Review Article

Nutrition and pubertal development

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ABSTRACT

Nutrition is one of the most important factors affecting pubertal development. Puberty entails a progressive nonlinear process starting from prepubescent to full sexual maturity through the interaction and cooperation of biological, physical, and psychological changes. Consuming an adequate and balanced healthy diet during all phases of growth (infancy, childhood and puberty) appears necessary both for proper growth and normal pubertal development. Girls begin puberty at an earlier age compared to past decades. Excessive eating of many processed, high-fat foods, may be the cause of this phenomenon. Overweight or obese children are more likely to enter puberty early. Some evidence suggests that obesity can accelerate the onset of puberty in girls and may delay the onset of puberty in boys. Moreover, the progression of puberty is affected by nutrition. On the other hand, puberty triggers a growth spurt, which increases nutritional needs including macro and micronutrients. Increased caloric, protein, iron, calcium, zinc and folate needs have to be provided during this critical period of rapid growth. Severe primary or secondary malnutrition also can delay the onset and progression of puberty. The higher incidence of anorexia nervosa and bulimia in adolescents imposes a nutritional risk on pubertal development. Moreover, many environmental endocrine disruptors (EDs) have been identified that can significantly impair the normal course of puberty. This mini-review sums up some important findings in this important complex that link nutrition and pubertal development.

Key words: Adolescents, androgens, growth, IGF-I, insulin, malnutrition, nutrition, obesity, thelarche

Introduction

Nutritional status during childhood has a significant effect on pubertal development and can explain as much as 25% of the variation in the timing of puberty. Over-nutrition and obesity seem to trigger pubertal onset. Neonatal shortness and thinness are associated with earlier pubertal maturation.[1]

Most girls enter puberty between age 8 and 13 years, while boys enter puberty from age 10 to 15 years. In 2009, Biro *et al.* studied a baseline cohort of girls (n = 1239). At 7 years, 10.4% of white and 23.4% of black girls had attained breast stage ≥2 and at 8 years, 18.3%, 42.9%, respectively.[2] In a more recent survey, the median age at onset of breast stage 2 was 8.8, 9.3, 9.7, and 9.7 years for African American, Hispanic, white non-Hispanic, and Asian participants, respectively. Strong associations were found between all pubertal timing parameters on the one hand and BMI and percent body fat on the other hand. Increased consumption of processed, high-fat foods may be blamed for this phenomenon.[2-4] Some controversy exists about the effect of obesity on pubertal onset in males. An expert panel reviewing existing American pubertal data from boys in 2005 could not confirm a secular trend in male pubertal timing.[5] National Health and Nutrition Examination Survey III findings reported a mean age of 10.4 years for Caucasian boys entering Tanner stage G2.[6] Furthermore, the Copenhagen Puberty Study reported a 3 month decline in pubertal onset during a 15-year period (from 11.92 years in 1991 to 11.66 years in 2008). In contrast a negative association between obesity and early puberty was found in the National Institute of Child Health and Human Development study. Other studies in males have not been able to document an association between prepubertal BMI and age at pubertal.[6]

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Progression of puberty has been shown to be affected by prepubertal body composition in healthy boys and girls in a longitudinal study. Higher prepubertal BMI and fat mass resulted in earlier attainment of pubertal stages. Both clearly predicted the age at peak height velocity (APHV) and puberty duration in both sexes and age at menarche in girls.[7,8]

Nutrition and puberty programming in animal models

Body energy stores can influence the onset of puberty.[9] The effects of early life (pre- or postnatal) overnutrition or under-nutrition on pubertal timing and endocrine make-up are studied in rats of both sexes.[10] Rats exposed to gestational under-nutrition (UNG) or peripubertal (SUB) sub-nutrition or raised in large (LL; underfeeding) or small (SL; overfeeding) litters were examined. The following results have been demonstrated:

- Gestational under-nutrition resulted in insulin resistance in males
- Postnatal overfeeding resulted in advanced external signs of puberty in overfed males
- Postnatal over-nutrition consistently increased LH, FSH, leptin, and insulin levels only in pubertal females
- Postnatal high fat diet after weaning tended to advance puberty in females and increased gonadotropin levels in overfed males
- Postnatal under-nutrition delayed puberty in males more than in females
- Peripubertal sub-nutrition delayed the onset of puberty in females but not in males.

