Puberty is one of the most important milestones in life. It not only represents the step into maturity, but also involves important body and physiological changes. There is increasing evidence for a link between prenatal growth and pubertal development, but the data concerning the timing, duration and progression of puberty in these children are scarce and the results are difficult to compare due to the various methodologies employed. In girls most studies document a relationship between intrauterine growth retardation and earlier pubertal development or normal timed puberty but with rapid progression. This review attempts to discuss the factors that could influence pubertal development in girls born small for gestational age and the information reported to date.

KEY WORDS
small for gestational age, puberty, adrenarche, menarche, pubarche

INTRODUCTION
Puberty is one of the most important milestones in life. It not only represents the step into maturity, but also involves important body and physiological changes\(^1\).

The adaptation of the fetus to conditions of undernutrition in utero involves a gene-environment interaction called fetal programming. The most exciting thought in fetal programming is that the intrauterine environment may modify gene expression permanently. A heritable change in gene expression without a change in DNA sequence is called epigenetic. The adaptation of the fetus to conditions of undernutrition in utero involves alterations of endocrine set-points of the insulin, insulin-like growth factor (IGF), and growth hormone (GH) pathways, and probably also the pituitary-gonadal axis.

Restricted prenatal growth may thus be followed by a permanent reset of endocrine axes that co-determine pubertal development, but studies concerning the timing, duration, and progression of puberty in children born small for gestational age (SGA) are scarce, and the results are difficult to compare due to various methodologies, definitions, follow-up periods, and inclusion criteria, implying still limited data concerning the effects of being SGA on pubertal development\(^2-5\).

There are some studies in animals that have correlated intrauterine growth retardation (IUGR) and changes in pubertal timing\(^6-11\). In addition, a number of studies in humans show a secular trend in the onset of puberty, towards earlier pubertal development with earlier menarche in girls in the United States\(^12\), Asia\(^13\) and The Netherlands\(^14\), with stabilization over the last decades. Most of these reports are in association with environmental changes and improvement of socio-economic standards. These data are important to dissect the effects of being born SGA from secular trends.
The aim of this review is to discuss the literature about factors that could influence pubertal development in girls born SGA and the information reported to date.

**ANIMAL STUDIES**

It is well established that malnutrition during critical periods in early life has implications for further development15-17. In two rat models with growth failure, either IUGR or postnatal food restriction (FR) show persistent postnatal growth failure. At the onset of puberty, IUGR and FR rats had a lower body weight compared to controls, indicating that no threshold for body weight is needed for the onset of puberty. In female rats with IUGR, puberty was delayed, and at vaginal opening, first cycle and 6 months of life the ovaries showed a decline in the number of follicles. In contrast, FR rats had normal pubertal timing. These data indicate that early malnutrition during different critical developmental time windows may result in different long-lasting effects on pubertal development in rats6.

In lambs there is evidence that maternal undernutrition may modify the time of onset of puberty10,11. In one study using a pregnant sheep model, prenatal growth restriction was not detrimental to the onset of puberty (defined as first ovulation) when female lambs were fed ad libitum after birth18. In contrast, severe maintenance of low weight resulted in a delay or even failure to reach puberty10,19.

**EPIDEMIOLOGICAL STUDIES**

**Onset and development of puberty**

Variations in pubertal timing and progression in the SGA child, as in the rest of the population, are likely to be related to many factors, including ethnicity, genetic background, nutrition and other unknown factors.

Epidemiological studies have been performed in different populations in Europe with emphasis on the height attained after puberty in girls and boys born SGA. After adjustment for target height, however, a significant deficit in final height was found in those who were born SGA (men: -4.50 cm, women: -3.94 cm)20.

Although short, SGA children also start puberty at a normal age; most of the time the age is relatively early for their actual height5. Lazar et al. in Israel5 and Vicens-Calvet et al. in Spain3 reported that children born SGA who were persistently short had a normal pubertal course with a distinct pubertal growth pattern, compromising final height when compared with their target height. Studies on bone age (BA) in children born SGA reported that BA is a poor predictor of pubertal timing and of adult height. Thus, its assessment is not recommended during routine follow-up22.

