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IUGR: Genetic influences, metabolic problems, environmental associations/triggers, current and future management

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The children with intrauterine growth restriction (IUGR) especially if they make a catch-up growth in early life have a higher risk for long term problems including short stature and also developing metabolic syndrome, Type 2 diabetes, insulin resistance and cardiovascular diseases. The studies also support that these children may have abnormalities in pubertal timing, adrenarche and reproductive function. The aim of this review was to summarize the published reports mainly on puberty and reproductive functions in children born IUGR at older ages in association with metabolic problems that they encounter. Possible mechanisms explaining these outcomes are discussed. Lastly strategies that may be taken for the prevention of IUGR related morbidities at later life are shortly presented.

Introduction

Intrauterine growth restriction (IUGR) defines diminished growth velocity in the fetus occurring *in utero*, as documented by at least two intrauterine growth measurements [1]. The term small for gestational age (SGA) on the other hand refers to the size of the infant at birth and is defined as birth weight and/or birth length being less than −2 SDS according to gestational age and gender, compared to reference data [2]. Not all IUGR babies are born SGA and not all SGA born babies are IUGR. However, in studies these terms have been used interchangeably.

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Normal fetal growth depends mainly on sufficient delivery of oxygen and nutrients *via* the placenta. There are several causes of IUGR, encompassing maternal, fetal and placental factors [1]. Genetic factors also play an important role and several maternal, fetal and placental genes have been identified in the etiology of IUGR [3].

Alteration in fetal nutrition may result in developmental adaptation that permanently changes the physiology and metabolism of the offspring. This is the basis of the hypothesis "fetal origins of adult disease" [4]. Further studies have shown that not only the intrauterine environment but early postnatal environment from birth to 2 years of age and epigenetics have an impact on the development of adult diseases, thus in a broad sense the theory has changed to "developmental origins of health and disease" [5]. The children with IUGR especially if they make a catch-up growth in early life have a higher risk for long term problems including short stature and also developing metabolic syndrome, Type 2 diabetes, insulin resistance and cardiovascular diseases [5].

About 86% of children born SGA show catch-up growth and attain normal adult height. However the rest do not show catch-up growth and end up as short adults [6].

Puberty is an important phase of life, the transition period from childhood to adulthood, and disorders in puberty have an effect on adult height, body composition, psychology and also future reproductive health. Although the results of published reports are difficult to interpret, mainly due to methodological differences, timing of the onset of puberty and tempo of puberty have been found altered in SGA born children.

Adrenarche

Premature pubarche (PP) is defined as the appearance of pubic hair before the age of 8 years in girls and 9 years in boys and it is mostly due to premature adrenarche (PA) which is due to the maturation of the zona reticularis of the adrenal gland with an increase in dehydroepiandrosterone (DHEA)/DHEA sulphate (DHEAS) levels. Pubic hair may be associated with axillary odor and/or axillary hair. SGA birth has been associated with PA or exagerated adrenarche [7,8].

In the "Avon Longitudinal Study of Parents and Children" (ALSPAC) study, a large cohort study from the UK [9], in a group of 770 children, at 8 years of age, adrenal androgens and DHEAS levels were found to be inversely related to weight, length and ponderal index at birth and positively correlated with current body size. Both boys and girls who had rapid postnatal weight gain in the first 3 years of life, had the highest androgen levels. This was continuous throughout the birth weight range. In further studies from the same cohort, the investigators showed that the children with IUGR and rapid weight gain during the first 2 years of life were taller and fatter at 5 years of age with an increase in central adiposity [10], lower insulin sensitivity [11] and, irrespective of current body composition, those children with a rapid weight gain ($\geq$0.67 SD) in the first 2 years of life had higher insulin like growth factor 1 (IGF1) levels at 5 years of age [12].

There are other studies that have shown high DHEAS levels at prepubertal ages in SGA born children either related to birth weight *per se* or birth weight and postnatal weight gain [7,8,13–16]. In a study by Ibanez L et al. [7] it has been shown that nonobese girls with PP or a history of PP had low birth weight and PP, ovarian hyperandrogenism and insulin resistance were consecutive manifestations of IUGR; less severe growth restriction was associated with PP whereas with increasing severity of growth restriction ovarian hyperandrogenism and hyprinsulinemia developed. DHEAS levels were high in SGA children even without PP [13,15,16]. In a retrospective analysis of 89 children with PP studied around 7 years of age, the children had a more frequent likelihood of being SGA and premature and had an increased incidence of obesity [14]. SGA born nonobese adolescents had higher DHEAS, androstenedione and insulin levels [8]. On the other hand, in a cohort of children (n = 173) with PA from Chili [17] studied at around 7 years of age and followed for 15–60 months, it was shown that although SGA children did have a more pronounced weight gain, hormone levels including DHEAS and body mass index (BMI) were similar in SGA and AGA born children and the frequency of exagerated adrenarche was not more common in SGA born children. Similarly, in SGA born children (n = 181) (boys and girls) studied between 3 and 9 years of age, PP was not more frequent and DHEAS levels were not increased compared to control group [18].

Puberty

Studies on the onset and tempo of puberty in SGA children are somewhat conflicting, mainly due to methodological differences. In a large population based Swedish study (n = 3650) those SGA born children who made a catch-up growth entered puberty at a normal age whereas those who did not show catch-up growth entered puberty at an earlier age [19]. In another study, in boys, age at onset of puberty did not differ between boys with perinatal complications including SGA birth compared with boys without perinatal complications. Only in girls light for gestational age, puberty started 5 months earlier (10.7 ± 1.0 years vs 11.1 ± 1.0 years) [20]. In a longitudinal study by Lazar L et al. [21], 76 SGA and 52 AGA children were followed until near final height. Age at onset of puberty in SGA boys was significantly earlier (12.0 ± 0.9 years) than in AGA counterparts (13.0 ± 1.1 years) and also significantly earlier in girls (10.4 ± 1.3 years vs 11.4 ± 1.3 years). 13% of SGA boys entered puberty between 9 and 10.5 years and 20% of SGA girls entered puberty between 8 and 9.5 years compared to 5% and 3% in AGA boys and girls. In this study it has been shown that the only predictor for timing of entry to puberty was birth weight standard deviation score (SDS) however it explained only a small percentage of the variance. In a Hong Kong cohort (n = 7366), there was no effect of birth weight SDS or SGA status on the onset of puberty [22]. An increased childhood height and linear growth were associated with earlier onset of puberty.

