Endocrinology and Gynecology of Girls and Women with Low Birth Weight

Lourdes Ibáñez^{a, b} Abel López-Bermejo^c Marta Díaz^{a, b} Maria Victoria Marcos^d

^aEndocrinology Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, ^bCentro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), ISCIII, Madrid,

^cPediatric Endocrinology, Dr. Josep Trueta Hospital and Girona Institute for Biomedical Research, Girona, and

^dEndocrinology Unit, Hospital de Terrassa, Terrassa, Spain

Key Words

Prenatal growth • Low birth weight • Adrenarche • Pubarche • Puberty • Menarche • Insulin • Adiponectin • Androgen excess • Polycystic ovary syndrome • Lipids • Body composition • Adiposity • Abdominal fat • Subcutaneous fat • Visceral fat • Metformin

Abstract

In girls, low birth weight (LBW), when followed by postnatal catch-up growth, is accompanied by endocrine-metabolic abnormalities which include a more adipose body composition (with increased visceral fat), insulin resistance and a less favorable adipokine profile as early as in the pre-school age. These girls also exhibit follicle-stimulating hormone hypersecretion both in early infancy and early post-menarche, with reduced uterine and ovarian size in adolescence. These endocrine and gynecological changes result in a decreased ovulation rate and in an advanced tempo of adrenarche, pubertal development and menarche (by nearly a year, compared to non-LBW girls). The earlier maturation in LBW girls may result in a loss of about 1 SD in height, as compared with target height. During the post-menarcheal period, LBW girls are at increased risk of developing polycystic ovary syndrome. Early insulin sensitization may prevent or delay some of the endocrine-metabolic abnormalities associated to LBW.

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Introduction

In humans, the most dynamic growth phase of life occurs before birth. During prenatal life, there are critical windows of time which often coincide with episodes of rapid growth and during which target tissues are in a sensitive (or vulnerable) phase of plasticity [1]. A suboptimal nutrition in utero can not only lead to adverse fetal growth patterns, but also impact upon and permanently alter – or ‘program’ – whole-body metabolism, including the endocrine axes [2, 3]. Over the last decade, a large body of epidemiological evidence substantiates that type 2 diabetes, obesity, hypertension and cardiovascular disease can be programmed early in life and that low birth weight (LBW) – a surrogate of fetal growth – followed by rapid weight gain during early postnatal life is associated with features of the metabolic syndrome [4–6].

Here, we review the endocrine-metabolic and reproductive function of girls, adolescents and young women who experienced a degree of prenatal growth restraint. We will focus on the early longitudinal changes of LBW girls who developed a spontaneous catch-up growth, and on the effects of LBW on uterine and ovarian size, ovulation rate, adrenarche, pubertal tempo and menarche and the development of polycystic ovary syndrome (PCOS). We will also review novel insights suggesting that early insulin sensitization may prevent or delay some of the

endocrine-metabolic abnormalities associated to LBW. About 3–10% of children are born small for gestational age (SGA); therefore, the consequences of early growth restraint are of major relevance for girls and women worldwide.

Longitudinal Follow-Up of LBW Girls with Spontaneous Catch-Up: Early Development of Hyperinsulinemia and Body Adiposity

In most LBW children, catch-up is largely completed by the age of 2 years; by then, height and weight are similar to those in children born appropriate for gestational age (AGA) [7]. In a longitudinal study of body composition, we have shown that LBW girls gain progressively more body fat and abdominal fat mass than AGA girls between the age of 2 and 4 years. These differences occur despite the LBW girls having already completed their catch-up growth by the age of 2 years, and with similar changes in overall body weight, height and body mass index (BMI) as compared to the AGA girls [8]. The risk of adiposity at the age of 4 years is mostly related to the early weight gain from birth to the age of 2 years. The changes in body composition are accompanied by a shift from insulin sensitivity to insulin resistance, and also by rises in neutrophil count and insulin-like growth factor-I levels [8]. Other studies in LBW subjects with spontaneous postnatal catch-up have shown that some infants already develop insulin resistance by the age of 1 year [9], and that this resistance progresses rapidly in many infants by the age of 3 years [10].

