a secular trend towards increasing adiposity as well as an earlier menarche (Wattigney et al., 1999). Obese children tend to reach puberty at an earlier age. Also, childhood obesity tends to track into adulthood (He & Karlberg, 2001). The effect of tracking is greater in puberty than in early childhood (Guo & Chumlea, 1999). During normal female puberty, total — and relative fat mass increases, which, in an evolutionary perspective, would give a survival advantage during pregnancy and lactation. In an analysis of more than 16.000 white participants in two major studies, timing of menarche was a major determinant of fatness in adulthood; early maturers were 30% fatter than late maturers (Garn et al., 1986). However, there is little information on pubertal changes in body composition in IUGR-children. Since adipose tissue and nsCUG are well documented risk factors for numerous diseases including NIDDM and CHD, it would be of interest to longitudinally explore pubertal changes in adiposity and features associated with NIDDM and CHD in IUGR-children (Forsen et al., 1999; Forsen et al., 2000; Kopelman, 2000). Pubertal changes may also influence the risk of NIDDM and CHD through other mechanisms that are unrelated to adipose tissue (e.g. sex hormones).

Polycystic Ovary Syndrome

As mentioned previously, pubarche and adrenarche can be placed in a broad definition of puberty and are related to fetal growth (Ibanez et al., 1998). Ovarian hyperandrogenism, including polycystic ovary syndrome (PCOS) is associated with higher levels of adrenal — and gonadal androgens (dehydroepiandrosterone(-sulphate), androstenedione and testosterone) and has been found to be more common in girls who experience an early pubarche (45% vs. 3% in the normal population; Ibanez et al., 1993). Girls with premature pubarche and — adrenarche already have microcystic ovaries before further pubertal development (Teixeira et al., 2001). Ibanez et al. (1998) reported lower birth weight in girls experiencing premature pubarche and even lower birth weight in those who subsequently developed ovarian hyperandrogenism. By contrast, Cresswell et al. (1997) found heavier newborns to be at risk of developing PCOS. The exact mechanisms behind premature pubarche,

adrenarche and ovarian hyperandrogenism are unclear and are worth more research, since it is clear that, apart from PCOS, there are more health risks in this population such as insulin resistance and lipid disorders (Ibanez et al., 1998). Relatively young (45-54 yrs.) women suffering from PCOS have been found to have a four times increased risk of developing NIDDM and a two-and-a-half times increased risk of developing hypertension (Elting et al., 2001).

Links Between Hyptheses on Pubertal Development and Hypotheses on the Associations of IUGR With Long Term Health Risks

Currently, the exact role of IUGR in its association with long term health risks such as NIDDM remains to be determined. The findings of IUGR-related changes in pubertal development, as well as derangements in functional systems first appearing during puberty, raise the question whether or not these changes can be embedded in hypotheses on the role of IUGR in chronic diseases of adulthood. Biological plausibility can add to the proof of a relationship between IUGR and pubertal development. The ongoing debate on the role of IUGR has primarily been a debate of nature or nurture. However, a degree of interaction with nurture (e.g. 'thriftiness') is more or less obligatory in most nature-favouring hypotheses. Mutatis mutandis, factors that are seemingly on the nurture-side, such as obesity, may have genetic origins. In addition, some effects may be epi-genetic; a study in rats, for example, has demonstrated that the effects of generations of marginal malnutrition leads to a 45% reduction in maternal size at birth, the effect of which on birth weight carried as far as the third generation after refeeding (Stewart et al., 1980). Ibanez et al. (2000) found IUGR-girls to have a reduced ovarian and uterine size. Cross-breeding experiments and embryo-transfer in animals have shown that the fetus adapts to maternal size (Brooks et al., 1995). Pubertal development may, therefore, have significant intergenerational effects, which are worthwhile being studied in further detail. Twin studies on the initiation of puberty suggest a larger influence of genetic than of environmental factors, although, to our knowledge, the effect of IUGR has never been studied in such populations (Meyer et al., 1991). We suggest future longitudinal studies on the relationship between IUGR and pubertal development in mono- and dizygotic twins discordant for birth weight to be of particular interest.

Nature

One of the hypotheses tempting to explain the long term consequences of IUGR is the Thrifty Genotype Hypothesis, which poses that a gene, improving survival of a malnourished fetus, becomes detrimental in an environment of affluence (Neel, 1962). Later, it has been suggested that a gene, causing insulin resistance, leads to altered function of organs and tissues by diverting nutritional flow away from less important tissues such as fat — and muscle tissue and splanchnic organs towards vital body parts such as the brain (McCance et al., 1994). The Fetal Insulin Hypothesis, which, at least in part, considers IUGR to be a confounder of long term disease is another hypothesis in which genetic

influences predominate. In this hypothesis it is suggested that monogenic or polygenic factors which cause impairments in insulin's actions would result in both IUGR and long term diseases when acting in conjunction with environmental factors. Insulin, next to IGF-I, is an important fetal growth factor (Hattersley & Tooke, 1999). Strikingly, many studies find only a weak link between IUGR and related long term diseases if no correction for current weight or length is made, implying that the change in body proportions during childhood is of particular importance. It has been hypothesized that skeletal catch-up growth and non-skeletal catch-up growth are important independent predictors of the diseases associated with IUGR (Lucas et al., 1999). sCUG and nsCUG are typical examples of factors that may have genetic origins, although depending on environmental influences. It is mentioned here under 'nature' because the underlying links with pubertal development are probably primarily genetic.