Menarcheal age can be a good parameter for the tempo of puberty. Menarcheal age has been found at similar ages between AGA and SGA born children in some studies [23–25] however it was earlier in the study by Lazar L et al. [21] (12.6 ± 1.6 years in SGA vs 13.0 ± 1.4 yeas in the controls) ($p \leq 0.01$) and by Perssson et al [20] (12.7 ± 1.1 years in SGA vs 13.1 ± 1.0 years in AGA controls). There was no difference in boys. In a large prospective cohort study (n = 349), it was shown that both birth weight and BMI at 8 years of age were associated with age at menarche and this correlation existed across all birth weight and BMI ranges [26]. In the study by Bhargava SK et al. [27] (n = 45) age at menarche was 12 months earlier in SGA children compared to controls (median age 13.6). In the study by Ibanez et al. [28], the follow up of 187 girls with PP showed that menarcheal age was 11.5 ± 0.1 years in children with a birth weight SDS < 2SD (n = 50) vs 12.3 ± 0.1 years in children with a birth weight SDS > 2SD (n = 43). In a cohort of 1060 girls besides birth weight, BMI at 14 years of age had an influence on the timing of menarcheal age [29].

In the study by Lazar L et al. [21], bone age development was normal in SGA born children in early childhood however showed a significant acceleration at onset of puberty in girls and at Tanner stage 2–3 in boys compared to AGA born children. Total pubertal growth and peak height velocity (PHV) have been found similar between SGA and AGA born children [21,30] or an earlier and shorter PHV has been reported [15].

In conclusion, existing data support, albeit some controversial findings, that SGA birth and PP show an association. In most studies puberty starts within normal age ranges but relatively on the earlier side. Rapid advancement of bone age and puberty may compromise final height.

Reproductive function

In girls, associated with reduced fetal growth, ovarian hyperandrogenism and ovarian function abnormalities like polycystic ovarian syndrome (PCOS) phenotype have been reported [7,31]. In a retrospective analysis of 467 girls with PCOS, low birth weight and high BMI in adolescence were predictors of PCOS [32]. In boys intrauterine restriction has been associated with male infertility [33]. Reduced testicular size and low testosterone levels have been shown in some adolescent boys borm SGA [34]. In a large cohort study (n = 423), the proportion of men with a sperm count less than 25th centile were 38.9% in SGA compared to 25% and 13% in AGA and large for gestational age, respectively [35]. Adolescent girls born SGA were found to have a decreased ovulation rate [36]. However in a prospective study in 230 girls ovarian reserve, evaluated by ultrasound findings of ovaries and anti-Mullerian hormone (AMH), inhibin B and follicle stimulating hormone (FSH) levels were not affected by variations in fetal growth [37]. Among girls with PCOS (n = 170), SGA birth was seen in only 9% of adolescents, implicating that other factors are responsible [38].

IUGR status is associated with elevated FSH levels in early infancy in SGA born boys and girls [39,40]. In the study by Ibanez L et al. [40] FSH secretion at 3–6 months in boys and girls were 2–3 fold higher than in AGA controls. Postmenarcheal girls born SGA were found to have elevated FSH and lower estradiol concentrations [41]. In a Chilean study at onset of puberty SGA girls with a normal BMI had similar FSH and luteinizing hormone (LH) concentrations however 2 years later FSH was lower but LH and estradiol higher suggesting that faster pubertal progress may be due to this finding [42]. In a prospective study by Jensen RB et al. [43], SGA born adolescent (20 SGA vs 32AGA) boys had no difference with respect to gonadotropin, testosterone and inhibin B levels. Similar findings were reported in SGA born young adults [44]. Reduced uterine and ovarian size were noted in adolescent girls born SGA [45]. However this was not a finding in the study by Hernandez et al. [42]. In a large study (n = 279) including young women 18–24 years, SGA birth with or without catch-up growth did not affect AMH levels [46].

In a study consisting of 75 adolescents (28 followed longitudinally) at around 19 years of age, reduced uterine and ovarian size and persistent elevation of FSH were shown suggesting reduced fertility [47]. In one case report, premature ovarian failure developed in SGA, diagnosed as Silver Russel syndrome [48]. In a community based cohort of young adults (579 SGA, 703AGA) based on a questionnaire, fertility was not reduced [49].

In conclusion data from studies are conflicting and population studies do not fully support reproductive axis abnormalities in SGA born population.

Metabolic problems

It has been shown in several studies that SGA born children who show catch-up growth even in the absence of obesity, demonstrate insulin resistance in infancy, in childhood, adolescence and in adulthood [23,50–55] and in animal studies as well [56,57]. Insulin resistance may be present as early as 1 year of age in SGA born children as has been shown in a longitudinal follow up of SGA(n = 85) and AGA (n = 23) children from birth to one year of age [58]. Fasting insulin was significantly higher in those with a catch-up growth in weight.

