

REVIEW ARTICLE

Endocrine Events Involved in Puberty: A Revisit to Existing Knowledge

Shaista Aslam

ABSTRACT

Puberty is a multifaceted complex phenomenon, comprised of a series of events, controlled by hormones and other regulatory factors. It is the transition period between childhood and adolescence with key important changes occurring in physical, biological, cognitive, psychological and social spheres of an individual's life. These changes are not only important in the personal life of an individual but also affect his/her relationship with others in the society. The interaction between the hypothalamus and anterior pituitary is crucial for the onset of puberty. Leptin, secreted by adipocytes, provides the first signal to the hypothalamus that sufficient energy reserves are present to initiate the process of puberty. These signals are followed by a cascade of hormonal changes broadly referred to as adrenarche, gonadarche, and a puberty growth spurt. This is an overview of the current state of knowledge in the hormonal regulation of the events leading to puberty.

Key Words: Adrenarche, Gonadarche, Leptin, Pubertal Growth Spurt, Puberty.

How to cite this: Aslam S. Endocrine Events Involved in Puberty: A Revisit to Existing Knowledge. *Life and Science*. 2020; 1(1): 37-48.
doi: <https://doi.org/10.37185/LnS.1.1.43>

Introduction

The transition period between childhood and adolescence is referred to as puberty. This era of development is marked with rapid physiological changes comprising of the appearance of secondary sexual characteristics, gonads maturation, behavioral changes, brain development, accelerated growth and eventually attaining capacity to reproduce.¹ The complex phenomenon of puberty comprises of a multifaceted series of hormonal and other changes. Increased production of leptin is considered as a first signal that enough energy reserves are present for the initiation of pubertal development. However, the pubertal development is broadly characterized into three main events including adrenarche, gonadarche and pubertal growth spurt² Adrenarche is the activation of hypothalamic-pituitary-adrenal (HPA) axis and is characterized by the release of androstenedione ($\Delta 4$ -A), dehydroepiandrosterone (DHEA), its sulfate (DHEAS) and cortisol.³ Gonadarche, activation of hypothalamic-pituitary-gonadal (HPG) axis, is monitored through the production of follicle and

stimulating hormone (FSH) luteinizing hormone (LH) by gonadotropes in the anterior pituitary⁴ FSH and LH stimulate gonadal maturation and the secretion of sex hormones [testosterone (T) and estrogen (E)/estradiol (E₂)]² that contribute to the appearance of secondary sex characteristics, and finally pubertal growth spurt caused by activation of hypothalamic-pituitary-somatic (HPS) and hypothalamic-pituitary-thyroid (HPT) axis which increases growth hormone (GH) secretion which accelerates physical growth. The thyroid-stimulating hormone (TSH), thyroxine (T₄) and triiodothyronine (T₃) secretions meet energy demands of the body and results in transformation of a child to an adult. Moreover, there are certain other hormones which contribute in the progression of puberty. The aim of this review is to highlight the key hormonal changes and the role of gonadal and non-gonadal hormones in the pubertal development. There are many reasons to focus upon the hormonal components of the pubertal maturation. Firstly, puberty is the fundamental basis of childhood to adolescent transition. Secondly, biological processes during pubertal maturation provide targets for the development and testing of mechanistic hypotheses. Thirdly, the study of hormonal progression of pubertal processes creates unique opportunities for translational research with animal studies. Finally, pubertal development has a crucial role in channelizing the developmental pathways which may have long-term effects on social interactions,

Department of Biological Sciences

National University of Medical Sciences, Rawalpindi

Correspondence:

Dr. Shaista Aslam

Assistant Professor, Biological Sciences

National University of Medical Sciences, Rawalpindi

E-mail: shaista.aslam@numspak.edu.pk

Funding Source: NIL; Conflict of Interest: NIL

Received: Mar 27, 2019; Revised: Dec 30, 2019

Accepted: Jan 01, 2020

education, health and well-being of an individual.

1. Pubertal Processes

Puberty is the phase of development that is characterized by appearance of secondary sexual characteristics, pubertal growth spurt and attainment of reproductive capacity. The process of puberty initiates by the HPG axis re-activation, which remains dormant after first six months of life. The increased nocturnal and pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from hypothalamic neurons results in initiation of sexual maturation. The HPG axis is active during fetal life and in early childhood, but then becomes quiescent until onset of puberty. The regulatory networks gather and interpret hormonal, metabolic, nutritional, and environmental signals within the body and control the reactivation of HPG axis at puberty. The well-balanced and sophisticated interplay of these signals determine the timing of the onset of puberty.

2. Kisspeptin/GPR54 Signaling

The kisspeptin/GPR54 system has a central role in the onset of puberty. The failure to attain sexual maturity in humans and mouse models with null mutations of GPR54 provides evidence for the role of kisspeptins in puberty.^{5,6} The mechanism of involvement of kisspeptin/GPR54 system in the onset of puberty can be broadly categorized into major four event⁷ Firstly, increase in the endogenous kisspeptins secretion, sufficient to fully activate the GnRH/gonadotropin axis. Secondly, elevated sensitivity of GnRH/LH responses to the kisspeptins stimulatory effects as present at earlier stages of postnatal development. Thirdly, enhanced signaling efficiency of GPR54 coupled with the inconsistent increase in the expression of GPR54. Fourthly, an increase in the number of kisspeptins projections to GnRH neurons from anteroventral periventricular nucleus (AVPV) areas of hypothalamus.^{8,9}

3. Adrenarche

Adrenarche, an enigmatic phenomenon of adrenal gland maturation, is characterized by increased production of adrenal androgens (Δ^4 -A, DHEA, DHEAS) and T without increased cortisol levels.¹⁰ Zona reticularis, the

morphological equivalent of the fetal adrenal cortex, develops during the maturation process. The fetal adrenal cortex disappears during the early months of infancy and DHEA and DHEAS production ceases, resuming later at the age of 6 to 8 years in humans.¹¹⁻¹² Hence, a progressive increase in DHEAS heralds the onset of adrenarche.¹³ The hypothalamus-pituitary-adrenal (HPA) axis governs the process of adrenarche and maintains physiological homeostasis in basal as well as pathophysiological environments.¹⁴ Cortisol and androgen (DHEA and its sulphate) are produced from the adrenal cortex and catecholamine, epinephrine (E), and norepinephrine (NE) are produced from the adrenal medulla. The adrenal cortex and medulla have both anatomical and functional interrelationships. It is hypothesized that this adrenomedullary interplay may have some role in adrenarche.¹⁵ A close rather inverse relationship has been shown between E and DHEAS levels suggesting the modulation of androgen production from adrenals and function of the adrenomedullary system.¹⁶ The possible reasons that secretion of DHEAS and E are interdependent include the presence of β_2 -receptors on cells of the cortex¹⁷ anatomical proximity of cortical and chromaffin cells¹⁸ and innervation of adrenal medulla and cortex nerve fibers.¹⁹

