Impact of being born small for gestational age on onset and progression of puberty

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Children born small for gestational age (SGA) are at higher risk for perinatal morbidity, mortality and chronic diseases in later life. There is increasing evidence for a link between prenatal growth and pubertal development, but studies 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. Most boys born SGA have normal pubertal timing, but often attain an adult height below the target height. In girls, most studies document a relationship between intra-uterine growth retardation and earlier pubertal development or normal timing but with rapid progression. This chapter will discuss the factors that could influence pubertal development in children born SGA and the information reported to date.

Key words: small for gestational age; puberty; adrenarche; menarche; pubarche.

Children born small for gestational age (SGA) are at higher risk for perinatal morbidity, mortality and a number of chronic diseases in later life.1,2 The accepted hypothesis explaining the development of these long-term alterations relates to an adaptive response to intra-uterine malnutrition called ‘developmental origins’. This hypothesis includes the additional contribution of growth patterns and environmental factors in infancy and childhood.3,4 The adaptation of the fetus to conditions of undernutrition in utero involves an alteration in endocrine setpoints for insulin, insulin-like growth factor and growth hormone (GH) pathways, and probably also in the pituitary–gonadal axis.

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.5 Restricted prenatal growth may be followed by a permanent resetting of endocrine

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axes that co-determine pubertal development. However, studies concerning the timing, duration and progression of puberty in children born SGA are remarkably scarce, and the results are difficult to compare due to various methodologies, definitions, follow-up periods and inclusion criteria; as such, data concerning the effects of being SGA are still limited.6–9 Some animal studies have correlated intra-uterine growth retardation (IUGR) and changes in pubertal time, especially in female rats and lambs.10–15

In addition, a number of human studies have demonstrated a secular trend in the onset of puberty towards earlier pubertal development with earlier menarche in girls in the USA16, Asia17 and The Netherlands18 with stabilization over recent decades, generally in association with environmental changes and improved socio-economic standards. These data are important to separate the effects of being born SGA from secular trends. This chapter will discuss the factors that could influence pubertal development in children born SGA and the information reported to date.

ANIMAL STUDIES

In animals, as in humans, the onset of puberty occurs though interactions between the neuroendocrine and reproductive axes. Results of animal studies indicate that postnatal reproductive ability may be largely determined by appropriate development of the hypothalamic–pituitary–gonadal axis during fetal life.19

It is well established that malnutrition during critical periods in early life has implications for further development.20–22 Studies evaluating puberty in animals have shown that IUGR results in delayed onset of puberty in female rats. In contrast, postnatal food restriction leads to onset of puberty at the same age as controls. In males, both models showed delayed onset of puberty, as well as impaired testicular function demonstrated by decreased testosterone levels.10

These data indicate that early malnutrition during different critical developmental time windows may result in different long-lasting effects on pubertal development in rats.10–13

In lambs, there is evidence that maternal undernutrition may modify the time of onset of puberty. In lamb models (10–45 weeks)14, prolonged undernutrition after weaning prevented the initiation of reproductive activation at a normal age.15

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 birth.23 In contrast, severe maintenance of a low weight resulted in a delay or even failure to reach puberty.14,24 In contrast, in male lambs, prenatal growth restriction was followed by delayed onset and magnitude of sexual development, indicating that nutritionally induced fetal growth restriction had a significant impact on the onset of puberty.23