These results demonstrate important sex differences in the impact of early under-nutrition on the onset of puberty.[10-12]

In the rat, obesity and related metabolic sequelae have been induced in offspring by exposure to maternal under-nutrition, a maternal low protein (MLP) diet; maternal uterine artery ligation, and others.[13] Both maternal under-nutrition and high fat nutrition during pregnancy have been shown to significantly accelerate the onset of puberty in male and female rat offspring. This proves an important effect of maternal prenatal diet on pubertal development of her child.[10-18]

On the other hand, rats with intrauterine growth retardation (under-nutrition) due to ligation of the uterine arteries had delayed onset of puberty. Females had anovulation during the first cycle and their ovaries showed a lower number of follicles.[19] In males, testosterone production was low.[20] In the sheep fetus, a developmental change in circulating and adipose tissue-derived leptin is suggested to mediate the long-term consequences for appetite regulation, development of obesity and puberty.[21,22]

In lambs, prepubertal under-nutrition prevented initiation of ovulation through inhibition of LH secretion. Refeeding resulted in catch-up growth and beginning of ovulation.[23]

Fetal nutrition and timing of puberty

The relationship between human fetal growth and timing of puberty is often controversial because of the different etiologies of intrauterine insults leading to children born small for gestational age. Several studies showed that maternal exposure to unfavorable environmental factors during pregnancy and/or lactation can increase the risk of developing later obesity and metabolic disease.[19] Rapid brain development during intrauterine and early postnatal environments has a major impact on different metabolic and neural development that regulates energy homeostasis and possibly pubertal axis. Permanent changes in appetite control brought during this critical intrauterine period of development can significantly increase the occurrence of obesity and other metabolic disorders later in life.[20]

One study examined the relationship between birth weight and the onset of puberty and pubertal progression in different groups of healthy children. In girls, no differences were observed in timing and progression of puberty between groups of different birth weights. In boys, a relatively delayed onset of puberty was observed in those with low birth weight, with a normally timed progression.[23]

Other studies showed that boys born SGA had high levels of follicle-stimulating hormone (FSH) and low levels of inhibin B and a small testicular volume during adolescence. In girls born SGA, the age at pubertal onset and the age at menarche were advanced by about 5-10 months. Their ovulation rate was found to be reduced in and an insulin-sensitizing therapy was capable of raising this low ovulation rate. They may have also smaller internal genitalia. Menarche is definitely advanced in girls born SGA with precocious pubarche and in those with an early-normal onset of puberty. Current evidence suggests that insulin resistance is a key mechanism linking a post-SGA state to early menarche; hence, insulin sensitization may become a valid approach to prevent early menarche and early growth arrest in girls born SGA.[23-26]

Studying the biochemical pathways and evolution of human puberty specified strong connection between intrauterine and infantile malnutrition (early critical periods) that was followed by catch-up growth in childhood appears to accelerate the onset of puberty and increase the risk of developing non-communicable diseases (NCDs) in later life.[25]

Infancy-childhood -Nutrition and onset of Puberty

Nutrition is an important regulator of growth and obesity is usually associated with tall childhood stature and earlier pubertal development. Longitudinal studies have recognized that timing of puberty is closely related to infancy weight gain and suggested an early window for programming of growth and development. Earlier puberty in the UK MRC 1946 birth cohort was related to smaller size at birth and rapid growth between 0 and 2 years.[27,28]

An extensive systematic review of published studies investigating the association between infant feeding and obesity was performed. In these studies, breastfeeding was associated with a reduced risk of obesity, compared with formula.[27,28] Girls who were heavy at birth reached menarche earlier than others with similar infant growth. Rapid growth during infancy was related to early pubertal maturation.[29] Other studies showed that when low birth weight offspring were over nourished with rapid infantile catch-up growth they had evidence of increase body weight, body fat and leptin resistance as adults. Conversely, if catchup growth is delayed by nutrient restriction, these offspring exhibit normal body weight, body fat and plasma leptin levels as adults. Rodent data confirmed that prevention of early catchup growth can reverse glucose tolerance and obesity.[30-32] A recent study showed that breast fed girls (with slower growth during early infancy) had later onset of breast development compared to formula fed infants (with faster growth during early infancy) and the duration of breastfeeding was also directly associated with age at onset of breast development.[33,34]

These findings supported the likelihood that timing of puberty (menarche) may be set in utero or early in life, even though it can be modified by changes in nutrition, body size and composition in childhood.[29]