The regulatory mechanism of adrenarche remained unknown for a long time. However, it has recently been established that adrenocorticotropin, 3β -hydroxysteroid dehydrogenase, and nutritional status contributes to the mechanism of adrenarche.²⁰ It has been documented that normal body growth combined with inhibition of 3β -hydroxysteroid dehydrogenase type 2 (3β HSD2) under the influence of intra-adrenal cortisol may lead to adrenarche.²¹ Furthermore, serine phosphorylation of P450c17 is stimulated by increased activity of insulin or insulin-like growth factor, IGF-1, which enhances the action of $17,20$ -lyase and promotes the production of adrenal androgen.²⁰ The increased secretion of IGF-1 and insulin has previously been reported in girls and boys with premature adrenarche.²²

Adrenal androgens are known to trigger the activation of puberty.²³ The increased levels of adrenal androgen heighten infancy growth and earlier onset of puberty.²⁴ The adrenarche and gonadarche are interlinked yet independent processes. Adrenarche initiates a couple of years prior to the process of gonadal maturation.²⁵

Cortisol

Cortisol, a stress hormone, is produced in the adrenal gland and is a corticosteroid in nature. Physiological concentrations of cortisol are required for the normal, non-stressed daily activities. Cortisol plays a metabolic role and increases nutrient concentration in the blood to meet increased energy demands during mental and physical activities. Glucose homeostasis and lipolysis are affected by even the smallest variations in plasma concentrations of cortisol.²⁶ It has been observed that physiological glucocorticoid doses may permit the anabolic effect of GH on protein metabolism and excessive doses exert an opposite effect. Adrenal glucocorticoids, particularly cortisol, decrease the growth rate by stimulating catabolism of cytoplasmic proteins and generation of lipids and carbohydrates.²⁷ Furthermore; glucocorticoids exert a direct inhibitory effect on the secretion of GH at the level of the hypothalamus. Thus, exogenous administration of glucocorticoids has been shown to decrease GH responses to GHRH in normal humans.²⁸ The stimulation of cortisol secretion is carried out through the release of the hypothalamic corticotropin-releasing hormone (CRH) and subsequent secretion of adrenocorticotrophic hormone (ACTH) from the pituitary. The well-documented circadian secretory pattern of cortisol is constant and reproducible in stable physiological conditions²⁹ and possess marked inter-individual variability³⁰ the pulse amplitude of cortisol is highest in the morning shortly after wakeup and falls to the lowest levels around midnight.³¹

The circadian rhythm of cortisol is not witnessed in the newborns, but it attains a well-established pattern by two years of age. However, there are contradictory findings on the effects of age, gender, or pubertal status on the homeostasis of

the HPA axis.³² The factors which are known to influence HPA axis maturation and circadian rhythmicity of cortisol secretion include genetics, early life events, stress factors, wake-sleep patterns, episodic secretion and feedback between the pituitary secretion of ACTH and adrenal cortisol secretion.^{14,33}

Catecholamines

The adrenomedullary and sympathetic systems are among the important regulators of energy metabolism and homeostasis in humans. The sympathetic system produces norepinephrine (NE) which is converted to epinephrine (E) in the medullary part of the adrenal gland. NE and E are converted to inactive metabolites, normetanephrine (NMN) and metanephrine (MN) respectively, through the enzyme Catechol-O-methyltransferase.³⁴

The variations in plasma catecholamines and metanephrine concentrations have been documented with differences in the sex and stages of pubertal development¹⁷ E is known to stimulate metabolic rate in humans³⁵ while NE results in increased T levels in boys. Concentrations of plasma E and its metabolite MN decrease, while plasma NE increases significantly with advancing puberty. The adrenomedullary function is linked to the plasma leptin and sex steroid concentrations¹⁶ In response to Estradiol (E₂) exposure, the suppression of in vitro E production,³⁶ basal and stress-induced NE and E concentrations in male³⁷ and female³⁸ subjects and catechol-o-methyltransferase down-regulation³⁹ has been documented in the literature. In contrast, E has both suppressive⁴⁰ and stimulatory⁴¹ effects on plasma T secretion. E stimulates lipolysis⁴² and energy consumption³⁵ and decreases the production and release of leptin from adipocytes.⁴³ The baseline and stimulated levels of E are repeatedly documented to be depressed in obese persons.^{37,44}

4. Gonadarche

Gonadarche is the earliest set of gonadal changes, which indicate that true central puberty has begun. The enlargement of testes is considered as the first physical sign of gonadarche and is accompanied by enhanced

sex steroids production.⁴⁵

Leptin

Leptin, secreted by adipocytes, is considered as a structural organizer of the hypothalamic controlling circuit for body energy balance.⁴⁶ It also provides signals to higher brain centers that there are sufficient energy reserves in the body to initiate growth and reproductive processes for attaining puberty and transforming a child into an adult.⁴⁷ Furthermore, leptin serves as a messenger for the hypothalamus and is known to stimulate GnRH secretion and regulates the reproductive system.⁴⁸⁻⁴⁹ Interestingly, the secretory pattern of leptin possesses diurnal and circadian oscillations. In normal females, leptin pulsatility is synchronous to LH and E₂ pulsatility. It is suggestive that leptin might have a significant contribution to the physiological regulation and rhythmicity of the hormones of the reproductive axis.⁵⁰ Leptin secretion is also stimulated by cortisol and is interrelated in a time-related reciprocal manner. The corticotrophin-releasing factor (CRF) stimulates the sympathetic system which excites the adrenergic receptors to augment peripheral NE secretion and leptin release inhibition.⁵¹

Ghrelin

Ghrelin has wide physiological roles that include promotion of GH release, maintenance of glucose homeostasis⁵² and to report availability of the fuel in the body to hypothalamus. There is an inverse relationship between HPG axis reactivation and ghrelin levels. Ghrelin is possibly involved in the regulation of puberty and sexual function. The rise in ghrelin levels coincides with the decline in GnRH activity in the first two years of life. The fall in the concentrations of ghrelin levels is found to be associated with progression of puberty and is inversely correlated with the awakening of gonadal axis. Ghrelin is a known signal of energy insufficiency and its role in the onset and progression of puberty has been investigated through the administration of repeated doses of exogenous ghrelin to both male and female rats at different stages of their pubertal development.^{53,54,55} The studies showed that repeated administration of ghrelin results in

lower concentrations of LH and testosterone during peripubertal period and the delayed pubertal maturation in the male rats. However, the release of LH and sex hormones was influenced by ghrelin administration in female rats at prepuberty.⁵³ Ghrelin has shown deleterious effect on the development of pubertal signs in pubertal female rats.⁵⁵ These effects are, however, pubertal stage dependent and are predominant in males than females.