The addition of GH therapy at different doses (1 or 2 mg/m²/d) and different regimens does not change the age at onset and progression of puberty in children born SGA compared with normal-statured appropriate for gestational age (AGA) children. Thus GH use and dose does not seem to substantially modulate the duration of puberty23,24. Furthermore, a rapid weight gain in infancy has been shown to predict earlier secondary maturation25,26.

**ADRENAL AND GONADAL FUNCTION IN GIRLS BORN SGA**

Over the last decades growing evidence has been documented in girls on the relationship between IUGR and earlier pubertal development or normal timed puberty but with rapid progression. In addition, morphological changes in the uterus and the ovarian size of these girls have been reported with an increased risk of the development of a pattern of ovarian function resembling polycystic ovary syndrome associated with subsequent fertility problems and other metabolic diseases. Importantly, these observations were made in a selected population27,28.

**Pubarche**

Pubarche is defined by the appearance of sexual pubic hair and is considered normal when it occurs after the age of 8 years in girls. Adrenarche is the process in which the reticularis zone of the adrenal
gland matures and increases the secretion of sex steroids (dehydroepiandrosterone [DHEA]/DHEA sulfate [DHEAS]), and is manifest by the development of axillary hair, axillary odor and pubarche.

In girls the development of precocious pubarche and early and exaggerated adrenal androgen secretion before puberty has been linked with the history of being born with low birth weight. A study of Catalanian girls (n = 102) between 5 to 18 years with precocious pubarche secondary to exaggerated adrenarche (elevated androstenedione and DHEAS levels), compared with 80 short statured girls, found a relationship between a history of precocious pubarche during childhood and low birth weight SDS, particularly in those girls who subsequently developed idiopathic functional ovarian hyperandrogenism. Most of these studies, however, are retrospective and are biased by recruiting girls with precocious pubarche, not girls born SGA. Ong et al. reported from the ALSPAC cohort that a continuous inverse relationship exists between birth weight and DHEAS levels through the range of birth weights. Small infants who gained weight rapidly during early childhood had the highest levels of adrenal androgen at age 8 years.

In a retrospective Australian study of 89 children (79 girls) with precocious pubarche, 65% were overweight/obese at diagnosis, and 35% had a history of SGA and 24% of prematurity. In this study both prematurity and SGA were associated with precocious pubarche, as was overweight/obesity, irrespective of size or gestational age at birth. Thus, excess weight gain in childhood may predispose to precocious pubarche in susceptible individuals. Along this line, Ong et al. reported the long-term risk for central obesity and insulin resistance in low birth weight infants who developed rapid weight gain between birth and 2 years. These SGA children showed a dramatic transition towards central adiposity and insulin resistance between the ages of 2 and 4 years. Insulin resistance may increase adrenal androgen secretion and free IGF-I which also increases adrenal androgen secretion. Oberfield et al., evaluating the relationship between premature adrenarche and insulin sensitivity and metabolic risk in both girls and boys, found in both groups an increase in total and free IGF-I and higher levels of triglycerides, especially in obese children with premature adrenarche not attributable to differences in body mass index (BMI) or BMI z-score, suggesting that obese children with premature adrenarche may be a higher risk group. These authors suggest that boys and girls with premature adrenarche should be monitored for the development of insulin resistance and associated complications. These findings have not been reported by other authors.

Ibañez et al. have suggested that treatment of normal weight girls with a history of precocious pubarche and low birth weight with an insulin sensitizer may preclude the development of associated metabolic abnormalities and ovarian hyperandrogenism. These findings have not been confirmed by other groups.

Recently we published the preliminary results from a sample of lean, healthy girls, studied at the age of puberty, recruited from the community, born either SGA or AGA; no differences in the presence of pubic hair, axillary hair, or apocrine odor were found. Androgen levels were within the normal range and the two groups of girls did not show differences in the levels of DHEAS. SGA girls of this cohort had higher leptin levels and insulinogenic index at the beginning of puberty - both may be early indicators of an underlying subtle degree of insulin resistance - despite similar BMI and body composition compared to AGA girls. In another Chilean survey of 139 girls with precocious pubarche, only 8.6% had been born SGA, which corresponds to the expected number in the cohort when using the 10th percentile of birth weight as the cut off. In a Chilean cohort of term SGA children who have been followed from birth until 5 years of age, no differences in the levels of DHEAS were found.