EPIDEMIOLOGICAL STUDIES

Onset and development of puberty

Variations in pubertal timing and progression in children born SGA, 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 from Europe with emphasis on the height attained after puberty in girls and boys born SGA.
In a Swedish follow-up study of singleton pregnancies from birth until 16 years of age, prematurely born children [SGA and appropriate for gestational age (AGA)] behaved similarly to children born AGA at term in terms of pubertal timing. SGA term boys started puberty at a mean age of 12.1 ± 1.1 years, similar to those born AGA. SGA girls, however, started pubertal and menarche 5 months earlier than AGA girls. In terms of onset of puberty, the effect appeared to be sexually dimorphic, but boys and girls born SGA (birth weight or birth length < 2 standard deviations (SD)) were 4 cm shorter at the onset of puberty. In another Swedish population-based study (n = 3650), where 3% (n = 111) were born SGA by weight (<2 SD), 3.9% (n = 141) were born SGA by length (<2 SD) and 1.5% (n = 54) were born SGA by both weight and length, children who showed full catch-up growth in height attained puberty at a normal age with a mean adult height of −0.7 SD. The children who remained short started puberty at a relatively ‘early age’ but no exact data were provided. In a French population-based study (the Haguenau cohort) of 236 full-term SGA subjects (birth length or birth weight below the third percentile) and 281 subjects 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). However, after adjustment for target height, a significant deficit in final height was found in those who were born SGA (men −4.5 cm, women −3.94 cm).

Pubertal development in boys born SGA has been reported and the results are somewhat controversial. The majority of studies report an interaction between IUGR and postnatal growth rate. Rapid weight gain in infancy has been shown to predict earlier secondary sexual maturation. However, most studies in boys born SGA report normal pubertal timing, but attainment of an adult height that is below the target height. Only a few studies have reported delayed pubertal onset in children born SGA compared with controls. In some of these studies, boys exhibited little catch-up growth in length during puberty and thus these studies may be biased.

Although short SGA children also start puberty at a normal age, the age is usually relatively early for their actual height. Lazar et al in Israel and Vincens-Calvet et al in Spain 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 the target height. Studies of bone age in children born SGA reported that bone age was a poor predictor of pubertal timing and adult height. Thus, its assessment is not recommended during routine follow-up.

The addition of GH therapy with different doses (1 or 2 mg/m²/day) and different regimens does not change the age at onset and progression of puberty in children born SGA compared with normal-stature AGA children. Thus, the use and dose of GH does not seem to modulate the duration of puberty substantially.

A longitudinal analysis comparing the pubertal course of persistently short children born SGA (45 girls) with idiopathic short stature AGA subjects (30 girls) showed that puberty was attained at normal age in girls (77 vs 78% in SGA and AGA, respectively). However, the prevalence of early puberty in SGA girls was higher (20% vs 3%) than in the AGA group. This may be attributed to rapid weight gain during infancy, which is a risk factor for future obesity and also predicts earlier secondary sexual maturation.

A multiple regression analysis showed that the only prepubertal predictor of age at onset of puberty was birth weight SD score. Analysis of the auxological data at onset of puberty showed that bone age of the girls in the SGA group was significantly more advanced than in the AGA girls. However, the progression of bone maturation was faster in the SGA subjects (girls and boys) compared with the AGA subjects;
therefore, final height was compromised in the SGA subjects. The duration of puberty was similar in the SGA and AGA groups.\textsuperscript{7}

**PUBERTY IN SGA CHILDREN**

**Boys**

The majority of studies exploring the association between low birth weight (LBW) and the pituitary–gonadal axis have focused on female reproductive function. Information on the influence of fetal growth on male gonadal function is remarkably scarce, and most studies have focused on the relationship between LBW and testis dysgenesis syndrome that is hypothesized to have a fetal origin.\textsuperscript{36,37} An adverse effect of toxic or environmental agents (such as oestrogens) on the developing fetal reproductive system is suspected.\textsuperscript{38,39} Testis dysgenesis syndrome comprises cryptorchidism\textsuperscript{40,41}, hypospadias\textsuperscript{40–42}, and testicular cancer in adult life.\textsuperscript{43} An increased risk of infertility or poor semen quality, especially with maternal smoking, has been reported by some studies but not confirmed by others.\textsuperscript{44–47}