In a prospective study of longitudinal follow up of 50 SGA children from 0 to 3 years of age, it was shown that IGF-1 levels were related to beta cell function and growth in the 1st year. At age 3 years IGF 1 was related to BMI and insulin resistance [59]. The same group of investigators showed that in addition to increase in insulin resistance at 3 years of age, SGA children showed a reduced compensatory beta cell secretion [52]. In a study of 477 children at 8 years of age, both low birth weight and high fat mass at 8 years of age were associated with insülin resistance, dyslipidemia, and higher insulin levels [50]. In prepubertal SGA children (n = 29) hyperinsulinemic clamp studies showed that inulin sensitivity was lowest in those who showed catch-up growth and had a BMI > 17kg/m2. Oral glucose tolerance test (OGTT) results were comparable [55]. It has been shown by Ibanez L et al. [54] that following weight gain up to 2 years of age, between 2 and 4 years of age SGA children showed a dramatic increase in central adiposity and insulin resistance in spite of a similar BMI to that of AGA controls. In the ALSPAC study low birth weight, higher catch-up growth at 3 years of age predicted high BMI, lower insulin sensitivity at 8 years of age [11]. In contrast, lower insulin secretion was related to smaller size at birth, independent of postnatal weight gain and insulin sensitivity. Lower insulin secretion was also independently related to shorter stature at 8 years of age relative to parental height and with lower plasma IGF-I levels at 5 years of age. Early pubertal SGA girls showed higher leptin and insulinogenic index despite similar BMI and body composition to AGA girls [60]. At 3–6 years of age nonobese SGA(n = 27) children had a thicker intima media and more hepatic fat than AGA (n = 19) children [61]. Another cohort study (n = 87) showed that weight gain in the first 3 months of life predicted more fat, more central adiposity and reduced insulin sensitivity and higher insulin resistance in early adulthood, including SGA children with catch-up growth [62]. The same investigators in another cohort study (n = 323) showed that birth size is less important in the body composition of young adults [63].

Some studies showed no relation with catch-up growth and insulin resistance in SGA born children [64,65].

In a study of adolescents at 18 years of age (30 SGA, 57AGA) weight gain in the first 3 months of life was associated with insulin resistance, dyslipidemia and higher blood pressure [66].

Insulin resistance is a risk factor for Type 2 diabetes. Other than insulin resistance, other abnormalities which are related to metabolic syndrome and cardiovascular diseases have been shown in SGA born children. An inverse relation was found between birth weight and blood pressure [67].

Adverse cardiologic parameters were observed in children and adolescents born SGA in a longitudinal study [68]. There may be a negative effect of IUGR in the structure and function of the cardiovascular system, albeit subclinical [69].

In a large cohort of 1308 individuals between 22 and 30 years of age over the follow up of 8 years the risk for developing metabolic syndrome was two fold higher in SGA after adjusting for BMI [70]. In a study at 8 years of age, SGA children had a two fold increase in the risk for metabolic syndrome after adjusting for BMI [66]. In the Haggenau cohort study from France which included more than 1500 young adults, at 22 years of age, SGA born young adults had a 2.4% frequency of metabolic syndrome compared to 0.4% in AGA born adults [23]. In spite of similar BMI in SGA and AGA, fat mass was elevated in SGA adults. Adjusting for other confounding factors, weight gain during 0–6 months of age predicted metabolic syndrome risk at 17 years of age independent of birth weight and early childhood weight gain (between 3 and 6 years of age) [71].

In a population study from Canada, SGA born children showed no cardiovascular risk factors between 6 and 12 years ($n = 2016$) including blood pressure, auxological parameters and laboratory investigations including lipid values [72]. In a longitudinal cohort study, term SGA ($n = 59$) born young adults were at a higher risk for metabolic syndrome [73]. Results of 2218 adults from the Vellore Birth Cohort from India showed that the greater height or weight gain during childhood or in adolescence was associated with an increased risk in metabolic syndrome parameters. Taller adult heigh was associated with increased waist circumference and insulin resistance but lower glucose levels. Shorter length and lower BMI at birth was associated with higher glucose values in women [74].

In conclusion for this part, children born SGA have an intrinsic insulin resistance and rapid catch-up growth increases long term risks for metabolic problems [75,76]. At later years lower insulinegic index consistent with impaired beta cell function puts the child at risk for Type 2 diabetes.

Possible mechanisms

As has been shown in the studies previously mentioned, alterations in fetal and early life nutrition may result in developmental adaptations that permanently change glucose –insulin metabolism of the offspring, predisposing individuals to metabolic, endocrine and cardiovascular diseases. Several epidemiological, clinical and animal studies support the developmental origins of disease theory [4,5,56,77]. Some possible mechanisms are summarized below.

Animal studies with respect to puberty

In the animal models, malnutrition during critical periods in early life has been shown to affect further development [78]. A study in male and female rats investigated whether *in utero* malnutrition or immediate postnatal food restriction (FR) (between 2 and 24 days) had an effect on puberty. Malnutrition during late gestation or directly postnatally delayed puberty in IUGR and FR male rats and in IUGR female rats but not in FR female rats. In both models rats showed growth failure and there was no threshold for body weight for onset of puberty [79]. In a further study [80] the authors showed that IUGR rats did not have adequate number of follicules but in postnatal FR rats the number of follicules were increased but did not respond to gonadotropin stimulation. Thus malnutrition during different stages had a different effect on ovarian development and further reproductive capacity. In a study done in prenatally growth restricted lambs [81] in females there was no difference in pubertal onset and ovarian function. However in males testosterone values and testicular mass were lower than the controls.

Several different studies in animals have reported long term consequences after perinatal challenges. In rats, maternal caloric restriction results in offspring with low birth weight that show accelerated neonatal growth and early vaginal opening [82,83] with sexual dimorphism and no

difference in males [83]. However, early onset puberty is not always evident and it may be normal or delayed [84,85]. Delayed puberty and lower number of Leydig Cells and low testosterone levels have been shown in IUGR rats with postnatal FR. Maternal undernutrition in rats results in offspring that have reduced number of primordial and antral follicules and mRNA levels of regulating genes associated with ovarian oxidative stress [86].

The arcuate nucleus located in the mediobasal hypothalamus has been shown to be sensitive to perinatal nutritional conditions affecting hypothalamic Kiss 1 expression and timing of puberty in female rats [87]. Intrauterine undernutrition has an adverse effect on the production of kisspeptin in rats and has an effect on timing of puberty.