At least one direct genetic influence on both IUGR and an early and rapidly progressive puberty has been found in the existence of a maternal uniparental disomy of chromosome 14 (Fokstuen et al., 1999). However, this probably does not explain the larger part of the associations between IUGR and pubertal development.

Although the relationship between birth weight and the onset of puberty in girls adopted from third world countries has not been subject of study as such, it could provide indirect evidence of the existence of a relationship between the two. Adopted girls from Third World countries are at a higher risk of developing precocious puberty, both in relation to peers from the country of origin and the indigenous population. Although still lagging behind, these children experience rapid CUG (Virdis et al., 1998). Therefore, it is probable that these children have been underfed both in utero and postnatally. A role for nsCUG is compliant with secular trends towards an earlier menarche in developed countries. The role of nutrition is further demonstrated by the well-known effect that starvation results in a delay in the onset of puberty and suppresses GnRH secretion (Beumont et al., 1976). Cooper et al. (1996) found the influence of prepubertal weight on the age of onset of puberty to be greater than the influence of height. In a sample ($n = 848$) of the ALSPAC study cohort, Ong et al. (2000) found children who showed CUG > 0.67 SD after 2 years. to be significantly lighter, shorter and thinner at birth. These children grew up to be heavier, taller and had a BMI (and waist) that was significantly higher than non-CUG children at the age of 5 years. IUGR-children showing CUG thus experienced an early adiposity rebound (i.e. the point of age at which body mass index increases after an initial decrease; Ong et al., 2000). In conjunction with this indirect evidence He and Karlberg (2001) found nsCUG, as judged by BMI, to be negatively correlated with the age at onset of puberty, as judged by the age at peak height velocity. In support of this observation, Cooper et al. (1996) found age at menarche to be inversely related to weight at the age of seven years and noted that girls of low birth weight who subsequently became heavier as a child were the first to reach puberty.

In the early seventies, Frisch and Revelle (1971) hypothesized that menarche occurs subsequently to reaching a critical body mass. After controversial reports, Frisch (1980) narrowed this so-called somatometer concept to a critical percentage of body fat, which readies the body for fertility. The observation of hypogonadotropic hypogonadism in mice with genetic defects in leptin production and the observation that female mice have an earlier onset of puberty after the administration of leptin has led to the hypothesis that leptin is crucial for the initiation of puberty (Chehab et al., 1996; Chehab et al., 1997). Similar observations of defects in leptin's actions have been made in humans (Clement et al., 1998). In addition to a proposed effect on pubertal development, a degree of leptin resistance has been proposed as a mechanism behind CUG (Jaquet et al., 1999). Leptin is an energy-regulating hormone which also acts as a GnRH-secretagogue in the hypothalamus through restraining the inhibitory actions of neuropeptid Y (Kiess et al., 2000). Whereas, with the use of isotope dilution to determine fat mass, Arslanian et al. (1998) found no differences in pubertal and prepubertal leptin levels after controlling for body mass, other studies suggest a threshold effect of leptin in the initiation of puberty (Matkovic et al., 1997).

Adopted girls from Third World countries experience sCUG as well. Because of the strong temporal relationship between the somatotropic- and gonadal-axis it has been suggested that GH and IGF-I play an important role in the central regulation of pubertal development. Recently, this concept has been extensively reviewed by Wilson (2001), who regarded animal studies as well as studies in humans. Studies in humans have been conflicting due to model-limitations. In short, Wilson (2001) used two criteria outlined by Foster et al. (1999). The first criterion is a rise of GH and/or IGF-I before puberty. Wilson (2001) concluded that levels of IGF-I rise in the prepubertal years, although it is unknown whether this rise originates centrally or peripherally. There was insufficient evidence to conclude GH rises during prepuberty. The second criterion demands withdrawal of IGF-I and/or GH to postpone or prevent puberty and replacement of these hormones to restore normal pubertal development. Again, data were insufficient to ascribe a critical role in determining GnRH-pulsatility to GH. Suppression of IGF-I leads to delayed pubertal development suggesting only a permissive role on GnRH-pulsatility, however, IGF-I-knockouts have more profound results and one must conclude IGF-I is essential. IGF-I may, on the other hand, have induced neuronal deficits leading to alterations in GnRH-secretion. GH-suppression and -knockout-models show an eventual pubertal onset, which may, however, result from a non-GH mediated source of IGF-I (Wilson, 2001). In addition to this review, it must be mentioned that adipose tissue has distinct effects on the availability of GH and IGF-I, either directly or through hyperinsulinemia.