Prolactin

The initiation of breast development is among the early signs of sexual maturation in girls. It is characterized by the appearance of breast bud underneath the areola. It is marked as Tanner stage 2 on Tanner classification of breast development. The onset of the larche depends on production of prolactin (PRL). During the reproductive life of females, PRL is involved in the regulation of mammary gland development at three stages: during puberty, during pregnancy and after delivery of baby.⁵⁶ The process of mammary morphogenesis is orchestrated with pituitary-driven reproductive events and changes in the systemic hormone environment. The mammary ductal network formation initiates during puberty and secretory alveoli are formed during pregnancy. Prolactin regulates the formation of mammary glands directly through stimulation of mammary epithelial cells and indirectly via regulation of the progesterone production from ovarian.⁵⁷

Melatonin

The available data demonstrates a constant and progressive decline in the nocturnal serum melatonin levels from infancy through childhood until adulthood.⁵⁸ The drop in nocturnal melatonin concentrations during pubertal development has been found related with the progression of Tanner stages⁵⁹ and sexual maturation processes.⁶⁰ Studies in human and animals have shown that the administration of exogenous melatonin can suppress secretion of GnRH.⁶¹ These observations have resulted in an emerging concern that the administration of exogenous melatonin may have adverse effect on the sexual maturation of children.⁶² However, well-designed clinical investigations and

laboratory studies in animal models are required to understand the effect of melatonin administration on the timings of puberty in adolescence.⁶³

Luteinizing Hormone

The HPG axis and programming of testicular function at puberty full mature during neonatal development in human males.⁶⁴ Puberty begins with the increased pulsatile secretion of GnRH/LH-releasing hormone (LHRH). GnRH is known to stimulate the secretion of LH and FSH from the pituitary gland, which plays a crucial role in the secretion of sex steroids and mature gametes production in gonads. At the initiation of pubertal development, the pulsatility and concentrations of LH and FSH become elevated along with enhanced production of nocturnal gonadotropins.^{65,66} In humans, plasma LH concentrations abruptly rise after a few minutes of birth⁶⁷, decline till the age of six months and remain undetectable until the initiation of pubertal development. During mid-puberty, both nocturnal and basal LH concentrations are more pronounced which raises LH pulse amplitude further. The pulsatile LHRH release establishes pubertal secretory patterns of LH release.⁶⁸ The LHRH pulse frequency initiates to increase in the prepubertal period and remain augmented during pubertal development. However, LHRH pulse amplitude increases at early puberty and continues to augment throughout adolescence. The nocturnal LHRH release is absent at prepuberty, observable at early puberty and is prominent at mid-puberty. After attaining puberty, the adult characteristics LHRH pattern of 1 pulse per hour is well-established with comparable LH and T secretion.⁶⁸⁻⁶⁹

Follicle Stimulating Hormone

Under the influence of GnRH, the anterior pituitary secretes follicle-stimulating hormone (FSH) and is glycoprotein in nature. Both, FSH and LH, regulate gonadal function, promote the production of sex steroids and gametogenesis after binding with specialized receptors present in the testis. Slightly elevated concentrations of FSH are seen in human males for 3 months postpartum. At the age of 6 months, the plasma

concentrations of LH, FSH, and T drop to a negligible level and the HPG axis enters the quiescent phase till the time it receives signals from higher brain centers to initiate maturation process at the time of puberty.⁷⁰

Inhibin

Inhibin isolated from follicular fluid is a glycoprotein which suppresses the secretion of FSH. Inhibin is present as a heterodimer with two dissimilar subunits which includes inhibin A with alpha-subunit and inhibin B with beta-subunit. Both the subunits are interconnected through disulphide bonds.⁷¹ Inhibins function as gonadal messengers and inhibit the release of pituitary FSH through negative feedback mechanism in rodents, ruminants, and primates. Furthermore, inhibins regulate the ovarian and testicular functions in a paracrine manner and are promising markers for infertility, gestational and gynecological disorders in both sexes.⁷² The physiological production of inhibin by the testis in adults is dependent upon FSH stimulation, normal Sertoli cells population and spermatogenesis. However, FSH stimulation and spermatogenesis are not essentially required for basal release of inhibin B. These factors attribute to the secretion of inhibin in hypogonadism, impaired spermatogenesis⁷³ and in T treated men.⁷⁴ However, experimental studies and clinical evidence have shown that the stimulation of Sertoli cells with FSH has stimulatory while LH has inhibitory effects on inhibin secretion.⁷⁵

Detectable levels of both Inhibin A and B are found in the serum of male fetuses during 14 and 16 weeks of gestation.⁷⁶ Serum inhibin B level has a direct correlation with serum T⁵⁹ and an inverse relationship with serum FSH⁷⁷ concentrations at mid-trimester. This is the same regulatory pattern of inhibin B, T and FSH witnessed during the later stages of life. In neonates, males have higher serum concentrations of inhibin B than females, but there is no correlation with serum FSH levels in both sexes. It is suggested that the testes have a probable role in inhibin production.⁷⁸ Serum inhibin B concentrations are detectable at birth⁷⁹, reach peak levels at the age of 3 and 4

months and then decline to low but detectable levels until the age of puberty.⁸⁰ There is a slight decline in inhibin B concentrations in elderly men with a reduction in testicular function.⁷⁴

Testosterone

The physical changes during puberty in boys are under the control of increased circulating testosterone (T) concentrations. The increased production of androgens controls pubarche (hair development in genital and pubic region).⁸¹ In boys, the main source of circulating T concentrations are the testes. Moreover, the peripheral conversion of androstenedione also produces small amount of T.⁸¹ Testosterone is higher in male than in female fetuses prenatally, particularly from about week 8 to 24 of gestation⁸² and about week 4 to 24 postnatal.^{83,84} The early postnatal elevated concentrations of T are referred to as mini puberty. Testosterone during mini puberty influences the male genitalia development and attainment of reproductive function.^{85,86} Furthermore, the development of gender-typical behavior is also controlled by the circulating T levels.^{84,87}

Estrogen and Progesterone

As the gonads become sensitized to gonadotropin stimulation, they grow and secrete sex hormones at steadily increased rates. Within 3 years of rising above the prepubertal range, estradiol increases an average of 20 pg/mL (73.4 pmol/L) yearly to reach the mid-adult range.⁸⁸ The female neuroendocrine system becomes capable of secreting a mid-cycle surge of LH when the ovaries are prepared for ovulation and have sustained level of estrogen secretion. Estrogen stimulates the female genital tract (endometrial growth, cervical mucus secretion) and breasts.⁸¹ Estrogen surge results in pubertal growth spurt, directly and indirectly via growth hormone, stimulates epiphyseal growth and epiphyseal maturation, and peak bone mass accrual.⁸⁹ Estrogen results in epiphyseal fusion and is a potent inhibitor of bone resorption after attaining pubertal growth spurt. During puberty, estrogen promotes lipogenesis, lower body fat distribution and increase of body mass index during puberty.⁹⁰ The menstrual cycle arises

from cyclic maturation of ovarian follicles that results in cyclic changes in estradiol and progesterone, which entrain cyclic changes in gonadotropin concentrations which select and nurture one dominant follicle to the point of ovulation for potential fertilization.⁹¹ The ovaries also secrete androgens along with the adrenal glands which are involved in the development of pubic hairs.⁸¹

5. Pubertal Growth Spurt

The multiplex process of growth initiates from conception and continues throughout the life of an individual. The control of growth progression is based on the age- and gender-dependent interactions among many factors including genetics, developmental processes, nutrition, metabolism, hormones, biochemical compounds, socioeconomic status, behavior and/or environment. However, it has previously been shown that genetic predisposition is the main contributor to the height velocity in the newborn.⁴⁶