**Hypospadias**

Hypospadias is one of the most common congenital anomalies recognized at birth, with an estimated prevalence of 1–2 per 1000 live male births.\textsuperscript{48} The aetiology of hypospadias remains unknown, with environmental exposure in the form of endocrine disruptors being the most likely explanation for the worldwide increase in incidence in the last three decades.\textsuperscript{47,49} There is a significant association between hypospadias and IUGR. A 13-year retrospective review in two neonatal intensive care units in Connecticut showed that 112 (1.66\%) of 6746 male infants had hypospadias of any degree (incidence increased 10-fold during the 13-year period of study), and the anomaly was three times more common in IUGR infants (\textless 10th percentiles in growth, length and cranial circumference).\textsuperscript{50} In the ALSPAC cohort (Avon Longitudinal Study of Parents and Children) in England in a sample of 7928 boys, there were 51 cases of hypospadias, and the anomaly was four times more common in boys whose birth weight was below 2500 g compared with those with a higher birth weight.\textsuperscript{51} In a study of discordant twin pairs, the twin with the lowest weight had hypospadias in 16 of the 18 pairs (mean difference in birth weight 498 g).\textsuperscript{52}

**Cryptorchidism**

Cryptorchidism is also a common congenital anomaly in males. The reported prevalence in term and/or normal-weight boys at birth varies between 2\% and 8\% in recent prospective studies\textsuperscript{53}, and LBW for gestational age is a recognized association.\textsuperscript{54} In a prospective cohort study performed in Denmark and Finland studying semen quality and testicular cancer rate, the prevalence of cryptorchidism was 9.0\% and 2.4\%, respectively. The striking difference in the prevalence of congenital cryptorchidism between the two Nordic countries was unexplained. In both countries, LBW and prematurity increased the risk of this condition.\textsuperscript{55}

Prematurity and being born SGA may affect the pattern of testosterone secretion during the first 3 months of life. Levels of testosterone in boys born SGA and premature are not lower than in AGA children, but the postnatal surge is sustained for a longer period, being longest in the premature group. A major obstacle to the
interpretation of these results is the higher incidence of cryptorchidism in boys born SGA. Perhaps intra-uterine levels of testosterone are inadequate, thus decreasing complete masculinization of the external genitalia.56

Body composition and hormone levels

A study performed in a clinic setting in Barcelona, Spain showed that adrenarche is exaggerated in girls born LBW with greater weight gain until 8 years of age. In these studies, the evidence suggests that early exaggerated adrenal androgen secretion may manifest as premature pubarche.57

Ekelund et al and Ibáñez et al reported the long-term risk for central obesity and insulin resistance in LBW subjects who exhibit catch-up weight gain between birth and 2 years. These SGA children showed a dramatic transition towards central adiposity and insulin resistance between 2 and 4 years of age.29,30 Insulin resistance may increase adrenal androgen secretion. In the large ALSPAC cohort, dehydroepiandrosterone sulphate (DHEAS) levels were increased in subjects born with lower weight and higher body mass index (BMI) at 8 years of age.57

In accordance with these results, Veening et al found that prepubertal SGA children (girls and boys) had higher DHEAS levels than AGA children.8 In contrast, Boonstra et al reported normal serum levels of DHEAS in prepubertal short boys born SGA and AGA. They did not find differences between the groups when they were matched by age, none of the 91 boys studied developed precocious pubarche, and no effect of GH treatment on DHEAS levels was demonstrated.58

LBW has been associated with higher levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), lower levels of inhibin-B and testosterone, smaller testicular volume in adolescence, and subfertility.59,60 During the minipuberty period in infancy, increased FSH secretion has also been reported.61

Interestingly, Jensen at al recently published their results from the follow-up of a prospective study in 52 adolescents born SGA compared with adolescents born AGA. The investigators did not find statistically significant differences in levels of testosterone, inhibin-B or LH/testosterone levels between the AGA and SGA groups. In addition, there were no differences in overnight secretory patterns of gonadotropins or testicular size or morphology. This study suggests that testicular function is not impaired in adolescent males born SGA.62

