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Adolescents with Delayed Puberty: Interactions between Growth Hormone and Sex Steroids

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Introduction

Puberty is that period of growth when the endocrine and gametogenic functions of the gonads have first developed to the point where reproduction is possible **[**1**]**

It appears with a lot of physical and emotional changes that sometimes can be stressful for the adolescents and their families. The pubertal age for females is 8-13 years and for males it is from 9 to 14 years. In females the first stage of puberty is termed as Thelarchae, the breast development. In males, the first sign of puberty onset is testicular enlargement by 4 ml or greater in the volume. On either side, early or late of this age range, the onset of puberty can take place; those are termed as precocious puberty and delayed puberty respectively. Early appearance of pubertal signs is termed as precocious puberty whereas delayed puberty has different definitions in males and females. In males, lack of testicular enlargement by 14 years of age or more than 5 years gap is present between testicular development and completion of puberty are termed as delayed puberty. In females, lack of thelarchae phase till the age of 13 years or more than four years gap between the onset and completion of puberty **[**2**]**

Puberty, a surge in somatic and gonadal growth, is the manifestation of maturation of the Hypothalamo – Pituitary - Gonadal (HPG) axis and several interactions of humoral factors. The onset of puberty is resulted by pulsatile release of gonadotropin releasing hormones (GnRH) from hypothalamus which earlier, has been suppressed by CNS via the release of inhibitory neurotransmitters. After the onset of puberty, the interplay of various factors such as growth hormone, sex steroids, Insulin like growth factor-1 (IGF-1), nutrition and leptin has important role in the regulation of overall growth **[**3**]**

Before discussing the hormonal interactions and their applications in abnormal pubertal conditions it is necessary to see each factors' role during puberty.

Gonadotropins: The two glycoproteins, FSH and LH, are the gonadotropins secreted by anterior pituitary in response to the pulsatile release of GnRH from hypothalamus. The major roles of gonadotropins are the development of gonads and release of sex steroids from them. At puberty, per pulse the amplitude of gonadotropin secretion increases **[**4,5**]**.

Growth hormone: During puberty, a parallel spontaneous rise in serum levels of growth hormone (GH) can also be observed. It will result in overall somatic development and body composition. The temporal relationship between the growth spurt of puberty and increased GH secretion has been observed with the gender difference. GH rises in girls during earlier stages of puberty and during later

stages in boys. Further differences between the genders have been observed as more entropy in pulsatile release seen in girls than in boys **[**6,7**]**

Sex steroids: Testosterone, dihydrotestosterone (DHT) , progesterone and estradiol are considered as sex steroids. Their secretions are influenced by the gonadotropins released from anterior pituitary. Gonadal maturation, secondary sexual characteristics and sexual behavior patterns are regulated by sex steroids **[**1**]**. Along with these functions, modulation of GH secretion and actions is an important function of sex steroids which can be applied therapeutically to treat growth and developmental issues **[**8**]**

Insulin-like growth factor-1 (IGF-1): This is a polypeptide hormone which is mainly produced by the liver when the endocrine GH is stimulated. It serves as an endocrine (also as paracrine and autocrine) hormone which acts as a mediator of growth hormone (GH)-related somatic growth in peripheral tissues such as muscle, cartilage, bone, kidneys, liver, skin and lungs. It was first identified in the year 1957 by Salmon and Daughaday and was originally named as "somatomedin C"9. The growth hormone(GH) and IGF-1 axis is an important factor for the linear growth and pubertal growth production; and IGF-1 deficiency causes stunted or delayed growth. IGF-1 plays an important role in determining the timing of puberty. It is believed that the GH/IGF-1 axis has a negative impact on gonadal function and pubertal development in SPIGFD (Severe primary IGF-1 deficiency) patients; where its deficiency causes delayed puberty **[**10**]**.