Growth Hormone

The pattern of linear growth during infancy, prepuberty, puberty and adolescence closely correlates with the secretory profiles of growth hormone (GH) by the anterior pituitary. GH is known to increase cell numbers in the body through mitosis and stimulates body growth.⁹² GH predominantly promotes the growth of muscles, bones, and cartilage. The age-dependent change in the 24h secretory pattern of GH has been observed in both human and experimental animals. The spontaneous pulsatile secretion of GH can be witnessed in human infants during the first one to two days and it keeps on increasing in both pulse frequency and amplitude during infancy. The nadir, frequency, and amplitude of GH secretion decrease as the infant approaches childhood. Studies on the 24 h pattern of spontaneous GH secretion in prepubertal children revealed peaks of GH both during waking and sleeping hours.⁹³ Nevertheless, GH secretion per 24h is highest in boys at late puberty and is about three folds of GH levels during prepuberty. Shortly after attaining the final adult height, the peripheral GH and concentration pulse pattern returns to

prepubertal levels. GH profiles of prepubertal boys and young men are remarkably similar.⁹⁴ The total GH secretion in young adults drops to almost one-half of the GH concentrations in boys at late puberty, while the 24 hour spurt frequency of GH remains the same in both late pubertal boys and young adults.⁹⁵

Insulin-like Growth Factors

Insulin-like growth factors are polypeptides having high sequence similarity with insulin and are part of a complex system that facilitates the communication of cells with their physiological environment. The production of circulating IGF-1 takes place in the liver and is primarily controlled by the GH. Other factors that modulate the secretion of IGF-1 include caloric restriction, sex steroids and malnutrition associated diseases.^{96,97} IGF-1 is required for maximal growth through increased cell proliferation and reduced cell death. IGF-1 is also involved in neural development⁹⁸ and the development of olfactory organs.⁹⁹

Very low serum IGF-1 concentration is observed at birth, attaining peak at late puberty, dropping to half its pubertal levels at early adulthood and then declining through the rest of life.¹⁰⁰ Age has been found positively correlated with serum IGF-1 concentrations during pre-, early- and mid-pubertal development, while this association is negative at late puberty.¹⁰¹⁻¹⁰²

During pubertal development, there are conflicting reports on the correlation of serum IGF-1 and sex steroid concentrations. Some authors have reported that the serum IGF-1 levels are significantly associated with sex steroids concentration in both boys and girls¹⁰³⁻¹⁰⁴ while according to another study, such positive association is only found in girls and not in boys.¹⁰⁵

The growth rate of an individual is influenced by a combination of hormonal and metabolic changes.¹⁰⁶ Body length is predominantly upregulated by GH, which interacts with insulin, thyroid and sex hormones, calcitonin and parathormone.¹⁰⁷ Androgens of the adrenal cortex and gonads exert a direct influence on puberty. Both types of androgens are anabolic in effect and influence bone tissue, enhance the

body growth and increase working capacity and endurance.¹⁰⁸

Thyroid hormones

The hypothalamic-pituitary-thyroid (HPT) axis contributes to the initiation of puberty through increased secretion of thyroid hormones to meet increased energy demands. A transient surge of thyroid-stimulating hormone (TSH) is observed with the onset of pubertal development and triggers an increase in the thyroid volume. The change in thyroid volume is known to occur mainly between 11 to 15 years.¹⁰⁹⁻¹¹⁰ Nevertheless, at the age of 9 to 9.5 year, a prepubertal TSH surge is witnessed, which transiently increases the levels of thyroid hormones (T4 and T3) and augments peripheral T4 to T3 conversion.¹¹¹ As puberty approaches, TSH levels decline or may remain constant but the levels of circulating thyroid hormones decline progressively.¹¹¹⁻¹¹³ The increase in thyroid volume is related to the progression of pubertal development and it is suggestive that numerous growth factors may positively modulate the HPT axis, possibly through TSH-independent pathways. Further, it has been suggested that growth factors may alter the sensitivity of TSH receptor and/or other endogenous pathways of the thyroid gland.¹¹⁴ A study in healthy adolescents has demonstrated the positive modulation of the HPT axis with a striking rise in plasma IGF-1 and GH concentrations. Furthermore, concentration of T3 remains constant while levels of total and free T4 are decreased in boys during mid- to late puberty.¹¹²⁻¹¹³ The sex steroid receptors are known to have a differential effect in normal and pathological human thyroid tissues. The androgens have a restraining influence on the thyroid gland.¹¹⁵⁻¹¹⁶ It is suggested that growth factors that modulate somatic development and sex steroids influence the growth of the thyroid gland during puberty.¹¹⁷

Parathyroid Hormone

Parathyroid hormone-related protein (PTHrP) is expressed in the epiphyseal growth plate and sends signals to the PTH/PTHrP receptor on proliferating chondrocytes and works as a limiting factor and slows the process of

chondrocyte differentiation.¹¹⁸ The expression of PTHrP has been reported in human pubertal growth plate which provides a clue that it might also be involved in the regulation of pubertal growth.¹¹⁹ Furthermore, PTHrP expression is higher in hypertrophic chondrocytes in early puberty in comparison with late puberty. PTHrP expression is negative in the resting and proliferative chondrocytes throughout pubertal development. Further investigations are needed to fully elucidate the underlying mechanism of the expression of PTHrP during pubertal development and ultimately the pubertal growth spurt.^{119,120}

Peptide YY

The anorexigenic effects of peptide YY (PYY) are well-documented and they are potentially involved in the long-term modulation of nutritional status.^{121,122} The available data have reported that lower concentrations of circulating PYY results in increased GH levels.^{123,124} Thus, the physiological drive to eat, reproductive function and weight gain are influenced by the alterations in circulating levels of PYY. At the time of puberty, the rapid processes of growth and maturation requires coordinated regulation of appetite regulatory signals and energy balance.^{125,126}

Conclusion

The attainment of puberty is a sensitive and complex multifactorial process comprised of a cascade of hormone secretions from various endocrine glands. However, the role of these triggers in the initiation of puberty and interplay of various hormones have been a great puzzle for scientists for many years. All the hormones play a pivotal role in the progression of puberty and culminate into reproductive competence. The reproductive system is under the control of a complex regulatory network. The pulsatile secretion of GnRH from the hypothalamus stimulates the pituitary gonadotropins and gonadal sex steroids. The regulatory mechanisms involved in the secretion of GnRH is not completely understood, but the identification of leptin has provided a clue for initiation of GnRH secretion. The other hormones including the metabolic hormone, ghrelin, are involved in the regulation of puberty and the reproductive axis. Further, the availability of new powerful technologies has contributed to the

expansion of knowledge of regulation of pubertal development. The increased understanding of the regulation of puberty will be helpful in improving the treatment of reproductive disorders.