Prepubertal attainment of a critical body weight and/or fat mass (FM) has been thought to have a noticeable role in the start of sexual maturation whereas underfeeding and malnutrition in humans has been related to delayed pubertal onset.[35-38] In a large population-based study done in Sweden, large growth data showed that an increase of one BMI unit between ages 2 and 8 was associated with an average of 0.11 years earlier for peak height velocity. In addition children with higher changes in BMI had significantly earlier timing of pubertal onset. This suggests that over-nutrition in early childhood can result in an earlier onset of puberty in both sexes.[39] Girls with a higher percentage of body fat and BMI at age 5 and 7 had significantly earlier pubertal development at or by age 9. A strong correlation was reported between percentage body fat at age 7 and breast development at age 9.[39,40]

Nutrition–hormone interaction during critical periods of growth plays an essential role in the control and prediction of metabolic adaptation and pubertal development later in life.[19] Rapid early weight gain leads to taller childhood stature and higher insulin-like growth factor I (IGF-I) levels, possibly through early induction of growth hormone (GH) receptor numbers, and such children are also at risk of childhood obesity.[41] In the Avon Longitudinal Study of Parents and Children, rapid infancy weight gain was associated with increased risk of obesity at 5 and 8 years, with evidence of insulin resistance, exaggerated adrenarche and reduced levels of sex hormone binding globulin (SHBG). Theoretically the increased IGF-I and adrenal androgen levels can increase aromatase activity and free sex steroid levels which consequently can early arouse the GnRH pulse generator. Besides, obese infants and children have higher leptin levels with a proven permissive factor in initiating LH pulsatility.[42,43-46]

Pubertal growth spurt and nutritional requirements

Linear growth increases markedly during puberty in both sexes from approximately 5 cm/year in prepubertal males and females to 8.3 cm/year in pubertal females and 9.5 cm/year in pubertal males. Weight velocity increases from 3 kg/year in prepubertal males to 9 kg/year during puberty; the gain is composed almost entirely of lean tissue. Although increased rates of protein accretion could be mediated through increased protein intake, recorded intakes of protein do not change at puberty when adjusted for body weight. Similar intakes of protein (150 and 147 mg nitrogen/kg per day) are sufficient to maintain nitrogen retention during puberty. This is due to the markedly increased efficiency of utilization of dietary protein for retention relative to intake, reflected by a decreased rate of leucine oxidation in the fed state, and increased net leucine retention in pubertal than in prepubertal subjects. In addition, decreased energy requirement relative to protein may be another mechanism of increased protein gain.[47-50]

According to the Dietary Guidelines for Americans 2010, girls ages 9 to 13 generally require 1400 to 2200 calories and girls ages 14 to 18 usually need 1800 to 2400 calories each day during puberty. Active pubescent girls require more calories than those with low activity levels.[51] Boys during puberty need more calories than girls because their larger frames and bigger muscle mass. Boys ages 9 to 13 need 1600 to 2600 calories, and teen boys ages 14 to 18 require 2000 to 3200 calories per day to maintain healthy body weights. Teenage athletes who regularly participate in vigorous sports training may require up to 5000 calories per day.[51] According to Hasbro Children's Hospital, children ages 7 to 12 need 27.3 to 34.1 calories per pound of body weight, while preteens and teens ages 12 to 18 require about 13.6 to 27.3 calories per pound of body weight each day. Using

these weight-calorie guidelines, a 115-pound, 13-year-old pubescent boy needs 1564 to 3140 calories, and a 110-pound, 13-year-old pubescent girl requires between 1496 and 3003 calories per day depending on activity level.[51,52]

Interaction between nutrition, hormones and pubertal growth

During puberty, changes in lean body mass and protein metabolism are regulated by numerous hormonal mechanisms.[53] Pubertal growth acceleration is largely due to the synergetic effects of increased secretion of gonadal sex steroids, growth hormone (GH), and IGF-I and insulin. During puberty, free insulin, IGF-I, and IGF-binding protein 3 (IGFBP-3) concentrations correlate positively with leucine retention (protein accretion). IGF-I and GH decrease leucine oxidation[54] and regulate the efficiency of protein utilization during puberty. IGF-I also slows energy expenditure, and may exert protein-sparing effects indirectly through its effects on energy metabolism during feeding.[54-56] Plasma insulin levels markedly rise during puberty with a strong positive correlation with IGF-I [Figure 1].[57]