Body composition and adipose tissue studies

Adipose tissue plays a role in the fetal origins of disease [88,89]. If postnatal supply of nutrients is more than intrauterine supply, enhanced growth and fat deposition will occur and will lead to insulin resistance [90]. Adipocytokines have been implicated to have a role in the adult diseases following IUGR. Leptin has a permissive role in pubertal development and in the maintenance of reproductive function. Adiponectin has been shown to have a role in linking energy homeostasis and control of the hypothalamo-pituitary-gonadal axis. Ghrelin, an orexigenic compound, also induces growth hormone secretion. Ghrelin may take part in the regulation of gonadotropin secretion and play a role in timing of puberty. PYY $_{3-36}$,a gastrointestinal hormone, is involved in food intake and energy balance. Also PYY $_{3-36}$ modulates GnRH and gonadotropin release in some animal studies [91–94].

It has been shown that intrauterine hypo- or hyperleptinemia may program the energy regulating systems. In most studies low leptin levels, lower or normal adiponectin, higher ghrelin and visfatin levels in the IUGR sate, all these may put the individual at risk for development of obesity and insulin resistance and abnormalities in gonadotropic axis [88].

It has been shown that in SGA born adults percentage of body fat and fat mass were higher than muscle mass and fat free soft tissue and a higher trunk to limb fat ratio [95].

Brown adipose tissue which is protective against metabolic disorders has been found to show abnormalities in SGA children [96].

It is not clear whether this predisposition to central adiposity is due to low birth weigh or to catch-up-growth but there is some evidence suggesting that IUGR is associated with a decreased capacity to store subcutaneous fat [97].

Hyperinsulinism and hyperandrogenemia

The low birth weight associated with PP and subsequently early menarche, followed by hyperandrogenism and PCOS may be linked to accumulation of visceral fat, following early weight gain, insulin resistance and hyperinsulinism [28,98]. Furthermore, IGF1 is positively correlated with insulin levels [11]. Both insulin and IGF1 are capable of stimulating androgen production [99]. Insulin resistance is the key factor in the development of hyperandrogenism [100]. Insulin resistance and hyperinsulinemia will also reduce sex hormone binding globulin (SHBG) levels and have an effect on the bioavailability of sex steroids [101].

For this reason, as an insulin sensitizer, metformin therapy has been used in early puberty in SGA girls (22 treated vs 12 untreated) [102]. After 3 years of therapy metformin resulted in slower pubertal progress, prolonged total pubertal growth and increased final height. Metformin therapy also resulted in lower insulin, leptin, and IGF1 levels and higher SHBG levels and IGFBP1 levels together with a less atherogenic profile and leaner body composition. These findings in body composition were still relevant after 18 months of discontinuation of therapy [103]. In a further study, low birth weight born prepubertal girls with PP were treated with metformin for 4 years (19 treated vs 19 untreated) The treated ones were less insulin resistant, less hyperandrogenic, had lower IGF1 levels, less atherogenic and more number of girls were premenarcheal [104,105].

These studies show the importance of insulin as the triggering factor in the onset and tempo of puberty.

Epigenetics

Epigenetics is the study of heritable changes in gene expression depending on specific tissue and environment [3,5,93,106] and has been implicated in regulation of body weight and onset of puberty in SGA through methylation and histone modification and posttranscriptional control by microRNA causing different functioning of a range of physiological processes, like for example, altered promoter methylation and gene expression have been shown for the hepatic glucocorticoid receptor and the peroxisome proliferator-activated receptor α (PPAR-α) influencing carbohydrate and lipid metabolism. Through epigenetic changes, environmental factors like maternal nutrition or endocrine status during development affect the phenotypic variation of the off-spring and experimental evidence suggests that the effects of maternal nutrition on phenotype and associated epigenetic changes continue in subsequent generations [107].

In a prospective mother-offspring cohort ($n = 987$), factors were analyzed that had an effect on birth weight and adiposity development upto 2 years of age. Apart from some perinatal environmental factors, neonatal methylation markers from seven gene loci were studied. Methylation levels at some birth weight loci showed association with perinatal factors and with the development of adiposity [108]. Epigenetic marks measurable at birth explain more than 25% of the variation in adiposity in 6–9 year old children [109].

Current and future management

Although the number of SGA births may not be available worldwide, roughly between 2.3 and 10% of all infants are born SGA [1]. Being born SGA brings with it an increased risk of morbidities. Moreover, low birth weight can continue over two successive generations; a low birth weight mother has a 2.8 times risk delivering a low birth weight baby ($p = 0.0.2$) [110]. Several animal, epidemiological and human studies have shown that early life events result in an increase in noncommunicable chronic diseases in adult life including obesity, Type 2 diabetes and cardiovascular diseases [5]. Poor intrauterine environment induces a reduced development of skeletal muscle and increased visceral fat deposition which favors survival in poor environment; however if the subsequent postnatal environment is not poor, the off -spring may be susceptible to later diseases. The developmental origins of health and disease explains the process of developmental plasticity in the development of adult diseases [109]. Starting from gestation and even before gestation and following early postnatal life every effort should be taken for providing optimum and healthy nutrition to mothers and offsprings [106,111]. These children should be followed with respect to weight gain, signs of adrenarche and puberty, metabolic problems and reproductive abnormalities [112] Genetic and epigenetic causes are responsible for some patients and should be investigated if possible. In a systematic review, breastfeeding has been found to be protective against obesity, metabolic and/or cardiovascular features in SGA, albeit the heterogeneity of the papers [113]. Further studies on epigenetics and metabolomics will give more insight [114].

Last but not the least the prevention of SGA births is an important public health issue.

Summary

IUGR and early life events have a strong effect on the development of morbidities in later life. Earlier puberty with a rapid tempo may compromize final height. Premature adrenarche, hyperandrogenism, polycystic ovarian syndrome phenotype together with insulin resistance, increase in visceral fat, metabolic syndrome components will put the child and adolescent at a great risk for further comorbidities and cardiovascular diseases. These children should be followed closely for these morbidities. However more important is to take preventive measures starting from periconception, through gestation and early postnatal life to decrease the frequency of these disorders.