REFERENCES

1. Grumbach MM. Onset of puberty In: SR Berenberg (ed) Puberty Biologic and Social Components Stenfort Kroese Leiden Germany. 1975; pp: 1–21.
2. Reardon LE, Leen-Felder EW, Hayward C. A critical review of the empirical literature on the relation between anxiety and puberty. *Clin Psychol Rev.* 2009; 29: 1-23.
3. Parker CR. Dehydroepiandrosterone and dehydroepiandrosterone sulfate production in the human adrenal gland during development and aging. *Steroids.* 1999; 64: 640-7.
4. Witchel SF, Topaloglu AK. Puberty: Gonadarche and Adrenarche, Yen and Jaffe's Reproductive Endocrinology (Eighth Edition) Physiology, Pathophysiology, and Clinical Management. 2019; 16: 394-446.
5. Funes S, Hedrick JA, Vassileva G, Markowitz L, Abbondanzo S, Golovko A, et al. The KiSS-1 receptor GPR54 is essential for the development of the murine reproductive system. *Biochem Biophys Res Commun.* 2003; 312: 1357–63.
6. Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JS Jr, Shagoury JK, et al. The GPR54 gene as a regulator of puberty. *N Engl J Med.* 2003; 349: 1614–27.
7. Roa J, Aguilar E, Dieguez C, Pinilla L, Tena-Sempere M. New frontiers in kisspeptin/GPR54 physiology as fundamental gatekeepers of reproductive function. *Front Neuroendocrinol.* 2008; 29: 48–69.
8. Nazian SJ. Role of metastin in the release of gonadotropin-releasing hormone from the hypothalamus of the male rat. *J Androl.* 2006; 27: 444–9.
9. Melrose PA, Pickel C, Cheramie HS, Henk WG, Littlefield-Chabaud MA, French DD. Distribution and morphology of immunoreactive gonadotropin-releasing-hormone (GnRH) neurons in the basal forebrain of ponies. *J Comp Neurol.* 1994; 339: 269–87.
10. Castellano JM, Navarro VM, Fernández-Fernández R, Castaño JP, Malagón MM, Aguilar E, et al. Ontogeny and mechanisms of action for the stimulatory effect of kisspeptin on gonadotropin-releasing hormone system of the rat. *Mol Cell Endocrinol.* 2006; 26: 257–8.
11. Antoniou-Tsigkos A, Zapanti E, Ghizzoni L, Mastorakos G. Adrenal Androgens. *Endotext (Internet).* South Dartmouth (MA): MDText.com, Inc. 2000.
12. Babalola AA, Ellis G. Serum dehydroepiandrosterone sulfate in a normal pediatric population. *Clin Biochem.* 1985; 18: 184–9.
13. Mesiano S, Jaffe RB. Developmental and functional biology of the primate fetal adrenal cortex. *Endocr Rev.* 1997; 18: 378–403.
14. Biason-Lauber A, Zachmann M, Schoenle EJ. Effect of leptin on CYP17 enzymatic activities in human adrenal cells: new insight in the onset of adrenarche. *Endocrinol.* 2000; 141: 1446–54.

15. Honour JW. Hypothalamic-pituitary-adrenal axis. *Respir Med.* 1994; 88: 9–15.
16. Denburg MR, Silfen ME, Manibo AM, Chin D, Levine LS, Ferin M, et al. Insulin sensitivity and the insulin-like growth factor system in prepubertal boys with premature adrenarche. *J Clin Endocrinol Metab.* 2002; 87: 5604–9.
17. Weise M, Eisenhofer G, Merke DP. Pubertal and Gender-Related Changes in the Sympathoadrenal System in Healthy Children. *J Clin Endocrinol Metab.* 2002; 87: 5038–43.
18. Shima S, Komoriyama K, Hirai M, Kouyama H. Studies on cyclic nucleotides in the adrenal gland XI Adrenergic regulation of adenylate cyclase activity in the adrenal cortex. *Endocrinol.* 1984; 114: 325–9.
19. Bornstein SR, Gonzalez-Hernandez JA, Ehrhart-Bornstein M, Adler G, Scherbaum WA. Intimate contact of chromaffin and cortical cells within the human adrenal gland forms the cellular basis for important intraadrenal interactions. *J Clin Endocrinol Metab.* 1994; 78: 225–32.
20. Hinson JP. Paracrine control of adrenocortical function: a new role for the medulla? *J Endocrinol.* 1990; 124: 7–9.
21. Shi L, Wudy SA, Buyken AE, Hartmann MF, Remer T. Body fat and animal protein intakes are associated with adrenal androgen secretion in children. *The Am J of Clin Nutri.* 2009; 90: 1321–8.
22. Majzoub JA, Topor LS. A New Model for Adrenarche: Inhibition of 3 β -Hydroxysteroid Dehydrogenase Type 2 by Intra-Adrenal Cortisol. *Horm Res Pediatric.* 2018; 89: 311–9.
23. Liimatta J, Utriainen P, Voutilainen R, Jääskeläinen J. Girls with a History of Premature Adrenarche Have Advanced Growth and Pubertal Development at the Age of 12 Years. *Front Endocrinol (Lausanne).* 2017; 8: 291.
24. Ibanez L, DiMartino-Nardi J, Potau N, Saenger P. Premature adrenarche – normal variant or forerunner of adult disease? *Endocr Rev.* 2000; 21: 671–96.
25. Adair LS. Size at birth predicts age at menarche. *Pediatr.* 2001; 107: E59.
26. Idkowiak J, Lavery GG, Dhir V, Barrett TG, Stewart PM, Krone N, et al. Arlt Premature adrenarche: novel lessons from early onset androgen excess. *European Journal of Endocrinology.* 2011; 165: 189–207.
27. Dinneen S, Alzaid A, Miles J, Rizza R. Metabolic effects of the nocturnal rise in cortisol on carbohydrate metabolism in normal humans. *J Clin Invest.* 1993; 92: 2283–90.
28. Scott LV, Dinan TG. Vasopressin and the regulation of hypothalamic-pituitary-adrenal axis function: implications for the pathophysiology of depression. *Life Sci.* 1998; 62: 1985–98.
29. Miell JP, Corder R, Pralong FP, Gailard RC. Effects of dexamethasone on growth hormone (GH) releasing hormone arginine- and dopaminergic stimulated GH secretion and total plasma insulin-like growth factor-I concentrations in normal male volunteers. *J Clin Endocrinol Metab.* 1991; 72: 675–81.
30. Sherman B, Wysham C, Pfohl B. Age-related changes in the circadian rhythm of plasma cortisol in man. *J Clin Endocrinol Metab.* 1985; 61: 439–43.
31. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychobiological research: an overview. *Neuropsychobiol.* 1989; 22: 150–69.
32. Knutsson U, Dahlgren J, Marcus C, Rosberg S, Brönnegård M, Stiernä P, et al. Circadian Cortisol Rhythms in Healthy Boys and Girls: Relationship with Age Growth Body Composition and Pubertal Development. *J Clin Endocrinol Metab.* 1997; 82: 536–40.
33. Veldhuis JD, Sharma A, Roelfsema F. Age-Dependent and Gender-Dependent Regulation of Hypothalamic-Adrenocorticotrophic-Adrenal Axis. 2013; 42: 201–25.
34. Balbo M, Leproult R, Cauter EV. Impact of Sleep and Its Disturbances on Hypothalamo-Pituitary-Adrenal Axis Activity *Int J Endocrinol.* 2010; 759234: 16.
35. Eisenhofer G, Rundquist B, Aneman A, Friberg P, Dakak N, Kopin IJ, et al. Regional release and removal of catecholamines and extraneuronal metabolism to metanephrines. *J Clin Endocrinol Metab.* 1995; 80: 3009–17.
36. Staten MA, Matthews DE, Cryer PE, Bier DM. Physiological increments in epinephrine stimulate metabolic rate in humans. *Am J Physiol.* 1987; 253: 322–30.
37. Lopez MG, Abad F, Sancho C, de Pascual R, Borges R, Maroto R, et al. Membrane-mediated effects of the steroid 17-estradiol on adrenal catecholamine release. *J Pharmacol Exp Ther.* 1991; 259: 279–85.
38. Del Rio G. Adrenomedullary function and its regulation in obesity. *Int J Obes Relat Metab Disord.* 2000; 24: S89–S91.
39. Ceresini G, Freddi M, Morganti S, Rebecchi I, Modena AB, Rinaldi M, et al. The effects of transdermal estradiol on the response to mental stress in postmenopausal women: a randomized trial. *Am J Med.* 2000; 109: 463–8.
40. Xie T, Ho SL, Ramsden D. Characterization and implications of estrogenic down-regulation of human catechol-O-methyltransferase gene transcription. *Mol Pharmacol.* 1999; 56: 31–8.
41. Elman I, Goldstein DS, Adler CM, Shoaf SE, Breier A. Inverse relationship between plasma epinephrine and testosterone levels during acute glucoprivation in healthy men. *Life Sci.* 2001; 68: 1889–98.
42. Galbo H, Hummer L, Peterson IB, Christensen NJ, Bie N. Thyroid and testicular hormone responses to graded and prolonged exercise in man. *Eur J Appl Physiol Occup Physiol.* 1977; 36: 101–6.
43. Schifferlers SL, Saris WH, Boomsma F, Van Baak MA. $\beta_{(1)}$ - and $\beta_{(2)}$ -Adrenoceptor-mediated thermogenesis and lipid utilization in obese and lean men. *J Clin Endocrinol Metab.* 2001; 86: 2191–99.
44. Couillard C, Mauriege P, Prud'homme D, Nadeau A, Tremblay A, Bouchard C, et al. Plasma leptin response to an epinephrine infusion in lean and obese women. *Obes Res.* 2002; 10: 6–13.
45. Lee ZS, Critchley JA, Tomlinson B, Young RP, Thomas GN, Cockram CS, et al. Urinary epinephrine and norepinephrine interrelations with obesity insulin and the metabolic syndrome in Hong Kong Chinese. *Metabol.* 2001; 50: 135–43.
46. Weiner IB; Freedheim DK; Schinka JA; Velicer WF, Lerner RM. *Handbook of Psychology.* John Wiley and Sons. 2003. pp. 298.
47. Vickers MH, Glukman PD, Coveny AH, Hofman PL, Cutifield WS, Gertler A, et al. Neonatal leptin treatment reverses

