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Accelerated early pubertal progression, ovarian morphology, and ovarian function in prospectively followed low birth weight (LBW) girls

Abstract

Aim: To compare pubertal development in age-matched healthy girls born with low birth weight (LBW) or appropriate birth weight for gestational age (AGA).

Subjects and methods: Girls with breast in Tanner stage II and normal body mass index were followed for 3 years with a complete physical exam, bone age, pelvic ultrasound, and measurement of gonadal hormones using a leuprolide test.

Results: Forty-one girls (AGA 25/LBW 16) were followed up for 3 years. By 3 years, they had similar bone age, adjusted height, and body composition. In LBW girls, breast Tanner stage advanced faster during the first 2 years of follow-up, which was associated with higher serum androgens. Hirsutism score, ovarian volume, and number of follicles between AGA and LBW were not different nor was age of menarche. By the third year, basal and poststimulated levels of gonadotropins and androgens anti-Müllerian hormone and inhibin B were similar in both groups and did not show differences related to birth weight or degree of catch-up growth.

Conclusion: LBW recruits showed a slightly faster breast development but no differences in androgen excess signs, internal genitalia, and gonadal hormonal patterns.

Keywords: AMH; birth weight; growth; puberty.

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Introduction

Secular trends in earlier timing of puberty, which is one of the most important milestones in life (1), appear to continue. Obesity and intrauterine life appear as possible contributors in this trend. Contemporary data regarding the intrauterine life effect have shown conflicting results due to various methodologies, definitions, follow-up periods, and inclusion criteria.

In girls, some reports have shown that those born with low birth weight (LBW) as a proxy of an adverse intrauterine environment have an increased risk of adrenal and ovarian hyperandrogenism and accelerated puberty with decreased total height (2–9), whereas others have found no effect (10–13).

We have previously reported the clinical characteristics, adrenal and ovarian hormones, and gonadal morphology from a community sample of healthy girls born either with LBW or appropriate for gestational age (AGA) recruited at the beginning of puberty (breast Tanner stage II) (14). We hypothesized that gonadal hormonal patterns were not different at the end of puberty in these girls. Herein, we present the longitudinal follow-up data of these girls.

Subjects and methods

A prospective study was designed recruiting age-matched LBW vs. AGA girls ages between 7 and 12 years during early pubertal development (breast Tanner stage II) (15) invited from community schools.

A complete description of the recruiting process, protocol, consents, and institutional review board approval was described previously (14).

At enrolment, 71 girls (AGA 39/LBW 32) were included, and 41 of these (AGA 25/LBW 16) completed 3 years of follow-up (Figure 1). Girls who completed follow-up were not different in birth weight or anthropometry at recruitment compared with girls who did not complete the longitudinal study. Birth weight was classified as AGA (birth weight between the 10th and the 90th percentiles for gestational age) and LBW (birth weight below the 10th percentile for gestational age) (16).

At baseline and every 6 months for 3 years, after an overnight fast, the subjects underwent a complete physical and pubertal development exam (15, 17). Hirsutism (18) and the presence and severity of acne were determined and registered. Thereafter, between 0800 and 0900 h, the individuals underwent a gonadotropin stimulation test with 500 μg leuprolide acetate injected subcutaneously (19). Blood samples timing, processing, and analysis has been described elsewhere (14, 20). Briefly, we obtained basal samples for luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone sulfate, 17-hydroxyprogesterone (17-OHP), androstendione, anti-Müllerian hormone (AMH), inhibin B, testosterone, estradiol, and sex hormone binding globulin. After 3 h, a new sample for LH and FSH was obtained, and at 24 h, a sample for all the gonadal hormones was obtained. Yearly, a bone age (BA) (21) as well as transabdominal ultrasound was performed (14, 22).

Calculation and statistical analysis

Weights and lengths at birth and at enrolment were converted into standard deviation scores (SDS) using the national reference (at birth) and Centers for Disease Control and Prevention growth reference, shown to be applicable (16, 17).