It is observed that there is a significantly higher increase in DHEA-S during the year when a child had the highest rise in BMI compared with the year when the BMI rise is lower. This suggests that an increase in body fat may play a critical role in the turning on of adrenal androgen secretion and adrenarche. A study from France found that 32.5% of girls with appearance of public hair between the ages of 4 and 8 had BMI of >2SD and that the correlation between BMI Z score and serum DHEA-S was highly significant.[58]

Rodent and human studies propose that leptin may be the critical link between body fat (obesity) and earlier puberty.[59,60] Leptin deficiency leads to failure of puberty in mice and humans that can be treated by leptin administration. In rodents, leptin stimulates gonadotropin secretion both at the hypothalamic and the pituitary level. Consequently, LHRH stimulates the release of LH and FSH from the pituitary, which in turn stimulate the gonads to release testosterone and estradiol.[60] In human, leptin appears to play a permissive role rather than act as the critical metabolic sign initiating puberty.[58-65] Low leptin concentration in response to food deprivation can explain the starvation-induced suppression of the hypothalamic-pituitary-gonadal axes as well as the malfunction of several other neuroendocrine axes. It is becoming clearer that leptin may act as the link between adipose tissue, hypothalamic centers regulating energy homeostasis, and the reproductive system[61-65] [Figure 2].