- developmental programming. *Endocrinol.* 2005; 146: 4211-16.
48. Kiess W, Muller G, Galler A, Reich A, Deutscher J, Klammt J, et al. Body fat mass leptin and puberty. *J Pediatr Endocrinol Metab.* 2000; 13: 717-22.
 49. Lebrethon MC, Aganinia A, Fournier M, Gerard A, Parent AS, Bourguignon J. Effect of in vivo and in vitro administration of ghrelin, leptin and neuropeptide mediators on pulsatile gonadotrophin-releasing hormone secretion from male rat hypothalamus before and after puberty. *J Neuroendocrinol.* 2007; 19: 181-8.
 50. Bourguignon JP, Rasier G, Lebrethon MC, Gerard A, Naveau E, Parent AS. Neuroendocrine disruption of pubertal timing and interaction between homeostasis of reproduction and energy balance. *Molecul Cellul Endocrinol.* 2010; 324: 110-20.
 51. Licinio J, Mantzoros C, Negrao AB, Cizza G, Wong ML, Bongiorno PB, et al. Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. *Nat Med.* 1997; 3: 575-9.
 52. Ghizzoni L, Mastorakos G, Street ME, Mazzardo G, Vottero A, Vanelli M, et al. Leptin, Cortisol and GH Secretion Interactions in Short Normal Prepubertal Children. *J Clin Endocrinol Metab.* 2001; 86: 3729-34.
 53. Pradhan G, Samson SL, Sun Y. Ghrelin: much more than a hunger hormone. *Curr Opin Clin Nutr Metab Care .* 2013; 16: 619-24.
 54. Fernández-Fernández R, Tena-Sempere M, Navarro VM, Barreiro ML, Castellano JM, Aguilar E, et al. Effects of ghrelin upon gonadotropin-releasing hormone and gonadotropin secretion in adult female rats, In vivo and in vitro studies. *Neuroendocrinology.* 2005; 82: 245-55.
 55. Martini AC, Fernández-Fernández R, Tovar S, Navarro VM, Vigo E, Vazquez MJ, et al. Comparative analysis of the effects of ghrelin and unacylated ghrelin on luteinizing hormone secretion in male rats. *Endocrinology.* 2006; 147: 2374-82.
 56. Tena-Sempere M. Interaction between energy homeostasis and reproduction: central effects of leptin and ghrelin on the reproductive axis. *Horm Metab Res.* 2013; 45: 919-27.
 57. Horseman ND. Prolactin and mammary gland development. *J Mammary Gland Biol Neoplasia.* 1999; 4: 79-88.
 58. Oakes SR, Rogers RL, Naylor MJ, Ormandy CJ. Prolactin regulation of mammary gland development. *J Mammary Gland Biol Neoplasia.* 2008; 13: 13-28.
 59. Waldhauser F, Weissenbacher G, Tatzer E, Gisinger B, Waldhauser M, Schemper M, et al. Alterations in nocturnal serum melatonin levels in humans with growth and aging. *J Clin Endocrinol Metab.* 1988; 66: 648-52.
 60. Crowley SJ, Acebo C, Carskadon MA. Human puberty: salivary melatonin profiles in constant conditions. *Dev Psychobiol.* 2012; 54: 468-73.
 61. Waldhauser F, Weissenbacher G, Frisch H, Zeitlhuber U, Waldhauser M, Wurtman RJ. Fall in nocturnal serum melatonin during prepuberty and pubescence. *Lancet.* 1984; 1: 362-5.
 62. Roy D, Belsham DD. Melatonin receptor activation regulates GnRH gene expression and secretion in GT1-7 GnRH neurons. Signal transduction mechanisms. *J Biol Chem.* 2002; 277: 251-8.
 63. Kennaway DJ. Potential safety issues in the use of the hormone melatonin in pediatrics. *J Paediatr Child Health.* 2015; 51: 584-9.
 64. Boafu A, Greenham S, Alenezi S, Robillard R, Pajer K, Tavakoli P, et al. Could long-term administration of melatonin to prepubertal children affect timing of puberty? A clinician's perspective. *Nature and science of sleep.* 2019; 11: 1-10.
 65. Wu FCW, Butler GE, Kelnar CJH, Stirling HF, Huhtaniemi I. Patterns of pulsatile luteinizing and follicle stimulating hormone secretion in prepubertal (mid childhood) boys and girls and patients with idiopathic hypogonadotrophic hypogonadism (Kallmann's syndrome): a study using an ultrasensitive time-resolved immunofluorometric assay. *J Clin Endocrinol Metab.* 1991; 72: 1229-37.
 66. Wu FCW. GnRH pulse generator activity during human puberty. In: Plant TM Lee PA (eds) *The Neurobiology of Puberty.* 1995; pp: 185-97.
 67. Claypool LE, Watanabe G, Terasawa E. Effect of electrical stimulation of medial basal hypothalamus of pubertal female rhesus macaque re ensheathed with glia J *Neuroendocrineol.* 1990; 9: 881-5.
 68. Watanabe G, Terasawa E. In vivo release of luteinizing hormone releasing rhesus monkey *Endocrinol.* 1989; 125: 92-9.
 69. Chongthammakum S, Claypool LE, Terasawa E. Ovariectomy increases in vivo LHRH release in pubertal but not prepubertal female rhesus monkeys. *J Neuroendocrinol.* 1993; 5: 41-50.
 70. Witchell SF, Plant TM. Puberty: Gonadarche and adrenarche. In: Strauss JF, editor; Barbieri RL, editors. *Yen & Jaffe's Reproductive Endocrinology.* 7th Edition Philadelphia: Elsevier Saunders. 2014; P: 377-421.
 71. Kretser DM, Robertson DM. The isolation and physiology of inhibin and related proteins. *Biol Reprod.* 1989; 40: 133-47.
 72. Luisi S, Florio P, Reis FM, Petraglia F. Inhibins in female and male reproductive physiology: role in gametogenesis conception implantation and early pregnancy. *Hum Reprod Update.* 2005; 11: 123-35.
 73. Foresta C, Bettella A, Petraglia F, Pistorello M, Luisi S, Rossato M. Inhibin B levels in azoospermic subjects with cytologically characterized testicular pathology. *Clin Endocrinol.* 1999; 50: 695-701.
 74. Anderson RA. Clinical studies: inhibin in the adult male. *Mol Cell Endocrinol.* 2001; 180: 109-16.
 75. Ramaswamy S, Plant TM. Operation of the follicle-stimulating hormone (FSH)-inhibin B feedback loop in the control of primate spermatogenesis. *Mol Cell Endocrinol.* 2001; 180: 93-101.
 76. Muttukrishna S, Jauniaux E, McGarrigle H, Groome N, Rodeck CH. In-vivo concentrations of inhibins activin A and follistatin in human early pregnancy. *Reprod Biomed Online* 8: 712-9.
 77. Debieve F, Beerlandt S, Hubinont C, Thomas K. Gonadotropins prolactin inhibin A inhibin B and activin A in human fetal serum from midpregnancy and term pregnancy. *J Clin Endocrinol Metab.* 2000; 85: 270-4.
 78. De Schepper J, Verlinde F, Cortvrindt R, Callewaert M, Smits