Probably the relationship between the levels of androgens and exaggerated adrenarche/premature pubarche may be related to the prevalence of predisposing genetic variants of insulin and androgen sensitivity and infancy weight gain during
childhood more than the characteristic of being SGA.

**Menarche**

In most developed countries, when the onset of puberty is within the normal age range, menarche usually occurs 2 years after thelarche, between 12 and 13 years of age. Age at menarche is known to be regulated by factors surrounding the time of puberty and is the first indicator of reproductive capacity in women.

Girls with normal birth weight tend to have normal timing of menarche and normal adult height.

In a longitudinal follow-up from an urban Indian cohort evaluating the effect of prematurity and fetal growth retardation in 79 preterm AGA and 45 term SGA children, compared to controls, menarche occurred 6 months earlier in preterms and 12 months earlier in SGA girls. Similar results were communicated by Ghirri et al. in 38 girls (19 SGA and 19 AGA) evaluated after menarche (17.5-18.5 years); SGA girls had a slightly anticipated puberty (9.9 vs 10.4 years for initial breast development) and a lower age at menarche (11.9 vs 12.3 years).

In Spain, Ibáñez et al. reported in 187 girls with precocious pubarche a lower age of menarche when these girls were compared with the general population. Lower birth weight was an additional contribution to lower age of menarche by 8-10 months. The same group reported that if these girls experienced rapid catch-up growth with hyperinsulinemia, menarche could be even earlier. In a longitudinal assessment from Catalanian girls with early onset of puberty (breast development between 8 and 9 years), menarche occurred on average 1.6 years earlier in low birth weight (n = 12, <1.5 SD) girls and final height was 5 cm shorter than in girls whose birth weight was greater than -1.5 SD. The authors reported that treatment with metformin could delay menarche and enhance pubertal height gain.

Lazar et al. in a cohort of 45 SGA compared with 31 AGA girls found that most of the SGA girls attained puberty at normal age, and menarche occurred at normal age, although significantly earlier in the SGA group (12.6 ± 1.6 vs 13 ± 1.4 years, p = 0.01).

In a prospective cohort of 776 girls followed from fetal life to adolescence (12-14 years) in West Australia, 349 of them had reached menarche, 10.5% were growth restricted at birth. The earliest age at menarche was seen in girls with the lowest birth weight and the highest BMI at age 12.5 years (range 9.4-14.4 years). In this prospective cohort they demonstrated that birth weight and weight gain in childhood were both associated and have opposing influences on the timing of menarche.

In a Swedish follow up from birth until 16 years of age of children born from singleton pregnancies, prematurely born children (SGA and AGA) behaved similarly to AGA children born at term in terms of pubertal timing, but SGA girls started both puberty and menarche 5 months earlier than AGA girls.

In contrast to the previous data, however, several other groups, such as the Haguenau cohort in France, The Netherlands, and a Swedish cohort, have not been able to show earlier age of menarche in SGA girls. In a French population-based study (the Haguenau cohort) of 236 full-term girls born SGA (birth length or weight <3rd percentile) and 281 girls with normal birth weight (between 25th and 75th percentiles), no significant differences were found in mean ± SD age at menarche between the two groups (12.6 ± 1.6 vs 12.9 ± 1.7 years). After adjustment for target height, however, a significant deficit in final height was found in those who were born SGA (men: -4.50 cm; women: -3.94 cm).

In the ALSPAC cohort an earlier mother’s age at menarche predicted rapid infant growth and childhood obesity. Thus menarche may be a trans-generational marker of a faster growth tempo, characterized by rapid weight gain and growth, particularly during infancy, and leading to taller childhood stature, but likely earlier maturation and therefore shorter adult stature. This growth pattern may confer increased childhood and adult obesity risks.