There is less direct evidence for an association between impaired adult reproductive function and LBW. Results from the earliest studies suggested a relationship between LBW and testicular function, but these studies were performed in boys with congenital syndromes.63,64 Furthermore, men with reduced fertility are often recruited from fertility clinics and matched with ‘controls’ from the same population defined by normal sperm count. Therefore, they are not representative of the general population. This explains why data regarding function of adult testes in otherwise healthy men are scarce.65

In a Danish study of 296 males who took part in studies on male fecundity, males born with a birth weight of 3000–3999 g had slightly lower sperm counts and more abnormal spermatozoa. They also found a non-significant trend towards lower sperm count and higher FSH levels in men with a lower birth weight and a low ponderal index.66

On the other hand, there is a strong association between in-utero tobacco exposure and slightly reduced size of testes, reduction in sperm concentration and total sperm count, and a slight decrease in the percentage of morphologically normal sperm. In the same group, the contribution of birth weight in these alterations was much smaller than that of maternal smoking.44,45,59,67
**Testicular cancer**

LBW has been recognized as an important factor in the development of testicular cancer, increasing the risk by approximately two to three fold. In addition, multiple factors have been identified that affect the risk of testicular cancer, such as cryptorchidism, parity, twinning, family history, ethnicity, chromosomal abnormalities, drugs and maternal uterine bleeding.

In a recent meta-analysis by Michos et al investigating the association between birth weight and testicular cancer (13 epidemiological studies published between 1983 and 2004, encompassing 5663 patients with testicular cancer), men weighing less than 2500 g at birth and men with a birth weight above 4000 g had a higher risk for developing testicular cancer later in life compared with those born with a normal birth weight (2500–4000 g). Furthermore, LBW was a specific risk factor for seminomas.

**Girls**

Over recent decades, growing evidence has been documented on the relationship between IUGR and early pubertal development or normal timed puberty but with rapid progression in girls. In addition, morphological changes in uterine and ovarian size of these girls have been reported, with 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 performed in a selected population.

**Pubarche**

Pubarche is defined by the appearance of sexual pubic hair and is considered normal when occurring after 8 years of age in girls. Adrenarche is the process in which the reticularis zone of the adrenal gland matures and increases the secretion of sex steroids (DHEA/DHEAS), and manifests by the development of axillary hair, axillary odour and pubarche.

In girls, the development of precocious pubarche and early and exaggerated adrenal androgen secretion before puberty has been linked with a history of SGA. Most of these studies, however, were retrospective and were biased by recruiting girls with precocious pubarche rather than 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, and small infants who gained weight rapidly during early childhood had the highest levels of adrenal androgens. In an earlier study from the same group of 102 girls between 5 and 18 years of age with precocious pubarche secondary to exaggerated adrenarche (elevated androstenedione and DHEAS levels) compared with 80 short-stature girls, a relationship was shown between a history of precocious pubarche during childhood and LBW SD score, particularly in the girls who subsequently developed idiopathic functional ovarian hyperandrogenism. In a retrospective Australian study of 89 children (79 girls) with precocious pubarche, 65% were overweight at diagnosis, 35% had a history of SGA and 24% had a history of prematurity. In this study, both prematurity and SGA were associated with precocious pubarche, as was obesity, irrespective of size or gestation at birth.

Excess weight gain in childhood may therefore predispose to precocious pubarche in susceptible individuals. Denburg et al and Silfen et al, evaluating the relationship
between premature adrenarche and insulin sensitivity and metabolic risk in girls and boys, found a decrease in insulin sensitivity and higher levels of triglycerides in both groups, especially in obese children with premature adrenarche not attributable to differences in 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.78,79 As mentioned above, these findings have not been reported by other authors.34,58,80–82

Ibáñez et al reported that transition from LBW to normal or increased weight during childhood is commonly associated with the development of precocious pubarche, exaggerated adrenarche and an increased risk for subsequent polycystic ovary syndrome and hyperinsulinaemia.83 A common path to the abnormal ovarian function reported in these girls is the finding of insulin sensitivity, which has been documented in children with a history of LBW84 and in girls of normal body weight with precocious pubarche.85 The same group has suggested that treatment of normal-weight girls with a history of precocious pubarche and LBW with an insulin sensitizer may preclude the development of associated metabolic abnormalities and ovarian hyperandrogenism.86 To date, these findings have not been confirmed by other groups.