Total and abdominal adiposity further increases between the age of 4 and 6 years, and visceral fat excess is already present at the age of 6 years (even in the absence of overweight) [11]. Dyslipidemia, increased levels of leptin and dehydroepiandrosterone sulfate (the classic marker for adrenarche) and decreased levels of sex hormone-binding globulin and high-molecular-weight (HMW) adiponectin develop between the ages of 6 and 8 years [12, 13]. Dysregulation of adipokines – proteins secreted in adipose tissue – is emerging as an important mechanism by which adipose tissue contributes to systemic insulin resistance and metabolic disease [14]. Adiponectin is an adipokine produced mainly in subcutaneous fat [15]. Circulating adiponectin levels, specifically those of the HMW isoform, considered the active form of the protein, correlate positively with insulin sensitivity and seem to be protective for the subsequent development of type 2 diabetes [15]. In girls with LBW, adipocyte en-

largement and subsequent adipose tissue hyperexpansion may underpin these abnormalities, favor ectopic fat storage and ultimately lead to the development of PCOS (see below) [13, 16].

LBW, Hypergonadotropinemia, Small Uterine and Ovarian Size, and Central Adiposity

Prenatal life is a critical window in the development of the female external genitalia [17]. In postnatal life, the human gonadotropic axis has two phases of high activity: one in infancy and another starting in puberty and persisting into adulthood.

Prenatal growth restraint is followed by follicle-stimulating hormone (FSH) hypersecretion in early infancy [18] and also in early post-menarche [19], suggestive of a reduced granulosa cell reserve, and by reduced uterine and ovarian size in adolescence [20]. Longitudinal data from girls with LBW aged between 14 and 18 years indicate that these alterations persist into the reproductive age range [21]. For example, FSH levels are elevated by approximately 50% as compared to levels in AGA girls, and high levels of luteinizing hormone and fasting insulin as well as an excess of abdominal fat become readily detectable beyond puberty (fig. 1).

LBW and Reduced Ovulation Rate

Adolescent girls with LBW have a relatively low ovulation rate at the age of 15 years, as compared with age-matched AGA girls [22]. This reduced ovulation rate seems to be unrelated to completeness of spontaneous catch-up growth (fig. 2) [22]. Therefore, in girls with LBW, recovery of linear growth during childhood does not warrant normal ovulation function in adolescence. Conversely, persistent growth failure in these girls will not necessarily be followed by anovulation.

LBW, Adrenarche and Pubarche

Population studies have disclosed a relationship between lower birth weight and higher adrenal androgen levels in childhood, so that adrenal androgen concentrations are highest in those small infants who become heavier than average during early childhood [23]. This pattern is continuous throughout the range of normal birth weights and shows no gender differences.

Fig. 1. Serum luteinizing hormone (LH) and FSH concentrations (in the early follicular phase), uterine area and mean ovarian volume (by ultrasound) in young women aged 18 years and born either AGA or SGA. Values are mean/SD/SEM. Modified from Ibáñez et al. [21].

Fig. 2. Fractions of AGA and SGA adolescents (aged approximately 15 years) distributed by their number of ovulations over 3 months. Ovulation was assessed by weekly serum progesterone measurements; the ovulation rate in SGA girls was lower than in AGA girls. Values are means. * Indicates a significant AGA versus SGA difference. Modified from Ibáñez et al. [22]. DHEAS = Dehydroepiandrosterone sulfate.