Regarding the development of PCOS, Holte proposed that thrifty genes are at work here as well. 'It is suggested that PCOS is the result of "thrifty" genes, providing advantages in times of shortage of nutrition such as muscular strength, moderate abdominal fatness and decreased insulin sensitivity — an anabolic, energy saving constitution. However, when this constitution is exposed to unlimited food supplies and modern sedentary life style a full-blown PCOS with insulin resistance and infertility is triggered,

presumably via several mechanisms, which follow a logical amplification system between two basic anabolic hormones, insulin and testosterone' (Holte, 1998). Ibanez et al. (1998) proposed that there could be a common genetic defect in a serine kinase (Figure 2), which, via increased serine phosphorylation of the insulin receptor, would lead to reduced insulin-mediated fetal growth as well as insulin resistance and hyperinsulinaemia. In addition this would lead to an increased adrenal and ovarian P450c17 serine phosphorylation leading to hyperandrogenism.

Nurture

According to the Thrifty Phenotype Hypothesis and Fetal Origins Hypothesis, adaptations to IUGR, which are believed to be a consequence of environmental factors, may permanently programme structure and function, including set points of metabolic and hormonal pathways. The hypotheses further suggest that specific developmental windows in which hyperplasia and differentiation are predominant are crucial to this programming. Subsequent to the completion of a window, plasticity is lost and adequate readaptation to altered exogenous stimuli (i.e. thriftiness) during lifetime fails (Barker, 1997; Hales & Barker, 1992).

Concepts of influences on structure and function can be found in nature-favoring — as well as nurture-favoring hypotheses. In the early eighties, Scott and Johnston proposed that neuroendocrine activity and maturation of the central nervous system is primary to the onset of menarche, which seems incompatible with brain-sparing (Scott & Johnston, 1982). However, neurological deficits are frequently observed in IUGR-children, indicating brain-sparing is relative. Therefore, it is conceivable that alterations in the central regulation of puberty can occur, diminishing the 'intrinsic restraint' (i.e. increasing the resistance to a central inhibition) of the GnRH pulse generator as suggested by Conte et al. (1980). This is also in accordance with the Gonadostat Theory, which explains GnRH secretion by a decreased sensitivity to the negative feedback of estrogens (Grumbach et al., 1974). Bhagarva et al. (1995) postulated that growth retardation during the second half of pregnancy may reset the hypothalamic gonadostat resulting in decreased sensitivity to negative feedback and an earlier onset of puberty. Supporting this view, Lepthart and Ojeda (1990) observed a decreased aromatase activity and, hence, decreased estrogen levels in the brain of rats during puberty. Alternatively, there may be an increased end-organ sensitivity to GnRH or LH and FSH, leading to earlier or rapidly progressive puberty.
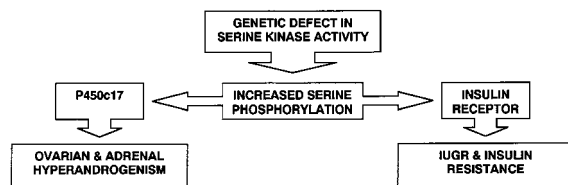
When, in 1996, Cooper et al., observed a positive relationship between age at menarche and birth weight in a large epidemiological study, they suggested an imprinting of the hypothalamic gonadotropin secretion and perhaps a modulation of end-organ sensitivity to gonadotropins occurring under the influence of androgens and food supply in utero, which may influence the onset of puberty. Manipulation of androgen or estrogen concentration can also lead to PCOS (Barker et al., 1995).

Conclusion

IUGR-related changes in puberty are of particular interest because of their relationship with chronic diseases of adulthood such as type II diabetes or coronary heart disease and their relationship with other diseases including polycystic ovary syndrome and short stature. In particular the question whether or not there is an earlier onset of puberty needs to be studied in further detail, for example in prospective studies measuring GnRH-pulsatility. Both the role of IUGR and mechanisms behind the initiation of puberty are still elusive. One view is that pubertal changes can be understood in the light of hypotheses on the role of IUGR in long-term diseases. It is obvious that parallels exist between these hypotheses and hypotheses on pubertal development, which adds to the biological plausibility of a relationship. It is also obvious that most hypotheses are not mutually exclusive. Therefore effort must be put in falsifying existing hypotheses, while at the same time basic research may raise new hypotheses on the connection between IUGR an pubertal development. There is a great degree of mutual dependency of genetic and environmental factors. In order to judge between them, research on pubertal development in mono- and dizygotic twins discordant for birth weight can be of great interest.

Figure 2

A model of a genetic defect leading to IUGR, hyperandrogenism and insulin resistance as proposed by Ibanez et al., (Ibanez et al., 1998).

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