Practice points

- Children and adolescents born with intrauterine growth restriction (IUGR) should be followed closely for the development of adverse consequencies including pubertal problems and reproductive function abnormalities
- Rapid weight gain in early life needs a special attention in these children
- Metabolic disorders, obesity and cardiovascular risk factors which may start in childhood need close follow-up
- Good nutrition and healthy life style should be encouraged

Research agenda

- Further studies on the genetic, epigenetic, matabolic and endocrine aspects of IUGR
- Unraveling the mechanism from fetal growth restriction to metabolic disturbances for early diagnosis of IUGR and take preventive measures

References

*[1] Saenger P, Czernichow P, Hughes I, et al. Small for gestational age: short stature and beyond. Endocr Rev 2007;28:219–51.
[2] Clayton PE, Cianfarani S, Czernichow P, et al. Consensus Statement : management of the child born small for gestational age through to adulthood: a consensus statement of the international societies of Pediatric Endocrinology and the Growth hormone Research society. J Clin Endocrinol Metabol 2007;92:804–10.
*[3] Sharma D, Sharma P, Shastri S. Genetic, metabolic and endocrine aspect of intrauterine growth restriction: an update. J Matern Fetal Neonatal Med 2017;30:2263–75.
[4] Barker DJ, Eriksson JG, Forsen T, et al. Fetal origins of adult disease: strength of effects and biological basis. Int J Epidemiol 2002;31:1235–9.
*[5] Hanson MA, Gluckman PD. Early developmental conditıoning of later health and dısease: physiology or pathophysiology? Physiol Rev 2014;94:1027–76.
[6] Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. Pediatr Res 1995;38:733–9.
[7] Ibanez l, Potau N, Francois I, et al. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. J Clin Endocrinol Metabol 1998;83:3558–62.
[8] Ibanez l, Potau N, Marcos MV, et al. Exaggerated adrenarche and hyperinsulinism in adolescent girls born small for gestational age. J Clin Endocrinol Metabol 1999;84:4739–41.
*[9] Ong KK, Potau N, Petry CJ, et al. Opposing influences of prenatal and postnatal weight gain on adrenarche in normal boys and girls. J Clin Endocrinol Metabol 2004;89:2647–51.
[10] Ong KK, Ahmed ML, Emmett PM, et al. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. Br Med J 2000;320:967–71.
[11] Ong KK, Petry CJ, Emmett PM, et al. Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. Diabetologia 2004;47:1064–70.
[12] Ong K, Kratzsch J, Kiess W, et al. Circulating IGF-1 levels in childhood are related to both current body composition and early postnatal growth rate. J Clin Endocrinol Metabol 2002;87:1041–4.
[13] Francois I, de Zegher F. Adrenarche and fetal growth. Pediatr Res 1997;41:440–2.
[14] Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. Arch Dis Child 2005;90:258–61.
[15] Veening MA, van Weissenbruch MM, Roord JJ, et al. Pubertal development in children born small for gestational age. J Clin Endocrinol Metabol 2004;17:1497–505.
[16] Dahlgren J, Boguszewski M, Rosberg S, et al. Adrenal steroid hormones in short children born small for gestational age. Clin Endocrinol Endocrinol (Oxf) 1998;49:353–61.
[17] Eyzaguirre FC, Bancalari R, Youlton R, et al. Precocious pubarche: experience in 173 cases. Rev Med Chil 2009;137:31–8 (in Spanish). (Revista médica de Chile).
[18] Boonstra VH, Mulder PGH, de Jong FH, et al. Serum Dehydroepiandrosterone sulfate levels and pubarche in short children born small for gestational age before and during growth hormone treatment. J Endocrinol Metabol 2004;89:712–7.
[19] Albertsson-Wikland K, Karlberg J. Natural growth in children born SGA with and without catch-up growth. Horm Res 2003;59(Suppl. 1):129.
[20] Persson I, Ahlsson F, Ewald U, et al. Influence of perinatal factors on the onset of puberty in boys and girls: implications for interpretation of link with risk of long term diseases. Am J Epidemiol 1999;150:747–55.