Recently, the authors published the preliminary results from a sample of lean, healthy girls born either SGA (n = 35) or AGA (n = 30), studied at the age of puberty, recruited from the community. No differences in the presence of pubic hair, axillary hair or apocrine odour were found. Androgen levels were normal and the groups of girls did not show differences in DHEAS levels.82 SGA girls of this cohort had a higher leptin level and insulinogenic index at the beginning of puberty, both of which may be early indicators of insulin resistance, despite similar BMI and body composition compared with AGA girls.87 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 (Eyzaguirre et al, manuscript in revision). In addition, in a Chilean cohort of term SGA children who were followed from birth until 5 years of age (Bazaes et al, submitted) and a preterm cohort evaluated between 5 and 7 years of age81, no differences in DHEAS levels were found.

The relationship between the levels of androgens and exaggerated adrenarche/ premature pubarche may be related to the prevalence of predisposing genetic variants of insulin sensitivity and infancy weight gain88 during childhood rather than the characteristic of being born SGA.

Menarche

In most developed countries when the onset of puberty is within the normal age range, menarche 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 a normal birth weight tend to have a normal timing of menarche and a normal adult height.

In a longitudinal follow-up study from an urban Indian cohort evaluating the effect of prematurity and fetal growth retardation in 79 preterm AGA and 45 term SGA children, compared with controls, menarche occurred 6 months earlier in the preterm group and 12 months earlier in the SGA group.28 Similar results were communicated by Ghirri et al in 38 girls (SGA n = 19, AGA n = 19) evaluated after menarche
SGA girls had a slightly early 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 a lower age of menarche in 187 precocious pubarche girls when these girls were compared with the general population. Lower birth weight was an additional factor contributing to lower age of menarche by 8–10 months. The same group reported that if these girls experienced rapid catch-up growth with hyper-insulinaemia, menarche could occur even earlier.

In a longitudinal assessment of Catalonian girls with early onset of puberty (breast development between 8 and 9 years), menarche occurred, on average, 1.6 years earlier in LBW ($n = 12, <1.5$ SD) girls and their final height was 5 cm shorter than girls whose birth weight was greater than $-1.5$ SD. Lazar et al, in a cohort of 45 SGA girls compared with 31 AGA girls, reported that most of the SGA girls attained puberty at normal age, and although menarche occurred at normal age, was significantly earlier in the SGA group compared with the AGA group (12.6 ± 1.6 vs 13 ± 1.4; $P < 0.01$).

In a prospective cohort of 776 girls followed from fetal life to adolescence (12–14 years) in Western Australia, 349 of the subjects had reached menarche and 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 12.5 years of age (range 9.4–14.4 years). In this prospective cohort, birth weight and weight gain in childhood were both associated and had opposing influences on the timing of menarche.

Contrary to the previous data, several other groups have not been able to show earlier age of menarche in girls born SGA. In the Chilean cohort, not all girls have reached menarche, so no definitive conclusions can be drawn.

In the ALSPAC cohort, earlier maternal age at menarche predicted rapid infancy growth and childhood obesity. Thus menarche may be a transgenerational 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.

**Internal genitalia and hormone levels**

Reduced prenatal growth has been associated with FSH hypersecretion and reduced size of internal genitalia without changes in morphology. Ibáñez et al evaluated levels of FSH, inhibin-B, LH and oestradiol, and free androgen index in a group of 46 (3–6 months) postnatal female infants, 10 of whom were born AGA and 16 of whom were born SGA. They found two-fold higher levels of FSH in the SGA group compared with the AGA group, and there were no statistical differences in the other parameters analysed.