Precocious adrenarche in girls refers to an early increase in adrenal androgen production that usually results in the development of pubic hair or pubarche before the age of 8 years; this process is independent of pubertal development [24]. Some girls with precocious pubarche may show amplified or exaggerated adrenarche, a term

usually applied when baseline dehydroepiandrosterone sulfate levels are above those seen in early pubertal girls [25]. These patients typically have an endocrine-metabolic profile reminiscent of the metabolic syndrome, even in the absence of obesity, with hyperinsulinemia, dyslipidemia, decreased sex hormone-binding globulin,

Fig. 3. Birth weight scores of post-menarcheal control girls (-, - and -) and post-menarcheal girls with a history of precocious pubarche without ovarian hyperandrogenism and without hyperinsulinemia (+, - and -), with ovarian hyperandrogenism and without hyperinsulinemia (+, + and -), and with both ovarian hyperandrogenism and hyperinsulinemia (+, + and +). STD. Dev. = Standard deviation; Std. Err. = standard error. Redrawn with permission from Ibáñez et al. [29].

Fig. 4. Distributions of menarcheal age in birth weight (BW) subgroups of girls with precocious pubarche (PP). Age at menarche was younger ($p < 0.001$) in lower-BW versus higher-BW girls; intermediate-BW girls showed an intermediate pattern. Median age at menarche is 12.8 years in the reference population. Modified from Ibáñez et al. [37].

visceral adiposity, an abnormal adipokine profile and a state of low-grade inflammation [26]. Long-term follow-up of these girls support the notion that precocious pubarche may be a forerunner of the metabolic syndrome and precede the development of ovarian androgen excess or PCOS in adolescence [27, 28]. This sequence occurs more frequently when precocious pubarche is preceded by a reduced fetal growth and followed by excessive postnatal catch-up in height and mainly in weight; hyperinsulinemia seems to play a key role in the development of these abnormalities (fig. 3) [29]. Further modulation of the endocrine-metabolic phenotype is exerted by genetic polymorphisms [30–32]. Weight excess may aggravate the phenotype or accelerate its emergence.

The development of overt and symptomatic ovarian hyperandrogenism is preceded by a silent clinical phase starting after menarche, when an increase in ovarian and adrenal androgens is already detectable [33, 34].

LBW and Puberty

In the general population of girls with LBW, the age at both pubertal onset and menarche is advanced by about 5–10 months [35, 36]. Adult height is, on average, below target height; this reduction in adult height has been attributed to subnormal growth during pre-puberty, rather than during puberty [35, 36].

In LBW girls who show a rapid postnatal catch-up and subsequently develop precocious pubarche, menarche occurs earlier than in the general population [37]. The age at menarche is further advanced by 8–10 months in those with a birth weight SDS less than -2, compared with those with a birth weight SDS greater than 0 (fig. 4). Adult height differs by approximately 1 SD between the upper and lower birth weight subgroups [37].

A retrospective study in Catalan girls with an early-normal onset of puberty (onset of breast development at the age of 8.0–9.0 years) indicated that the timing of menarche and adult height depend on prenatal growth [38]. Girls with a normal birth weight tend to progress slowly through puberty, as compared with LBW girls, and have a normal timing of menarche and an adult height within the target height range. In contrast, girls with LBW experience a faster progression to an early menarche and to a reduced adult height, with a loss of about 1 SD as compared with target height [38]. These findings have been corroborated in a subsequent prospective study performed in a similar population [39].

LBW and the Development of PCOS

Recent data indicate that enlarged adipocytes, hyperinsulinemia and an abnormal adipokine profile, highlighted by decreased circulating HMW adiponectin, are key pathogenic features of PCOS [40–42]. Enlargement of subcutaneous adipocytes occurs when there is an exhaustion of the capacity to expand subcutaneous adipose tissue in a metabolically safe way [16, 40]. When the subcutaneous adipose depot can no longer accommodate the caloric supply, a lipotoxic state emerges, with dyslipidemia, insulin resistance, an unfavorable adipokine profile and ectopic lipid deposition, for example, in the liver, muscle and pancreas [16, 40].