[21] Lazar L, Pollak U, Kalter-Leibovici O, et al. Pubertal course of persistently short children born small for gestational age (SGA) compared with idiopathic short children born appropriate for gestational age (AGA). Eur J Endocrinol 2003;149:425–32.
[22] Hui LL, Leung GM, Wong M-Y, et al. Small for gestational age and age at puberty: evidence from Hong Kong's "Children of 1997" Birth Cohort. Am J Epidemiol 2012;176:785–93.
[23] Leger J, Levy-Marchal C, Bloch J, et al. Reduced final height and indications for insulin resistance in 20-year-olds born small for gestational age: regional cohort study. Br Med J 1997;315:341–7.
[24] Chaudhari S, Otiv M, Hoge M, et al. Growth and sexual maturation of low birth weight infants at early adolescence. Indian Pediatr 2008;45:191–8.
[25] Shim YS, Park HK, Yang S, et al. Age at menarche and adult height in girls born small for gestational age. Ann Pediatr Endocrinol Metabol 2013;18:76–80.
[26] Slohoda DM, Hart R, Doherty DA, et al. Age at menarche: influences of prenatal and postnatal growth. J Clin Endorinol Metabol 2007;92:46–50.
[27] Bhargava SK, Ramji S, Srivastava U, et al. Growth and sexual maturation of low birth weight children: a 14-year follow-up. Indian Pediatr 1995;32:963–70.
[28] Ibanez L, Jimenez R, de Zegher F. Early puberty-menarche after precocious pubarche: relation to prenatal growth. Pediatrics 2006;117:117–21.
[29] Koziel S, Jankowska EA. Effect of low versus normal birthweight on menarche in 14-year-old Polish girls. J Paediatr Child Health 2002;38:268–71.
[30] Leger J, Limoni C, Collin D, et al. Prediction factors in the determination of final height in subjects born small for gestational age. Pediatr Res 1998;43:808–12.
[31] Ibanez L, Valls C, Potau N, et al. Polycystic ovary syndrome after precocious pubarche: ontogeny of the low – birthweight effect. Clin Endocrinol 2001;55:667–72.
[32] de Zegher F, Reinehr T, Malpique R, et al. Reduced prenatal weight gain and/or augmented postnatal weight gain precedes polycystic ovary syndrome in adolescent girls. Pediatr Obes 2017;25:1486–9.
[33] Francois I, de Zegher F, Spiessens C, et al. Low birth weight and subsequent male subfertility. Pediatr Res 1997;42:899–901.
[34] Cicognani A, Alessandroni R, Pasini A, et al. Low birth weight for gestational age and subsequent male goanadal function. J Pediatr 2002;141:376–9.
[35] Hart JR, Doherty DA, Keelan JA, et al. Early life events predict adult testicular function : data derived from the western Australian (Raine) birth cohort. J Clin Endocrinol Metabol 2016;101:3333–44.
[36] Ibanez L, Potau N, Ferrer A, et al. Reduced ovulation rate in adolescent girls born small for gestational age. J Clin Endocrinol Metabol 2002;87:3391–3.
[37] Hart R, Sloboda DM, Dorota A, et al. Prenatal determinants of uterine volume and ovarian reserve in adolescence. J Clin Endocrinol Metabol 2009;94:4931–7.
[38] Fulghesu AM, Manca R, Loi S, et al. Insulin resistance and hyperandrogenism have no substantive association with birth weight in adolescents with polycystic ovary syndrome. Am Soc Reprod Med 2015;103:808–8014.
[39] Hernandez MI, Mericq V. Impact of being born small for gestational age on onset and progression of puberty. Best Pract Res Clin Endocrinol Metabol 2008;22:463–76.
[40] Ibanez L, Valls C, Cols M, et al. Hypersecretion of FSH in. infant boys and girls born small for gestational age. J Clin Endocrinol Metabol 2002;87:1986–8.
[41] Ibanez L, Potau N, de Zegher F. Ovarian hyporesponsiveness to follicle stimulating hormone in adolescent girls born small for gestational age. J Clin Endocrinol Metabol 2000;85:2624–6.
[42] Hernandez MI, Martinez A, Capurro T, et al. Comparison of clinical, ultrasonographic, and biochemical differences at the beginning of puberty in healthy girls born either small for gestational age or appropriate for gestational age: preliminary results. J Clin Endocrinol Metabol 2006;91:3377–81.
[43] Jensen RB, Vielwcrth S, Larsen T, et al. Pituitary-gonadal function in adolescent males born appropriate or small for gestational age with or without intrauterine growth restriction. J Clin Endocrinol Metabol 2007;92:1353–7.
[44] Boonstra VH, Weber RFA, de Jong FH. Hokken-koelega ACS. Testis function in prepubertal boys and young men born small for gestational age. Horm Res 2008;70:357–63.
[45] Ibanez L, Potau N, Enriquez G, et al. Reduced uterine and ovarian size in adolescent girls born small for gestational age. Pediatr Res 2000;47:575–7.
[46] Kerkhof GF, Leunissen RW, Willemsen RH, et al. Influence of preterm birth and small birth size on serum anti-Mullerian hormone levels in young adult women. Eur J Endocrinol 2010;163(6):937–44.
[47] Ibanez L, Potau N, Enriquez G, et al. Hypergonadotrophinaemia with reduced uterine and ovarian size in women born small-for-gestational-age. Hum Reprod 2003;18:1565–9.
[48] Ehtisham S, Zacharin M. Primary ovarian failure and small for gestational age: a previously unrecognised association. J Paediatr Child Health 2009;45:313–6.
[49] Meas T, Deghmoun S, Lévy-Marchal C, et al. Fertility is not altered in young adults born small for gestational age. Hum Reprod 2010;25:2354–9.
[50] Bavdekar A, Yajnik CS, Fall CH, et al. Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? Diabetes 1999;48:2422–9.
[51] Hofman PL, Cutfield WS, Robinson EM, et al. Insulin resistance in short children with intrauterine growth retardation. J Clin Endocrinol Metabol 1997;82:402–6.
[52] Mericq V, Ong KK, Bazaes R, et al. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children. Diabetologia 2005;48:2609–14.
[53] Sancaklı Ö, Darendeliler F, Bas F, et al. Insulin, adiponectin, IGFBP-1 levels and body composition in small-forgestational age born non-obese children during prepubertal ages. Clin Endocrinol 2008;69:88–92.
[54] Ibanez L, Ong K, Dunger DB, et al. Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children. J Clin Endocrinol Metabol 2006;91:2153–8.