The same group evaluated healthy postmenarcheal adolescents (AGA $n = 33$, SGA $n = 15$), and found elevated serum levels of FSH (7.2 ± 0.7 in SGA vs 4.5 ± 0.3 in AGA) and lower oestradiol concentrations without differences in the inhibin-B levels between the two groups.

In the authors' cohort recruited from the community at the beginning of puberty, slight hormonal differences were observed between the groups of girls. The SGA group had increased baseline oestriadiol and anti-Mullerian hormone levels, and after a gonadotrophin-releasing hormone stimulation test (24 h), oestradiol and 17OHP-progesterone were higher in the LBW group, whereas FSH, LH, testosterone, inhibin-B and free androgen index were similar in both groups. No differences were found in the uterine or ovarian size on ultrasound assessment of these girls. After 2 years of following these girls, they showed similar characteristics in their internal
genitalia, although there was a tendency towards a higher number of follicles in the LBW group ($P = 0.08$). The LBW group had higher baseline 17OH-progesterone (1.4 ± 0.1 vs 1.1 ± 0.2 ng/mL; $P < 0.05$) and oestradiol (80.6 ± 9.7 vs 57.3 ± 4.2 pg/mL; $P < 0.05$), higher levels of LH 24 h after GnRH (187.6 ± 50.5 vs 79.6 ± 15 μIU/mL; $P < 0.05$), and lower baseline FSH levels (4.6 ± 0.4 vs 6.1 ± 0.5 μIU/mL, $P < 0.05$). No other gonadal or adrenal hormonal differences were detected in this preliminary sample of LBW and AGA girls. These results suggest that LBW girls display a different gonadotropin pattern with a higher LH/FSH ratio and higher oestradiol and 17OH-progesterone levels compared with AGA girls. These differences may allow a faster transition throughout puberty and an androgenic gonadal steroid pattern later. To date, there are insufficient data to support ovarian dysfunction, reduced fertility or early menopause in girls born SGA.

**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 resetting of endocrine axes that co-determine pubertal development.

Some animal studies have correlated IUGR and changes in pubertal timing. In addition, a number of human studies have demonstrated 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 studies in boys born SGA have shown normal pubertal timing, but attainment of an adult height below the target height. Information about the influence of fetal growth on male gonadal function is remarkably scarce, and most studies have focused on the relationship between LBW and testis dysgenesis syndrome which has a fetal origin. There is less direct evidence for an association between impaired adult reproductive function and LBW.

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

**Practice points**

- It is well established that malnutrition during critical periods in early life has implications for further development.
- Rapid weight gain in infancy has been shown to predict earlier secondary maturation, and this is more common in infants born SGA.
- Children with rapid weight gain and precocious pubarche should be monitored for the development of insulin resistance and associated complications.
- Although short SGA children usually start puberty at a normal age, most of the time, the age of onset of puberty is relatively early for their actual height, and final height is adversely affected when compared with target height.
• in males, most studies recognize a relationship between LBW and cryptorchidism, hypospadias and testicular cancer in later life
• studies in boys born SGA show normal pubertal timing
• the onset of puberty and menarche may be linked to intra-uterine and postnatal growth patterns

Research agenda

• information about the influence of fetal growth on male gonadal function is remarkably scarce and should be investigated
• evaluation of the results of longitudinal data on clinical, gonadal function and ultrasonographic images in cohorts from healthy girls born SGA recruited from the community
• it is necessary to establish whether slight differences in gonadal function patterns vary among different populations and correlate with environmental and genetic factors
• it is also necessary to accurately dissect the effect of birth weight and postnatal weight gain on consequences attributed to LBW, pubertal development and gonadal function

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