Weight and height gain during infancy were quantified by the differences between data at enrolment and at birth (change in SDS). Results are expressed as mean±SEM. Data were normalized by log transformation to use parametric statistics. Height adjusted by midparental heights was calculated as follows: (midparental height SDS)-(girl height at the third year of follow-up in SDS).

Continuous variables were evaluated at mean and SDS. Categorical variables, frequencies, and proportions were compared by χ^2-test for independent groups. Dichotomous variables were created for Tanner stage progression and for the Ferriman and Gallway scoring and evaluated by means of a logistic regression model using as a measurement of association the change in monthly odds ratios adjusted by the condition of AGA or LBW. Hormone levels through time and between groups were compared using mixed models; data were analyzed in Stata version 11.0.

Estimated cumulative differences in breast Tanner stage of the two groups were assessed by means of Kaplan-Meier survival analysis followed by a log-rank test. Pearson's correlation coefficients were obtained to evaluate the relationship between age at menarche and age at maternal menarche.

Results

Clinical characteristics of cohort at entry and at 3-year follow-up

LBW girls were lighter and shorter, and on entry into the study, they had achieved a greater growth in weight and height compared with girls born AGA. Chronological age, BA, body mass index (BMI), and height SDS were within normal ranges in all the subjects and were similar between both groups of subjects (Table 1). Data related to the evolution of height, weight, BMI, and BA during the follow-up are shown in Table 2. After 2 and 3 years of follow-up, height was lower in LBW girls. Third-year adjusted height (midparental height), however, was not different. The total height increase in centimeters during the 3 years of puberty was 19±3 in AGA and 17±4 cm in LBW girls (p=NS). At the third year, BA, as well as BA increase, was not different.

Pubertal characteristics

At enrolment, we found no differences in the Tanner stage of pubic hair or the presence of axillary hair/apocrine odor between the groups.

Follow-up

LBW girls showed a slightly faster breast development (Figure 2) at the first 2 years. The subgroup of LBW girls who advanced faster and reached breast Tanner stages IV and V within 6–12 months started with higher ΔBA-CA and advanced their BA faster (χ^2=0.84; p=0.03). These girls did not show differences in their weight gain (SDS) between enrolment and newborn period. We found no differences in the advancement of pubic hair staging or in the percent of acne or hirsutism during follow-up.

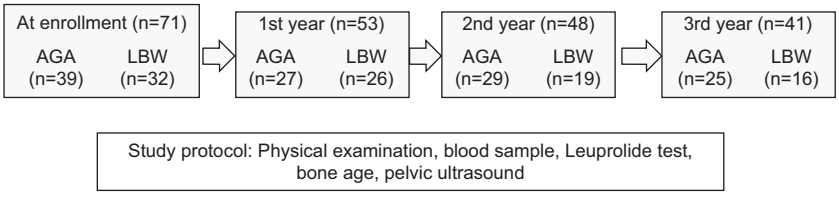

Figure 1 Study protocol and number of study subjects at enrolment and during follow-up.
At enrolment, 71 girls (39 AGA/32 LBW) were recruited. Fifty-three girls (AGA 27/LBW 26) completed 1 year, 48 girls (AGA 29/LBW 19) completed 2 years, and 41 girls (AGA 25/LBW 16) completed 3 years of follow-up.

Table 1 Clinical data of the subjects at birth and magnitude of catch-up growth in weight and height from birth to enrolment (breast Tanner stage II).

	Data at birth	
	AGA	SGA
Gestational age, weeks	38.7±0.2	37.4±0.4[a]
Birth weight (SDS), g	3331±52	2302±99[b]
	0.1±0.1	−2.1±1.1[b]
Birth length (SDS), cm	49.9±0.2	45.7±0.7
	0.3 ±0.1	−1.4±0.2[b]
Magnitude CUG in weight (SDS)	0.02±0.2	1.6±0.3[b]
Magnitude CUG in height SDS	−0.6±0.2	1.22±0.3[b]