Nutrition: It is considered to be an important factor which affects pubertal development. Consumption of a healthy and balanced diet during each stage of growth (infancy, childhood, puberty) is necessary for proper growth and normal pubertal development. Overweight or obese children show increased incidence of early onset of puberty especially in; however, boys may exhibit delayed onset. Puberty triggers a growth spurt which in turn accelerates the nutritional need. Children with higher changes in BMI had early timing of pubertal onset. This suggested that over-nutrition in early childhood led to early onset in both sexes **[**11**]**. Rapid weight gain in childhood leads to higher insulin-like growth factor (IGF-1) levels, probably due to early induction of growth hormone (GH) receptor numbers **[**12**]**

Leptin: It is an adipose hormone; known to play a vital role in regulation of puberty, especially in females. Leptin receptors are predominantly found in the hypothalamus, gonadotropin cells of the anterior pituitary, ovarian follicular cells and Leydig cells. Leptin hastens the gonadotropin-releasing hormone (GnRH) in the hypothalamic neurons. Obese children exhibit high levels of leptin which inhibits the functions of the gonads. In the anterior pituitary, leptin accelerates the release of LH and FSH. In boys, there is a prepubertal peak of serum leptin levels, along with an increase in GH , IGF-1

and free testosterone. In girls, however there is a continuous rise in leptin levels throughout puberty along with an increase in estrogen [13]. Children with a lack of leptin proteins have low levels of LH and FSH and do not attain pubertal maturity. However, leptin is probably not the signal to trigger the onset of puberty but serve as a metabolic gate for progression of puberty [14].

Initial stages of growth and development

Theorists such as Jean Piaget, Erik Eriksson and Lawrence Kohlberg have provided ways to understand the development and growth of children. There are three broad stages of growth: early childhood, middle childhood, and adolescence.

Early childhood (Birth-8 years)

It is a stage of tremendous growth in all areas of development; the primary developmental task being skill development. Birth to age three, there are rapid physical changes, where the typical three year old masters many skills such as walking, running, toilet training, scribbling , good hand and eye coordination. By age five the child develops good motor skills; their vocabulary expands and can phrase five-seven word sentences. Between age 5-8 years, children enter into a broader peer context and develop friendships. The preschool age begins somewhere around 3-5 years of age [15].

Middle childhood (8-12 years)

Sigmund Freud labelled this period as the latency stage, where sexual and aggressive urges are repressed. Cognitive skills, personality, motivation and interpersonal relationships develop during this stage and is primarily known as "integration". Children are cognitively more mature during this stage. Growth is slow and steady until onset of puberty. The age of onset varies among individuals, which has now been reduced over time, and may begin as early as 8 or 9 years. Recent social trends including eating disorders, depression, drug use, prevalence of school violence prevail during this period [16]

Adolescence (12-18 years)

It is a period which begins when individuals attain sexual maturity and ends when the individual has gained an identity as an adult within his or her social context. It is characterised by accelerated growth with various growth spurts; where females develop earlier than males. Sexual maturation is the most important development during this period -females mature at about 13 years and males at about 15 years. The pituitary gland is responsible for the sexual maturation through release of hormones testesterone (males) and estrogen (females) [17]

Self-limited Constitutional Delay of Growth and Puberty (CDGP)

Self-limited CDGP is the most common etiological factor for delayed puberty in both the sexes but frequently occurs in boys than in girls. Children exhibit a delayed longitudinal growth additionally and this condition seems to be inherited; as 50-80% of CDGP patients have a family history of delayed puberty. CDGP can be due to single-gene mutation showing an autosomal-dominant pattern. This self-limited delayed puberty is linked with a reproductive endocrine condition called idiopathic hypogonadotropic hypogonadism (IHH), which presents with absence of pubertal development or it may be stalled in adult age due to defects in secretion or action of GnRH **[**18,19**]**. However 20% of the IHH cases may undergo 'reversal' with the activation of the HPG axis and normalisation of the reproductive endocrine function in adulthood. More than 30 genes have been identified in the pathogenesis of IHH; wherein these genes regulate the development, migration and secretary function of GnRH neurons. There is a phenotypic resemblance between self-limited delayed puberty and IHH with reversal is suggestive that the variants in TAC3 and TACR3 (neurokinin B and its receptor respectively) may also contribute to the pathogenesis. The disruption in the neurokinin B pathway leads to a late-normal pubertal timing, frankly delayed puberty or even more severely delayed sexual maturation that does not occur until the age of 18 years, clearly demonstrating the crucial role of neurokinin B pathway in influencing pubertal timing **[**19**]**. Several potential pathogenic variants in IL17RD, a modulator of the FGF8/FGFR1 signalling pathway, possibly play an important role in the fate of specification of GnRH neurons. A recent study depicted a heterozygous variant in IL17RD in both an IHH proband and a parent with elated puberty and another variant in IL17RD in the homozygous state in an IHH proband and in the heterozygous state in a parent with delayed puberty **[**20**]**.