[55] Veening MA, Van Weissenbruch MM, Delemarre-Van De Waal HA. Glucose tolerance, insulin sensitivity, and insulin secretion in children born small for gestational age. J Clin Endocrinol Metabol 2002;87:4657–61.
[56] Mohan R, Baumann D, Alejandro EU. Fetal undernutrition, placental insufficiency and pancreatic β-cell development 2 programming in utero. Am J Physiol Regul Inteqr Comp Physiol 2018 Aug 15. https://doi.org/10.1152/ajpregu.00072.2018.
[57] Berends LM, Dearden L, Tung YCL, et al. Programming of central and peripheral insulin resistance by low birthweight and postnatal catch-up growth in male mice. Diabetologia 2018;61:2225–34.
[58] Soto N, Bazaes RA, Pena V, et al. Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort. J Clin Endocrinol Metabol 2003;88:3645–50.
[59] Inıquez G, Ong K, Bazaes R, et al. Longitudinal changes in insulin-like growth factor -I, insulin sensitivity and secretion from birth to age three years in small- for-gestational – age children. J Clin Endocrinol Metabol 2006;91:4645–9.
[60] Martinez-Aguayo A, Capurro T, Pena V, et al. Comparison of leptin levels, body composition and insulin sensitivity and secretion by OGTT in healthy, early pubertal girls born at either appropriate- or small-for-gestational age. Clin Endocrinol 2007;67:526–32.
[61] Sebastiani G, Díaz M, Bassols J, et al. The sequence of prenatal growth restraint and post-natal catch-up growth leads to a thicker intima-media and more pre-peritoneal and hepatic fat by age 3–6 years. Pediatr Obes 2016;11:251–7.
*[62] Leunissen RW, Kerkhof GF, Stijnen T, et al. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. J Am Med Assoc 2009;301:2234–42.
[63] Leunissen RW, Stijnen T, Hokken Koelega AC. Influence of birth size on body composition in early adulthood: the programming factors for growth and metabolism (PROGRAM)-study. Clin Endocrinol 2009;70:245–51.
[64] Giapros V, Vavva E, Siomou E, et al. Low-birth-weight, but not catch-up growth, correlates with insulin resistance and resistin level in SGA infants at 12 months. J Matern Fetal Neonatal Med 2017;30(15):1771–6.
[65] Torre P, Ladaki C, Scire G, et al. Catch-up growth in body mass index is associated neither with reduced insulin sensitivity nor with altered lipid profile in children born small for gestational age. J Endocrinol Invest 2008;31:760–4.
[66] Fabricius-Bjerre S, Jensen RB, Faerch K, et al. Impact of birthweight and early infant weight gain on insulin resistance and associated cardiovascular risk factors in adolescence. PLoS One 2011;6:e20595.
[67] Kahn LG, Buka SL, Cirillo PM, et al. Evaluating the relationship between birth weight for gestational age and adult blood pressure using participants from a cohort of same-sex siblings, discordant on birth weight percentile. Am J Epidemiol 2017;186:550–4.
[68] Chiavaroli V, Marcovecchio ML, de Giorgis T, et al. Progression of cardio-metabolic risk factors in subjects born small and large for gestational age. PLoS One 2014;9(8):e104278.
[69] Cohen E, Wong FY, Horne RS, et al. Intrauterine growth restriction: impact on cardiovascular development and function throughout infancy. Pediatr Res 2016;79:821–30.
[70] Meas T, Deghmoun S, Alberti C, et al. Independent effects of weight gain and fetal programming on metabolic complications in adults born small for gestational age. Diabetologia 2010;53:907–13.
*[71] Ekelund U, Ong KK, Linne Y, et al. Association of weight gain in infancy and early childhood with metabolic risk in young adults. J Clin Endocrinol Metabol 2007;92:98–103.
[72] Kuhle S, Maguire B, Ata N, et al. Birth weight for gestational age, anthropometric measures, and cardiovascular disease markers in children. J Pediatr 2017;182:99–106.
[73] Balasuriya CND, Stunes AK, Mosti MP, et al. Metabolic outcomes in adults born preterm with very low birthweight or small for gestational age at term: a cohort study. J Clin Endocrinol Metabol 2018. https://doi.org/10.1210/jc.2018-00464.
[74] Antonisamy B, Vasan SK, Geethanjali FS, et al. Weight gain and height growth during infancy, childhood and adolescence as predictors of adult cardiovascular risk. J Pediatr 2017;180:53–61.
[75] Kerkhof GF, Leunissen RW, Hokken-Koelega AC. Early origins of the metabolic syndrome: role of small size at birth, early postnatal weight gain, and adult IGF-I. J Clin Endocrinol Metabol 2012;97:2637–43.
[76] Chaudhari S, Otiv M, Hoge M, et al. Components of metabolic syndrome at 22 years of age – findings from pune low birth weight study. Indian Pediatr 2017;54:461–6.
[77] Osmond C, Barker DJ. Fetal infant and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 2000;108:545–53.
*[78] Zambrano E, Guzman C, Rodriguez-Gonzalez GL, et al. Fetal programming of sexual development and reproductive function. Mol Cell Endocrinol 2014;382:538–49.
[79] Engelbregt MJT, Houdijk MECAM, Popp Snijders C, et al. The effects of intrauterine growth retardation and postnatal undernutrition on onset of puberty in male and female rats. Pediatr Res 2000;48:803–7.
[80] Engelbregt MJT, van Weissenbruch MM, Popp-Snijders C, et al. Delayed first cycle in intrauterine growth-retarded and postnatally undernourished female rats: follicular growth and ovulation after stimulation with pregnant mare serum gonadotropin at first cycle. J Endocrinol 2002;173:297–304.
[81] Da Silva P, Aitken RP, Rhind SM, et al. Influence of placentally mediated fetal growth restriction on the onset of puberty in male and female lambs. Reproduction 2001;122:375–83.
[82] Sloboda DM, Howie GJ, Pleasants A, et al. Pre-and postnatal nutritional histories influence reproductive maturation and ovarian function in the rat. PLoS One 2009;4:e6744. https://doi.org/10.1371/journalpone.0006744.
[83] Sanchez-Garrido MA, Castellano JM, Ruiz-Pino F, et al. Metabolic programming of puberty: sexually dimorphic responses to early nutritional challenges. Endocrinology 2013;154:3387–400.
[84] Chernoff N, Gage MI, Stoker TE, et al. Reproductive effects of maternal and pre-weaning undernutrition in rat offspring: age at puberty, onset of female reproductive senescence and intergenerational pup growth and viability. Reprod Toxicol 2009;28:489–94.
[85] Gereltsetseg G, Matsuzaki T, Iwasa T, et al. Delay in the onset of puberty of intrauterine growth retarded female rats cannot be rescued with hypernutrition after birth. Endocr J 2012;59:963–72.
[86] Bernal AB, Vickers MH, Hampton MB, et al. Matemal undernutrition significantly impacts ovarian follicle number and increases ovarian oxidative stress in adult rat offspring. PLoS One 2010;5:e15558. https://doi.org/10.1371/journal.pone.0015558.