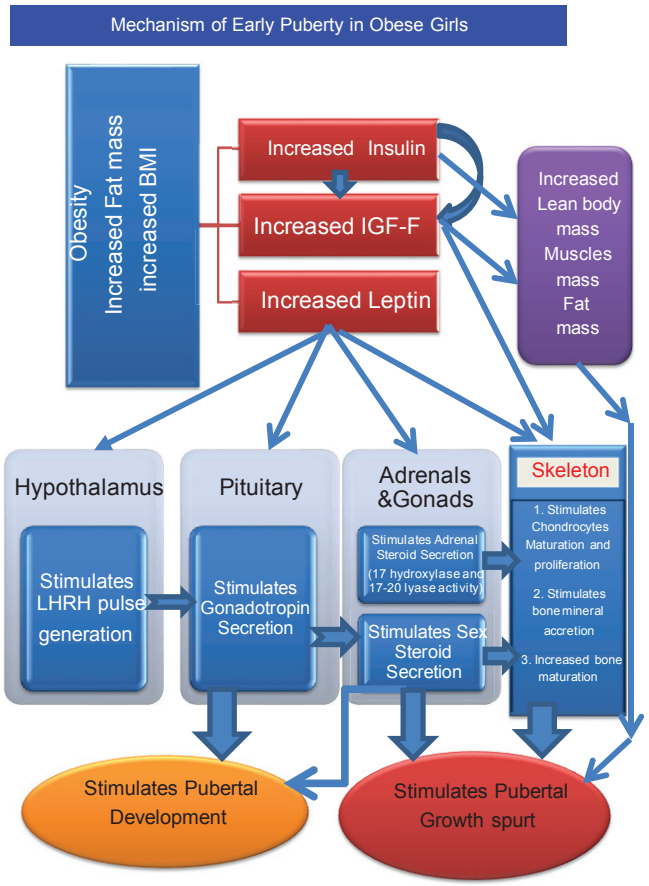

Figure 1: Mechanism of early puberty in obese girls

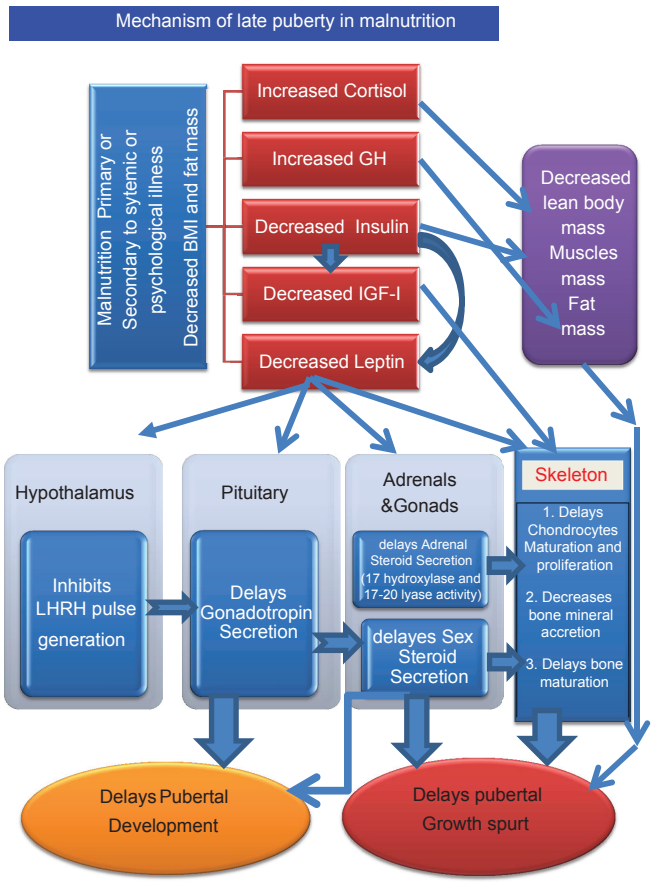

Figure 2: Mechanism of delayed puberty in malnutrition

Kisspeptins, the products of the KISS1 gene, and the GPR54 system are recently discovered essential gatekeeper that control pubertal development. Kisspeptins are stimulators of gonadotropin secretion, primarily through stimulation of gonadotropin-releasing hormone release. KISS1 also functions as an essential integrator for peripheral inputs, including gonadal steroids and nutritional signals, and for controlling GnRH and gonadotropin secretion. Studies in rats demonstrated a significant interaction between energy status and the hypothalamic KISS1 system. A marked reduction in central KISS1 tone occurs in conditions of negative energy balance (under-nutrition) that can inhibit the gonadotropic axis.[66,67]

Obesity, pubertal growth spurt and final adult height

Analysis of growth data for 1250 obese subjects (4-18 years) verified an increased growth that starts in the first years of life.[68] The height gain attained in the first years of life would be exploited and maintained up to the beginning of puberty and with a growth velocity equal to that of the lean subject. However, skeletal maturation is markedly increased and the bone age continued to be advanced during the whole period of pubertal development. During puberty obese subjects exhibit a less remarkable growth spurt when compared with lean subjects. The growth advantage gradually attained early declines and the final adult height of obese and normal subjects is equal.[68] In support, a multicenter, prospective study showed that overweight or obese young adults were taller in childhood compared with normal weight young adults, but had relatively decreased growth in height throughout the teenage years.[69] On the other hand, a longitudinal study which tracked advanced skeletal maturity and linear growth acceleration throughout infancy, childhood and adolescence in individuals who become overweight or obese showed that increased BMI in children on a path to becoming overweight adults preceded advancement in skeletal development and subsequently they had tall stature during puberty.[70]

Although adiposity in early childhood appears to be linked to advance puberty in girls it is important to recognize that, to some degree, weight gain during puberty is physiologic because normal puberty in girls is accompanied by increases of BMI and subcutaneous adiposity. Data suggest that increased adiposity precedes early puberty in many of these girls.[69-71]

Under-nutrition, chronic diseases and pubertal growth

Under-nutrition is the most important cause of growth retardation worldwide. Poverty in the poor countries and self-induced food restriction in the rich countries or malabsorption and chronic systemic diseases are the main causes. Primary or secondary malnutrition leads to serious consequences including impaired growth, osteopenia, anemia, and different syndromes caused by deficiency of vitamins, minerals, essential fatty acids and amino acids, and trace elements.[72-75]

Chronic primary malnutrition during childhood modulates the timing of adolescent sexual development in both sexes and is associated with later age of menarche (as well as secondary amenorrhea).[75-77]

Patients suffering from secondary malnutrition due to chronic diseases also have delayed onset of puberty and a reduced pubertal growth spurt. Although the etiology of abnormal puberty in these patients is multifactorial, nutritional deficiency largely contributes to their growth and pubertal delay.[78,79] Insufficient food supply due to decreased appetite, eating disorders and/or malabsorption of nutrients can be observed in these patients. Moreover, increased energy expenditure is another mechanism of hastening malnutrition in these children.[80] More specific factors due to the disease itself may be involved in growth and puberty disorders. Abnormalities of the growth hormone (GH-IGF-1) axis and gonadotrophin secretion have been described in patients with chronic renal failure, cystic fibrosis and Crohn's disease.[81-83]