	AGA		SGA	
	Enrolment	After 3 years	Enrolment	After 3 years
Chronological age, years	9.5±1.04		10.2±1.1	
BA, years	9.4±0.2	12.6±0.2	10.1±0.2	13.1±0.3
ΔBA at 3 years	3.1		3.2	
Height (SDS)	−0.43±0.2	−0.09±0.2	−0.55±0.28	−0.98±0.28[a]
ΔHeight at 3 years, cm		19±3		17±4[a]
BMI	0.41±0.13	0.36±0.19	0.28±0.16	−0.05±0.27
Midparental height (SDS)	−0.76±0.22		−1.33±0.3	

[a]$p<0.05$ (Mann-Whitney U-test). [b]$p<0.001$ (Mann-Whitney U-test). Data are presented as mean±SEM. Magnitude in catch-up growth means the difference of height SDS or weight SDS between enrolment and the newborn period. LBW, weight <2500 g for 37 weeks. CUG, catch-up growth.

Table 2 Secular trend in weight, height, BMI, and BA during the 3-year follow-up in AGA and LBW girls.

Month	AGA	LBW		
	Mean (SD)	Mean (SD)		
Z-weight				
0	0.07 (0.73)	−0.62 (0.98)		
12	0.13 (0.62)	−0.45 (0.75)	p_{trend} in AGA	<0.05
24	0.18 (0.68)	−0.22 (0.74)	p_{trend} in LBW	NS
36	0.30 (0.65)	−0.42 (0.69)	p for comparison trend between AGA-LBW	<0.01
Z-height				
0	0.04 (0.44)	−0.63 (0.54)		
12	−0.03 (0.44)	−0.69 (0.54)	p_{trend} in AGA	NS
24	−0.10 (0.44)	−0.76 (0.54)	p_{trend} in LBW	<0.05
36	−0.10 (0.64)	−0.93 (0.69)	p for comparison trend between AGA-LBW	<0.01
Z-IMC				
0	0.27 (0.85)	−0.11 (0.82)		
12	0.28 (0.69)	−0.03 (0.64)	p_{trend} in AGA	NS
24	0.23 (0.80)	0.06 (0.65)	p_{trend} in LBW	NS
36	0.35 (0.75)	−0.03 (0.66)	p for comparison trend between AGA-LBW	NS
EO				
0	9.59 (1.00)	9.88 (0.95)		
24	11.56 (1.28)	12.41 (0.96)	p_{trend} in AGA	<0.01
36	12.62 (0.99)	13.13 (1.08)	p_{trend} in LBW	<0.01
			p for comparison trend between AGA-LBW	NS
EO-EC				
0	0.15 (0.80)	−0.19 (0.76)		
24	0.21 (0.90)	0.27 (0.67)	p_{trend} in AGA	NS
36	0.18 (0.88)	0.23 (0.50)	p_{trend} in LBW	<0.05
			p for comparison trend between AGA-LBW	NS