- J. Serum inhibin B in normal term-born male and female neonates during the first week of life. *Eur J Pediatr.* 2000; 159: 465–9.
79. Florio P, Benedetto C, Luisi S, Santuz M, Di Carlo C, Marozio, L et al. Activin A, inhibin A, inhibin B parturition: changes of maternal and cord serum levels according to the mode delivery. *Br J Obstet Gynaecol.* 1999; 106: 1061–5.
 80. Chada M, Prusa R, Bronsky J, Kotaska K, Sidlova K, Pechova M, et al. Inhibin, follicle stimulating hormone, luteinizing hormone and testosterone during childhood and puberty in males: changes in serum concentrations in relation to age and stage of puberty. *Physiol Res.* 2003; 52: 45-51.
 81. Grumbach M, Styne D. Puberty: Ontogeny, neuroendocrinology, physiology, and disorders. 2003; 23: 1115–1286.
 82. Reyes FI, Boroditsky RS, Winter JSD, Faiman C. Studies on human sexual development. II. Fetal and maternal serum gonadotropin and sex steroid concentrations. *Journal of Clinical Endocrinology and Metabolism.* 1974; 44: 612-7.
 83. Forest MG, Sizonenko PC, Cathiard AM, Bertrand J. Hypophysio-gonadal function in humans during the first year of life. I. Evidence for testicular activity in early infancy. *The Journal of Clinical Investigation.* 1974; 53: 819-28.
 84. Lamminmaki A, Hines M, Kuiri-Hanninen T, Kilpelainen L, Dunkel L, Sankilampi U. Testosterone measured in infancy predicts subsequent sex-typed behavior in boys and in girls. *Hormones and Behavior.* 2012; 61: 611-16.
 85. Boas M, Boisen KA, Virtanen HE, Kaleva M, Suomi AM, Schmidt IM, et al. Postnatal penile length and growth rate correlate to serum testosterone levels; a longitudinal study of 1962 normal boys. *European Journal of Endocrinology.* 2006; 154: 125-9.
 86. Kuiri-Hanninen T, Seuri R, Tyrvaenen E, Turpeinen U, Hamalainen E, Stenman UH, et al. Increased activity of the hypothalamic-pituitary-testicular axis in infancy results in increased androgen action in premature boys. *Journal of Clinical Endocrinology and Metabolism.* 2011; 96: 98-105.
 87. Pasterski V, Acerini CL, Dunger DB, Ong KK, Hughes IA, Thankamony A. Postnatal penile growth concurrent with mini-puberty predicts later gender-typed behavior: evidence for neurobehavioral effects of the postnatal androgen surge in typically developing boys. *Hormones and Behavior.* 2015; 69: 98-105.
 88. Faiman C, Winter JSD. Gonadotropins and sex hormone patterns in puberty. clinical data in Grumbach M, Grave C, Mayer F, eds. *The Control of the Onset of Puberty.* New York, NY. John Wiley & Sons. 1974: 32–61.
 89. Cooper C, Westlake S, Harvey N, Javaid K, Dennison E, Hanson M. Review: developmental origins of osteoporotic fracture. *Osteoporos Int.* 2006; 17: 337–47.
 90. Deurenberg P, Yap M, Van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord.* 1998; 22: 1164–71.
 91. Bordini B, Rosenfield RL. Normal pubertal development: Part I: The endocrine basis of puberty. *Pediatr Rev.* 2011; 32: 223-9.
 92. Winter JSD, Faiman C, Hobsen WC, Prasad AV, Reyes FI. Pituitary-gonadal relations in infancy: I Patterns of serum gonadotropin concentrations from birth to four years of age in man and in chimpanzee. *J Clin Endocrinol Metab.* 1975; 40: 545-51.
 93. Miller JD, Tannunbaum GS, Colle E, Guyda HJ. Daytime pulsatile growth hormone secretion during childhood and adolescence. *J Clin Endocrinol Metab.* 1982; 55: 989-94.
 94. Martha Jr PM, Rogol AD, Veldhuis JD, Kerrigan JR, Goodman DW, Blizzard RM. Alterations in the pulsatile properties of circulating growth hormone concentrations during puberty in boys. *J Clin Endocrinol Metab.* 1989; 60: 563-70.
 95. Kowarski A, Thompson RG, Migeon CJ, Bilizzard RM. Determination of integrated plasma concentrations and true secretion rates of human growth hormone. *J Clin Endocrinol Metab.* 1971; 32: 356-60.
 96. Baxter R, Brown CS, Turtle JR. Radioimmunoassay for somatomedin C: comparison with radioreceptor assay in patients with growth-hormone disorders hypothyroidism and renal failure. *Clin Chem.* 1982; 28: 488–95.
 97. Veldhuis JD, Roemmich JN, Richmond EJ, Rogol AD, Lovejoy JC, Sheffield-Moore M, et al. Endocrine control of body composition in infancy childhood and puberty. *Endocr Rev.* 2005; 26: 114-46.
 98. Gunnell D, Miller LL, Rogers I, Holly JM. Association of Insulin-like Growth Factor I and Insulin-like Growth Factor-Binding Protein-3 with Intelligence Quotient Among 8- to 9-Year-Old Children in the Avon Longitudinal Study of Parents and Children. *Pediatric.* 2005; 116: e681.
 99. Whitfield JF, MacManus JP, Rixon RH. Stimulation by growth hormone of deoxyribonucleic acid synthesis and proliferation of rat thymic lymphocytes. *Horm Metab Res.* 1971; 3: 28-33.
 100. Juul A. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. *Growth Horm IGF Res.* 2003; 13: 113–70.
 101. Cacciari E, Cicognani A, Pirazzoli P, Tassoni P, Salardi S, Capelli M, et al. Differences in somatomedin-C between short-normal subjects and those of normal height. *J Pediatric.* 1985; 106: 891–4.
 102. Rosenfield RI, Furlanetto R, Bock D. Relationship of somatomedin-C concentrations to pubertal changes. *J Pediatr.* 1983; 103: 723–8.
 103. Löfqvist C, Andersson E, Gelander L, Rosberg S, Blum WF, Wikland KA. Reference Values for IGF-I throughout Childhood and Adolescence: A Model that Accounts Simultaneously for the Effect of Gender Age and Puberty. *J Clin Endocrinol Metab.* 2001; 86: 5870-6.
 104. Kanbur-Öksüz N, Derman O, Kinik E. Correlation of sex steroids with IGF-1 and IGFBP-3 during different pubertal stages. *Turk J Pediatr.* 2004; 46: 315–21.
 105. Imran SA, Pelkey M, Clarke DB, Clayton D, Trainer P, Ezzat S. Spuriously Elevated Serum IGF-1 in Adult Individuals with Delayed Puberty. *Intl J Endocrinol.* 2010; 2010: 370692.
 106. Sel'verova NB, Filippova TA. Development of the neuroendocrine regulation in Fiziologiya rasviya rebenka (physiology of growth and development) Moscow. 1995; 19: 465-8.
 107. Dzhhevetskaya IA. Endokrinnaya sistema rastushchego organizma (Endocrine system of the developing body). Vysshaya Shkola Moscow. 1987; 92: 86–92.