More recently, it has been shown that cytokines produced during chronic diseases such as juvenile idiopathic arthritis and CF may affect the GH-IGF-1 axis. The associated medication, namely corticosteroids, which are often given to these patients, also contribute to delayed puberty and poor pubertal growth.[84,85]

Anorexia nervosa (AN) is a common eating disorder with self-induced food restriction. Stunting of growth and arrest of prepubertal development and amenorrhea are frequent signs of AN when it occurs during puberty. In AN, GH hyper-secretion at least partially reflects malnutrition-induced peripheral GH resistance, which leads to reduced IGF-I synthesis and release. This implies an impairment of the negative IGF-I feedback action on GH secretion.[85] Leptin is reduced and can mediate an inhibitory effect on the hypothalamic pituitary gonadal (HPG) axis and pubertal development. Basal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are significantly lower and their responses of LH to GnRH are diminished. Regardless of the supposed central and peripheral alterations that occur in AN, it has to be emphasized that the activity of the GH/IGF-I and HPG axes is generally restored by nutritional rehabilitation and stable weight gain. It therefore reflects the severity and duration of impaired nutritional state.[82,83]

Endocrine disruptor (EDs) and pubertal development

EDs accumulate in the environment in the long term and are introduced into the human body through water, air, foodstuffs, or through equipment used in the office and home. Human studies have shown that several EDs including DDT/dichlorodiphenyldichloroethylene (DDE), PCBs, polybrominated biphenyls (PBB), hexachlorobenzene, endosulfan, dioxins, heavy metals and phthalates affect puberty in humans. A significant relationship has been found between intrauterine exposure to high doses of PBB pesticides and early thelarche and pubarche in girls. In addition, an association between serum DDT/DDE concentrations and early menarche was reported in textile workers. Exposure to phthalate esters (used as plastic softeners and in some cosmetic products, shampoo, and perfumes) has been linked with early thelarche. A bisphenol A (BPA) (found in huge amounts in baby feeding bottles), has also been suggested to have estrogenic effects causing precocious puberty. Heavy metal exposure especially lead was associated with delayed pubarche and menarche. Avoiding different methods of exposure to these EDs should be enforced to avoid abnormalities of pubertal development and reproduction.[86-89]

Conclusions

Obesity during infancy and childhood, especially in infants born SGA, is associated with accelerated linear growth and earlier puberty in girls. Girls with obesity are at risk for hyperinsulinemia and hyperandrogenemia. The relation between nutritional disorders (obesity and under-nutrition) and pubertal disorders and potential reproductive complications should be investigated more fully in order to develop better screening and preventive tools. Nutritional conditions and its effects on pubertal development among populations susceptible to poor nutrition groups as well as those to over-nutrition, during different phases of growth, should be explored worldwide, especially among groups undergoing rapid nutritional transition. Great attention should be paid both to maternal and early neonatal and childhood nutrition to assure proper timing and progression of pubertal development and prevent obesity-related reproductive complications.

Take-home message 1

- Nutritional status during infancy, childhood and Peripubertal period has a significant effect on pubertal development
- The median age for beginning of breast development ranges between 8.8 and 9.7 years among different populations
- Intrauterine and infantile (critical periods) malnutrition that is followed by rapid catch-up growth during childhood appears to accelerate the onset of puberty
- A strong association is found between onset of puberty and BMI and body fatness
- Higher prepubertal BMI and fat mass predicts a younger age at peak height velocity and puberty duration in both sexes. However, the final adult height of obese girls is not different than their non-obese controls
- Boys born SGA may have small testicular volume, high levels of FSH and low inhibin B levels during adolescence
- Girls born SGA have advanced pubertal onset by about 5-10 months and their ovulation rate may be reduced
- Chronic malnutrition during childhood is associated with delayed puberty and compromised pubertal growth spurt.

Take-home message 2

- Although pubertal growth spurt is associated with increased protein accretion, their required protein intake per kg does not increase because of increased efficiency of utilization of dietary protein for retention
- The interaction between nutrition and pubertal development involves many endocrine and metabolic pathways including: Kisspeptin and GPR54 system leptin system, glucose-insulin homeostasis and hypothalamic pituitary growth, hypothalamic pituitary gonadal and hypothalamic pituitary adrenal systems
- Proper antenatal care for all mothers to achieve adequate intrauterine nutrition, prevention and early management of obesity during infancy and childhood and discouraging high-fat high-caloric food intake can prevent significant pubertal and metabolic disorders.

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