[87] Iwasa T, Matsuzaki T, Murakami M, et al. Effects of intrauterine undernutrition on hypothalamic Kissl expression and the timing of puberty in female rats. J Physiol 2010;588:821–9.
*[88] Briana DD, Malamitsi-Puchner A. Intrauterine growth restriction and adult disease: the role of adipocytokines. Eur J Endocrinol 2009;160:337–47.
[89] Jaquet D, Deghmoun S, Chevenne D, et al. Dynamic change in adiposity from fetal to postnatal life is involved in the metabolic syndrome associated with reduced fetal growth. Diabetologia 2005;48:849–55.
[90] Jaquet D, Gaboriau A, Czernichow P, et al. Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. J Clin Endocrinol Metabol 2000;85:1401–6.
[91] Martos-Moreno GA, Chowen JA, Argente J. Metabolic signals in human puberty: effects of over and undernutrition. Mol Cell Endocrinol 2010;324:70–81.
[92] Proos L, Gustafsson J. Is early puberty triggered by Catch-up growth following undernutrition? Int J Environ Res Publ Health 2012;9:1791–809.
[93] Roth CL, Sathyanarayana S. Mechanisms affecting neuroendocrine and epigenetic regulation of body weight and onset of puberty: potential implications in the child born small for gestational age (SGA). Rev Endocr Metab Disord 2012;13:129–40.
[94] Fernandez-Fernandez R, Martini AC, Navarro VM, et al. Novel signals for the integration of energy balance and reproduction. Mol Cell Endocrinol 2006;254–255:127–32.
[95] Kensara OA, Wootton SA, Phillips DI, et al. Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. Am J Clin Nutr 2005;82:980–7.
[96] Malpique R, Gallego-Escuredo JM, Sebastian G, et al. Brown adipose tissue in prepubertal children: associations with sex, birthweight, and metabolic profile. Int J Obes (Lond) 2018 Sep 5. https://doi.org/10.1038/s41366-018-0198-7.
*[97] Maiorana A, Del Bianco C, Cianfarani S. Adipose tissue: a metabolic regulator. Potential implications for the metabolic outcome of subjects born small for gestational age (SGA). Rev Diabet Stud 2007;4:134–46.
[98] de Zegher F, Lopez-Bermejo A, Ibanez L. Adipose tissue expandability and the early origins of PCOS. Trends Endocrinol Metabol 2009;20:418–23.
[99] Mesiano S, Katz SL, Lee JY, et al. Insulin -like growth factors augment steroid production and expression of steroidogenic enzymes in human fetal adrenal cortical cells: implications for adrenal androgen regulation. J Clin Endocrinol Metabol 1997;82:1390–6.
[100] Ibanez L, Potau N, Zampolli M, et al. Hyperinsulinemia and decreased insulin-like growth factor-binding protein-1 are common features in prepubertal and pubertal girls with a history of premature pubarche. J Clin Endocrinol Metabol 1997;82:2283–8.
[101] Dunger DB, Ahmed ML, Ong KK. Early and late weight gain and the timing of puberty. Mol Cell Endcorinol 2006;254–255:140–5.
[102] Ibanez L, Valls C, Ong K, et al. Metformin therapy during puberty delays menarche, prolongs pubertal growth, and augments adult height: a randomized study in low-birth-weight girls with early-normal onset of puberty. J Clin Endocrinol Metabol 2006;91:2068–73.
[103] Ong K, de Zegher F, Valls C, et al. Persisting benefits 12-18 months after discuntinuation of pubertal metformin therapy in low birthweight girls. Clin Endocrinol 2007;67:468–71.
[104] Ibanez L, Lopez-Bermejo A, Diaz M, et al. Metformin treatment for four years to reduce total and visceral fat in low birth weight girls with precocious pubarche. J Clin Endocrinol Metabol 2008;93:1841–5.
[105] Ibanez L, Lopez-Bermejo A, Diaz M, et al. Early metformin therapy (age 8-12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. J Clin Endocrinol Metabol 2011;96:E1262–7. https://doi.org/10.1210/jc.2011-0555.
[106] Connor EN. Impact of fetal and neonatal malnutrition on the onset of puberty and associated noncommunicable diasease risks. Adolesc Health Med Ther 2011;2:15–25.
[107] Godfrey KM, Gluckmn PD, Hanson MA. Developmental origins of metabolic disease: life course an in İntergenerational perspectives. Trends Endocrinol Metabol 2010;21:199–205.
[108] Lin X, Lim IY, Wu Y, et al. Developmental pathways to adiposity begin before birth and are influenced by genotype, perinatal environment and epigenom. Bio Med Central Med 2017;15:50.
*[109] Hanson MA, DPhil MA, Gluckman PD. Developmental origins of health and disease – global public health implications. Best Pract Res Clin Obstet Gynaecol 2015;29:24–31.
[110] Agnihotri B, Antonisamy B, Priya G, et al. Intergenerational study of trends in human birth weight accross two succesive generaations. Indian J Pediatr 2008;75:111–7.
[111] Fleming TP, Watkins AJ, M Velazquez MA, et al. Origins of lifetime health around the time of conception: causes and consequences. Lancet 2018;391:1842–52.
[112] Giabicani E, Pham A, Brioude FB, et al. Diagnosis and management of postnatal fetal growth restriction. Best Pract Res Clin Endocrinol Metabol 2018;32:523–34.
[113] Santiago ACT, da Cunha LPM, Vieira NSA, et al. Breastfeeding in children born small for gestational age and future nutritional and metabolic outcomes: a systematic review. Jornal de Peditria (Rio J) 2018. https://doi.org/10.1016/j.jped.2018.06.013.
[114] Metrustry SJ, Karhunen V, Edwards MH, et al. Metabolomic signitures of low birth weight: pathways to insulin resistance and oxidative stress. PLoS One 2018 Mar 22;13(3):e0194316. https://doi.org/10.1371/journal.pone.0194316.