Hypogonadotropic Hypogonadism (HH)

Hypogonadism refers to the condition in which the male testes or the female ovaries produce little or no sex hormones. Hypogonadotropic hypogonadism (HH) is a type of hypogonadism which is due to a defect in the pituitary gland or hypothalamus. HH can be attributed to a variety of congenital origins which includes gene mutations, idiopathic forms and genetic syndrome. Acquired causes of HH include the central nervous system (CNS) insults such as trauma, radiation therapies and intracranial tumors. The most common cause of HH is the constitutional delay of growth and puberty (CDGP) which has already been mentioned in the above section **[**21**]**. LH and FSH are the two gonadotropins secreted by the anterior pituitary in response to the GnRH secretion by the hypothalamus. Both these

hormones control the reproductive physiology wherein, in males they drive the synthesis of testosterone ; and in females FSH stimulates production of estradiol, triggers follicle maturation and a surge in LH enhances ovulation [4]. Adequate functioning of the HPG axis is crucial for normal gonadal development and subsequent sex steroid production. Deficiencies at any stage of the axis lead to a hypogonadal state. In boys, it presents with a complete lack of secondary sexual development or failure of normal pubertal progression; and in girls, it presents with a failure of pubertal initiation, progression or menstrual irregularities [18]. This is of two types namely; functional hypogonadotropic hypogonadism (FHH) and permanent hypogonadotropic hypogonadism (PHH).

The steroidogenic factor-1 (SF-1) is an important nuclear receptor involved in gonadotropin secretion; it is a key gene regulator which is involved in sexual differentiation, steroidogenesis and reproduction. The target genes of SF-1 within the hypothalamus and pituitary gland include the gonadotropin releasing hormone receptor (GnRH) and the β subunit of LH 21. DAX-1 is a nuclear receptor which is involved in steroidogenesis and functions as a repressor of SF-1 mediated transcription. Males with DAX-1 mutations typically present with the early-onset adrenal insufficiency and subsequent delayed puberty secondary to hypogonadotropic hypogonadism [22]. Leptin deficiency is an outcome of loss of function mutations of the LEP gene, that encodes for the leptin protein. Leptin deficiency acts as a sign of nutritional deprivation and results in the suppression of the reproductive axis. The prominent features of leptin deficiency include hyperplasia, obesity and hypogonadotropic hypogonadism. Girls with leptin deficiency- HH present with delayed puberty, lack of pubertal growth spurt and reduced expression of secondary sexual features. Some may have irregular menses due to aromatization of subcutaneous fat to estrogen which stimulates uterine hyperplasia. Males with leptin receptor mutations exhibit diminished testosterone production and delayed puberty [23]. Various syndromes include neuroendocrine dysfunction as a potential feature; especially in case of Prader -Willi syndrome (PWS). These conditions present with hypothalamic dysfunction which leads to hypogonadism and may be related to absence of or abnormal location of GnRH neurons. Individuals with PWS show low circulating serum gonadotropins and in males increased testosterone response to human chorionic gonadotropin. Physical findings in boys include micropenis, scrotal hypoplasia, absent or delayed puberty. In girls; findings are less significant which includes hypoplasia of the clitoris or labia minora, primary amenorrhea and delayed puberty [21]. Traumatic brain injury (TBI) results in neurologic dysfunction and exhibits neurocognitive, neuropsychological and neuroendocrine sequelae. Anterior pituitary insufficiency may be noted in children with a history of TBI [24]. In children, resultant hypogonadotropic hypogonadism can present as an outcome of CNS tumor or due to therapeutic regimen needed to treat the lesion; specifically in radiation therapy. Gonadotropin deficiency and

delayed puberty are most common in children who receive 40 Gy or more of radiation; however, this can continue to evolve for many years after irradiation. Hence such children should be continuously monitored for gonadotropin deficiency and signs of pubertal delay **[**21**]**.