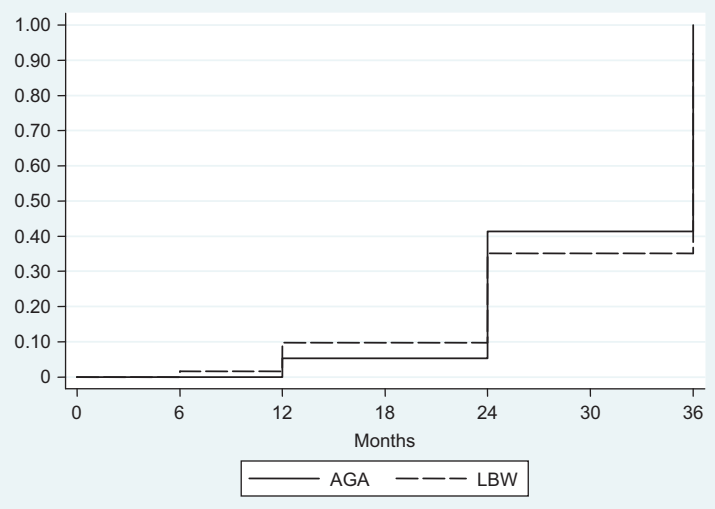

Figure 2 Estimated cumulative incidences in breast Tanner stage of the two groups of girls (AGA/LBW) were assessed by means of Kaplan-Meier survival analysis.
A subgroup of LBW girls advanced faster and reached breast Tanner stages IV and V in 6 to 12 months after entry. They started with higher ΔBA-CA and advanced their BA faster during the first year of follow-up (p=0.03). Breast development after 6 months of follow-up in 55% of AGA and 23% of LBW remained in Tanner stage II. After 1 year of follow-up, 59.3% of AGA and 34.6% of LBW girls remained in Tanner stage II and 40.7% and 57.7% were in Tanner stage III, respectively, whereas 7.7% of LBW and none of the AGA girls were in Tanner stage IV (p<0.05). After 2 years of follow-up, 48.3% of AGA and 35% of LBW girls reached Tanner stage IV and 27.5% vs. 55% breast Tanner stage V, respectively.

Age at menarche

AGA and LBW girls had similar age at menarche (Figure 3) even after adjustment for maternal age at menarche (p=0.067) and rate of progression from B2 to menarche. In addition, we did not find a correlation between age at menarche and BMI or differences in weight gain (SDS) between enrolment and birth.

Ultrasound findings

At enrolment, LBW girls had larger ovarian volume. However, the percent of ovaries with a volume larger than 2 cc was not different (62.8% vs. 66.6%). During the second year, LBW girls had a higher number of follicles (10.8±5.7 vs. 13.9±4.1; p=0.03). By the third year, however, no differences in internal genitalia were observed.

Hormonal assays

Although these hormones were obtained every 6 months, we analyzed the annual data to obtain more consistent findings.

At enrolment, LBW girls showed higher basal estradiol level (p<0.01), stimulated estradiol (p<0.01, p<0.05), and LH 3 h after test (p<0.05; Table 3).

At follow-up, during the first year, LBW girls had higher levels of basal LH, FSH, and androstenedione and stimulated LH, estradiol, and 17-OHP.

During the second year, LBW girls had higher levels of basal LH, estradiol, and dehydroepiandrosterone sulfate and poststimulated LH levels. However, neither FSH nor androgens were associated with a rapid progression of puberty. In addition, a stimulated 17-OHP level >1.6 ng/mL was found in 12.5% of AGA and 30% of LBW at enrolment and 41.6% of AGA and 75% of LBW girls at the third year (p<0.05). AMH levels were higher in LBW girls only at recruitment and correlated with their ovarian volume (r=2.5; p<0.05) and follicle number (r=1.28; p<0.01) at recruitment and at the third year (r=1.1; p<0.01). Thereafter, no differences in AMH levels were observed. Inhibin B levels were similar during all the study periods between groups.

After 3 years of follow-up, no differences in adrenal or ovarian hormonal levels were found in these girls (Table 3).

Discussion

Herein, we report on the longitudinal data on clinical, gonadal function, and ultrasonographic findings of internal genitalia obtained during the first 3 years of puberty in a cohort of healthy, lean, age-matched girls born either LBW or AGA recruited from the community. LBW girls

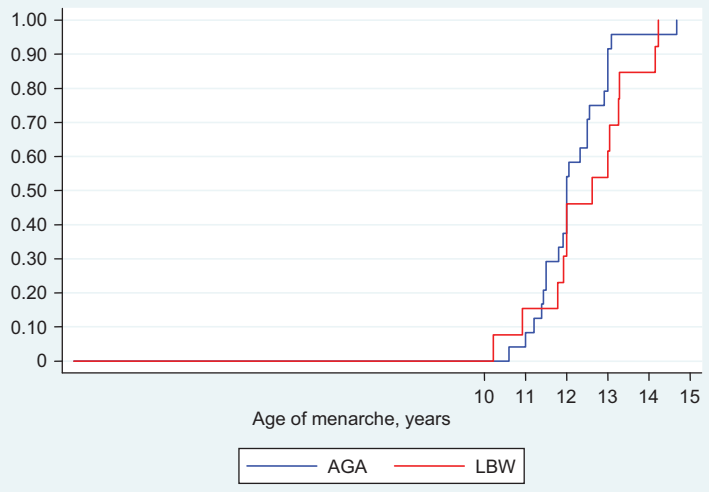

Figure 3 Estimated cumulative incidences of menarche of the two groups of girls (AGA/LBW) were assessed by means of Kaplan-Meier survival analysis.
The mean age at menarche was 12.1±0.8 years (AGA) vs. 12.4±0.1.1 years (LBW). Log-rank test for equality of survivor functions (p=0.2).