Girls with LBW characteristically have a reduced number of subcutaneous adipocytes; this deficit is already present before birth and is not reverted in postnatal life, mainly because during the phase of postnatal catch-up, they preferentially expand their fat-free mass [43]. Accordingly, an early catch-up in weight during infancy may result in a pre-PCOS state by mid-childhood [44]. An amplified adrenarche (with or without precocious pubarche) will herald the subsequent development of ovarian hyperandrogenism and full-blown PCOS [44].

Insulin Sensitization in Girls with LBW

Several lines of evidence support the notion that insulin resistance is a driving component of the setting leading to the combination of hyperandrogenism, central adiposity, dyslipidemia, altered adipokine profile and low-grade inflammation [40, 44].

Insulin Sensitization to Restore Ovulation

In LBW girls with a reduced ovulation rate, insulin-sensitizing treatment with metformin over 3 months results in an increase in the number of ovulatory cycles, which is accompanied by a decrease in abdominal fat excess, a gain in lean mass, a drop in fasting insulin and a less atherogenic lipid profile [45]. The normalizing effect of metformin on body composition and anovulation corroborates that insulin resistance is a driving force in this constellation.

Insulin Sensitization in the Modulation of Pubertal Timing

In LBW girls with an early-normal onset of breast development, metformin therapy for 36 months was capable of normalizing the timing of menarche and of pro-

Fig. 5. Cumulative fractions (%) of post-menarcheal LBW girls with precocious pubarche (mean age 8 years) randomized either to remain untreated or to receive metformin for 4 years. All girls were subsequently untreated at least until menarche. Menarcheal percentiles 3, 10, 25, 50, 75, 90 and 97 of each subgroup are plotted. Modified from Ibáñez et al. [50].

longing and augmenting pubertal growth up to adult height [39]. Metformin treatment also resulted in a leaner body composition and in a less adverse lipid profile [39]. These data support the concept that insulin is a major determinant of the pubertal tempo in girls, probably through interplay among body adiposity, leptin, insulin-like growth factor-I and gonadal steroids [39].

Insulin Sensitization to Prevent Progression from Precocious Pubarche to PCOS

LBW girls who develop precocious pubarche are at increased risks for an early onset and progression of puberty and an early menarche, for a shorter adult stature and for a progression to PCOS in adolescence, as defined by hyperinsulinemic hyperandrogenism, dyslipidemia, excess visceral fat and a state of low-grade inflammation [26, 37]. Most of these abnormalities are already present well before the development of the clinical symptoms of androgen excess [26]. In these girls, insulin sensitization with metformin starting 6–12 months after menarche prevents the progression to overt PCOS; however, these beneficial effects are reversed as soon as metformin therapy is discontinued [34, 46]. In contrast, early metformin therapy started in pre-puberty, at a mean age of 8 years, and maintained throughout puberty (for 4 years) reduces total, visceral and intrahepatic fat, delays menarche by

about 1 year towards normal and increases adult stature (fig. 5) [47–50]. The benefits of early metformin therapy, particularly on body composition, lipids, circulating insulin and testosterone, persist 2 years after stopping treatment, suggesting that early metformin intervention may be useful in delaying, attenuating or even preventing the development of PCOS [49, 50]. It remains to be assessed whether early metformin therapy is also effective in LBW catch-up girls with hyperinsulinemia and excess adiposity but without precocious pubarche.

Conclusions

Most LBW girls normalize their height and weight in early infancy. However, the timing and intensity of the catch-up growth that follows prenatal growth restraint may have consequences on the endocrine, metabolic and reproductive systems that persist over time.

Accordingly, the possibility of a LBW effect should be taken into account in the evaluation of girls and young women presenting with increased central adiposity, exaggerated adrenarche (with or without precocious pubarche), early-normal and rapidly progressive puberty and ovarian hyperandrogenism and anovulation.

Hyperinsulinemic insulin resistance is thought to be a key pathogenetic factor accounting for this sequence of events. There is growing evidence that early insulin sensitization with metformin, implemented during the critical time of puberty, can modify, prevent or reverse the development of these abnormalities.

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