Hypogonadotropic Hypogonadism (Hyper H) (Gonadal Failure)

It is defined as a deficiency in gonadal hormones (testosterone) which is accompanied by an elevation in the levels of pituitary gonadotropins (LH and FSH) as a compensatory mechanism. This leads to delayed puberty, lack of facial or body hair development, short stature, delayed or irregular menstrual cycle, underdeveloped testicles and penis in adolescents. Hyper H may present due to various congenital and acquired causes. Turner's syndrome is a condition affecting females who present with a partly or completely missing X chromosome which leads to gonadal dysgenesis. Delayed puberty, failure of sexual maturation, ovarian failure and limitations of future fertility are some of the classic signs of Turner's syndrome25. Primary presentation of delayed onset of puberty arising as a result of Klinefelter's syndrome is exceptional. New cases of this syndrome may present in adolescence with concern over the lack of pubertal progress, but not delayed onset. A delayed onset of puberty may exhibit in boys with more complicated karyotypes (such as 48,XXYY; 48,XXXY ; 49,XXXXY) or in boys with 47,XXY boys with other congenital or clinical problems26. Leydig cell hypoplasia causes LH insensitivity in boys; a related condition called FSH insensitivity in females (since LH plays an important role in the female reproductive system). The prime feature is hypogonadism; delayed, impaired or fully absent puberty associated with reduction or complete lack of secondary sexual characteristics; impaired fertility or complete sterility27. Acquired causes are due to the damage to or dysfunction of the gonads; in cases including ovarian torsion, anorchia (absence of both testes at birth), orchitis (inflammation of testicles), trauma, surgery, autoimmunity, chemotherapy , radiation, infections (STDs), toxins (Endocrine disruptors). These lead to delayed puberty in adolescents and other impaired reproductive functions **[**25**]**.

Interaction between nutrition, Hormones and Pubertal Growth

Nutritional status is considered to be one of the most critical factors involved in pubertal development; it was estimated to explain as much as 25% of the variation in the timing of puberty. Early and middle stage childhood nutrition may have an impact on the timing of pubertal onset. Several studies have proposed mechanisms by which energy imbalance, micro/macronutrient food content and dietary patterns may modulate the premature activation of the HPG axis **[**28**]**. Pubertal growth acceleration is

due to an increased secretion of gonadal sex steroids, growth hormone (GH) , IGF-I and insulin. There is a decrease in leucine oxidation and efficiency of protein utilization is regulated during puberty. IGF-I also slows down the energy expenditure, and may exert protein sparing effects indirectly through its effects on energy metabolism during feeding. Plasma insulin levels have a strong positive correlation with IGF-I which markedly increases during puberty **[**11**]**. A meta-analysis and systematic review by Li et al that obesity may contribute to early pubertal development. The evidence suggested that obesity and high BMI may promote early pubertal onset in girls **[**29**]**. Chronic primary malnutrition during childhood alters the timing of adolescent sexual development in both sexes and is associated with later age of menarche. Children suffering from secondary malnutrition due to chronic disease may have delayed onset of puberty and a reduced pubertal growth spurt. Anorexia nervosa (AN) is a common eating disorder with self-induced food restriction. This leads to stunted growth and arrest of prepubertal development and amenorrhea when it occurs during puberty. There is reduced synthesis and release of IGF-I in AN. Leptin is reduced and can lead to an inhibitory effect of HPG axis and pubertal development. Basal levels of LH and FSH are significantly lower **[**11**]**.

Conclusion

There is an increased incidence of delayed puberty among the adolescents. This delay may be due to genetic variation as seen in constitutional delay of growth and puberty (CDGP) or functional defects such as malnutrition or chronic illness. Other causes include a variety of hypothalamic, pituitary and gonadal disorders. Delayed puberty affects the development of sexual characteristics due to reduced secretion of sex hormones. There is an inter-relation between the gonadotropins, sex steroids, growth hormones, Leptin, IGF-I and nutrition which explains the mechanism behind the pubertal delay. This is also accompanied by growth retardation. It is essential to understand the pathophysiology which leads to this delay and effectively educate the parents about the early detection and the outcomes for any further treatment required.

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