showed quicker tempo of breast development and lower height gain, which was not explained by a higher BMI. Interestingly, this faster initial tempo of breast development and BA progression was not accompanied by a difference in age at menarche.

In addition, we did not find clinical evidences of hyperandrogenism in the LBW girls in agreement with Jaquet and Boonstra (8, 9). However, during the first and second years, they had higher serum androgens, which suggest a faster maturation of the reticularis adrenal zone and hypothalamic-pituitary-gonadal axis.

A rapid weight gain in infancy is a risk factor for cardiometabolic risk, earlier secondary sexual maturation, and adrenal and ovarian hyperandrogenism (23–28). The latter (28) appears mediated through increases in insulin and LH and appears to be reversible when decreasing weight (29). In this regard, the ovarian 17-OHP hyperresponse to gonadotropin-releasing hormone-α challenge has been proposed as a good indicator of ovarian hyperandrogenism (19). In this cohort, we did not find this association, suggesting that this ovarian response appears to be part of the maturational process of the hypothalamic-pituitary-ovarian axis characterized by a transient period of mild hyperandrogenism (30). AMH and inhibin B are accurate markers of the ovarian early antral follicle number and maturity process (31). In women with polycystic ovary syndrome, higher levels of serum AMH have been observed (31, 32).

LBW girls had higher levels of AMH only at recruitment, which is in agreement with a recent report (33). Therefore, birth weight at this range is not likely to have an effect in the ovarian follicle pool.

In our observational study, we found no differences in age at menarche, which was similar to their mothers, and in adult height. In a longitudinal study from India, menarche occurred earlier in the preterm and small for gestational age (SGA) girls (34). Similar results were communicated by Ghirri et al. (24) and Ibáñez (6, 35) and by the Raine cohort (26). Other groups, however, have not found such associations (10, 11). Because we did not find any differences in AGA and LBW girls in these parameters, we question whether the proposed anticipatory pharmacologic treatment of LBW girls is needed (36).

Ibáñez et al. (37) reported a reduced size of internal genitalia in LBW. In our cohort, at the beginning of puberty, we found mild differences, which did not persist.

The main limitations of our study are inherent to a longitudinal study of a small sample. These girls were recruited from the community and had no complaints or worries about their pubertal development; thus, some of our initial recruits dropped out. However, this does not bias our conclusions because comparisons of clinical characteristics at recruitment of the larger initial cohort with those who finished the follow-up did not show differences. Second, although we recruited girls in breast Tanner stage II, we do not know if they were at the beginning or at the end of Tanner stage II. This latter issue could have potential important implications on baseline hormonal concentrations and gonadal morphology but not on their rate of progression. Third, we chose to study similar BMI as inclusion criteria to exclude the known effect of obesity in androgen secretion (28–30) and we think that

Table 3 Hormonal assessment at enrolment and during the 3-year follow-up in girls AGA and LBW.