108. Savchenko ON, Arutyunyan NA, Proimina FI. Weak androgens their role in experiment and clinic. *J Fiziol Zh.* 1993; 79: 12-5.
109. Gutekunst R, Smolarek H, Hasenpusch U, Stubbe P, Friedrich HJ, Wood WG, et al. Goitre epidemiology: thyroid volume iodine excretion thyroglobulin and thyrotropin in Germany and Sweden. *Acta Endocrinol (Copenh).* 1986; 112: 494–501.
110. Müller-Leisse C, Tröger J, Khabirpour F, Pöckler C. Schilddrüseenvolumen- Normwerte Sonographische Messungen an 7-bis 20jährigen Schülern. *Dtsch Med Wochenschr.* 1988; 113: 1872–5.
111. Michaud P, Foradori A, Rodriguez-Portales JA, Arteaga E, López JM, Téllez R. A prepubertal surge of thyrotropin precedes an increase in thyroxine and 3539-triiodothyronine in normal children. *J Clin Endocrinol Metab.* 1991; 72: 976–81.
112. Parra A, Villalpando S, Junco E, Urquieta B, Alatorre S, Garcia-Bulnes G. Thyroid gland function during childhood and adolescence: Changes in serum TSH T4 T3 thyroxine-binding globulin reverse T3 and free T4 and T3 concentrations. *Acta Endocrinol (Copenh).* 1980; 93: 306–14.
113. Dunger DB, Perkins JA, Jowett TP, Edwards PR, Cox LA, Preece MA, et al. A longitudinal study of total and free thyroid hormones and thyroxine-binding globulin during normal puberty. *Acta Endocrinol (Copenh).* 1990; 123: 305–10.
114. Dumont JE, Lamy F, Roger P, Maenhaut C. Physiological and pathological regulation of thyroid cell proliferation and differentiation by thyrotropin and other factors. *Physiol Rev.* 1992; 72: 667–97.
115. Mizukami Y, Michigishi T, Nonomura A, Hashimoto T, Noguchi M, Matsubara F. Estrogen and estrogen receptors in thyroid carcinomas. *J Surg Oncol.* 1991; 47: 165–9.
116. Dalla VL, Ramina A, Vianello S, Fassina A, Belvedere P, Colombo L. Potential for estrogen synthesis and action in human normal and neoplastic thyroid tissues. *J Clin Endocrinol Metab.* 1998; 83: 3702–9.
117. Fleury Y, Melle VG, Woringer V, Gaillard RC, Portmann L. Sex-Dependent Variations and Timing of Thyroid Growth during Puberty. *J Clin Endocrinol Metab.* 2001; 86: 750–4.
118. Karp SJ, Schipani E, St Jacques B. Indian hedgehog coordinates endochondral bone growth and morphogenesis via parathyroid hormone-related protein and -independent pathways. *Development.* 2000; 127: 543–8.
119. Kindblom JM, Nilsson O, Hurme T, Ohlsson C, Säwendahl L. Expression and localization of Indian hedgehog (Ihh) and parathyroid hormone related protein (PTHrP) in the human growth plate during pubertal development. *J Endocrinol.* 2002; 174: 1–6.
120. Phillip, Moshe, Lazar, Liora. The Regulatory Effect of Hormones and Growth Factors on the Pubertal Growth Spurt. *The Endocrinologist:* 2003; 13: 465-9.
121. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med.* 2011; 365: 1597–1604.
122. Guo Y, Ma L, Enriori PJ, Koska J, Franks PW, Brookshire T, et al. Physiological evidence for the involvement of peptide YY in the regulation of energy homeostasis in humans. *Obesity (Silver Spring).* 2006; 14: 1562–70.
123. Tovar SA, Seoane LM, Caminos JE, Nogueiras R, Casanueva FF, Diéguez C. Regulation of peptide YY levels by age, hormonal, and nutritional status. *Obes Res.* 2004; 12: 1944–50.
124. Lloyd B, Ravi P, Mendes N, Klibanski A, Misra M. Peptide YY levels across pubertal stages and associations with growth hormone. *J Clin Endocrinol Metab.* 2010; 95: 2957–62.
125. Horner K, Lee S. Appetite-related peptides in childhood and adolescence: role of ghrelin, PYY, and GLP-1. *Appl Physiol Nutr Metab.* 2015; 40: 1089–99.
126. Cheng HL, Sainsbury A, Garden F, Sritharan M, Paxton K, Luscombe G, et al. Ghrelin and Peptide YY Change During Puberty: Relationships With Adolescent Growth, Development, and Obesity. *The Journal of Clinical Endocrinology & Metabolism.* 2018; 103: 2851-60.