In the Chilean cohort most of the girls have not yet reached menarche; therefore, we have no definitive conclusion regarding this fact.
**Internal genitalia and hormonal profile**

Reduced prenatal growth has been associated with follicle stimulating hormone (FSH) hypersecretion and reduced size of internal genitalia without changes in morphology. Ibáñez et al. evaluated the levels of FSH, inhibin-B, luteinizing hormone (LH), estradiol and free androgen index in a group of 46 (3-6 months) girls, ten born AGA and 16 born SGA. They found two-fold higher levels of FSH in SGA girls compared with the AGA girls, and no statistical differences in the other parameters analyzed\(^5\). The same group evaluated healthy post-menarcheal adolescents (33 born AGA, 15 SGA) and found elevated serum levels of FSH (7.2 ± 0.7 in SGA vs 4.5 ± 0.3 mIU/ml in AGA) and lower estradiol concentrations with no difference in inhibin-B levels between the two groups\(^28,54\). They postulated ‘gonadal resistance’ to gonadotropin as a fetal programming effect.

In the Chilean cohort (a sample recruited from the community) at the beginning of puberty we observed slight hormonal differences between the groups of girls. SGA girls had increased baseline estradiol and anti-Müllerian hormone levels, and after a gonadotropin releasing hormone (GnRH) stimulation test (24 hours), estradiol and 17OH-progesterone were higher in low birth weight girls, whereas FSH, LH, testosterone, inhibin-B and free androgen index were similar in both groups. We did not find differences in uterine or ovarian size in the ultrasound assessment of these girls\(^38\). After 2 years of following these girls they show similar characteristics in their internal genitalia although in SGA girls there was a tendency towards a higher number of follicles (p = 0.08). In addition, low birth weight girls had higher baseline 17OH-progesterone (1.41 ± 0.1 vs 1.13 ± 0.2 ng/ml, p <0.05) and estradiol (80.6 ± 9.7 vs 57.3 ± 4.2 pg/ml, p <0.05), and post-GnRH 24-h LH (187.6 ± 50.5 vs 79.6 ± 15 mIU/ml, p <0.05), and lower baseline FSH levels (4.6 ± 0.4 vs 6.1 ± 0.5 mIU/ml, p <0.05). No other gonadal or adrenal hormonal differences were detected in this preliminary sample of low birth weight compared to AGA girls. In conclusion, these results suggest that low birth weight girls display a different gonadotropin pattern with higher LH/FSH ratio and higher estradiol and 17OH-progesterone compared to AGA girls. These differences may allow a faster transition through puberty and an androgenic gonadal steroid pattern later\(^5\).

To date, there are not enough data to support ovarian dysfunction, reduced fertility or early menopause in girls born SGA\(^56\).

**SUMMARY**

Puberty is one of the most important milestones in life. It not only represents the step into maturity, but also involves important body and physiological changes. Restricted prenatal growth may be followed by a permanent reset of endocrine axes that co-determine pubertal development.

There are some studies in animals that have correlated IUGR and changes in pubertal timing. In addition, a number of studies in humans demonstrate a secular trend in the onset of puberty, towards earlier pubertal development with earlier menarche. Rapid weight gain in infancy has been shown to predict earlier secondary maturation.

Most frequently studies in boys born SGA show normal pubertal timing, reaching an adult height often below the target height.

In girls some studies have suggested the transition from low birth weight to normal or increased weight during childhood is commonly associated with the development of precocious pubarche, exaggerated adrenarche, early menarche and an increased risk for subsequent polycystic ovary syndrome and hyperinsulinemia, but these findings have not been confirmed by other groups. To date there are not enough data to support ovarian dysfunction, reduced fertility or early menopause in girls born SGA.

**Key points**

1. It is well established that malnutrition during critical periods in early life has implications for future development.

2. Rapid weight gain in infancy has been shown to predict earlier secondary maturation and this is more frequent in infants born SGA.
3. Children with rapid weight gain and precocious pubarche should be monitored for the development of insulin resistance and associated complications.

4. Although short SGA children usually start puberty at a normal age, most of the time the age is relatively early for their actual height and final height is affected when compared with their target height.

5. Evidence has suggested that the onset of puberty and menarche may be linked to intrauterine and postnatal growth patterns.

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