Year	LBW					AGA				
Hormone	**0**	**1**	**2**	**3**	**p-Value**	**0**	**1**	**2**	**3**	**p-Value**
LH-b, mIU/mL	0.8±0.8	2.6±1.7[a]	3.6±2.5[b]	4.6±3.7	0.00	0.6±0.7	1.1±0.8	2.4±1.6	5.2±4.0	0.00
LH-3, mIU/mL	15.1±16.0[b]	48.4±32.4[b]	140.2±129.8[a]	137.1±172.0	0.00	9.2±10.5	23.4±19.8	63.4±53.1	182.6±165.7	0.00
FSH-b, mIU/mL	2.9±1.8	6.3±2.6[b]	4.8±2.2	5.6±2.0	0.00	3.0±1.4	4.9±2.0	5.5±2.2	6.5±2.1	0.00
FSH-3, mIU/mL	17.4±6.1	24.1±10.4	23.2±10.3	24.9±10.2	0.00	18.9±6.6	21.5±6.9	23.9±10.9	35.8±18.0	0.00
Estradiol-b, pg/mL	33.8±18.1[a]	74.2±20.6	64.7±28.8[b]	69.7±60.1	0.00	23.1±13.2	65.6±30.2	50.4±20.3	99.1±53.0	0.00
Estradiol-24, pg/mL	138.3±85.0[a]	279.4±96.8[b]	219.4±146.5	231.5±96.4	0.00	91.1±66.2	212.0±107.0	217.8±105.6	244.5±87.4	0.00
Testosterone-b, ng/mL	0.3±0.2	0.5±0.2	0.5±0.2	0.4±0.1	NS	0.4±0.2	0.5±0.2	0.4±0.2	0.4±0.2	NS
Testosterone-24, ng/mL	0.4±0.1	0.7±0.4	0.5±0.3	0.5±0.1	0.02	0.5±0.3[b]	0.5±0.3	0.6±0.2	0.6±0.2	0.02
17-OHP-b, ng/mL	0.9±0.4	1.4±0.6	1.4±0.5	1.3±0.6	0.00	0.8±0.4	1.4±0.6	1.1±0.6	1.2±0.7	0.00
17-OHP-24, ng/mL	1.3±0.5	2.7±1.2[b]	2.7±1.6	2.4±1.0	0.00	1.2±1.2	1.9±1.4	1.9±1.4	2.8±1.5	0.00
Androstenedione, ng/mL	0.8±0.4	1.3±0.6[a]	1.4±0.6	1.5±0.6	0.00	0.9±0.3	0.9±0.4	1.1±0.4	1.5±0.7	0.00
DHEA-S, ng/mL	607.3±328.5	907.4±414.3	1014.1±460.1[b]		0.00	516.7±340.9	734.2±384.9	760.9±425.3		0.00
SHBG, nM	49.3±19.1	54.9±17.5	44.6±15.1	49.9±15.7	NS	49.4±15.1	60.1±23.4	49.7±23.5	45.9±15.7	NS
FAI	2.9±1.8	4.2±2.6	4.7±3.4	3.0±1.8	0.00	3.3±2.0	3.7±4.1	4.5±4.3	4.0±3.9	0.00
AMH, pM	27.8±17.9[b]	20.5±14.7	19.6±13.7	14.8±12.7	0.00	19.8±11.7	18.0±11.2	15.5±9.4	12.8±11.3	0.00
Inhibin B, pg/mL	75.0±49.1		80.4±47.5	36.5±22.2	NS	70.1±62.1		87.8±46.2	45.8±20.5	NS

[a]$p<0.01$; [b]$p<0.05$, comparisons between LBW and AGA at the same time (t-test). p-Value in columns 6 and 11 evaluated the secular trend within each group of girls (either LBW or AGA) across the study and p-value at the end the secular trend between LBW and AGA. Data presented as mean±SEM. LH-b, basal LH; LH-3, LH 3 h after leuprolide test; FSH-b, basal FSH; FSH-3 FSH 3 h after leuprolide test; estradiol-b, basal estradiol; estradiol-24, estradiol at 24 h after leuprolide test; 17-OHP-b, basal 17-hydroxyprogesterone levels; 17-OHP-24, 17-hydroxyprogesterone levels 24 h after leuprolide test; DHEA-S, dehydroepiandrosterone sulfate; FAI, free androgens index; SHBG, sex hormone binding globulin.

the effect of intrauterine environment perhaps is overweighed by the peripubertal adiposity.

In conclusion, in our unselected LBW girls, we found a slightly faster breast development but no persistent differences in internal genitalia and hormonal patterns. We are continuing to follow these girls to detect whether other differences develop late.

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