Normal Pubertal Development:
Part I: The Endocrine Basis of Puberty

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Author Disclosure
Drs Bordini and Rosenfield have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives
After completing this article, readers should be able to:

1. Explain how puberty is regulated by the hypothalamic–pituitary–gonadal axis.
2. Describe the hormonal interactions involved in pubertal development in boys and girls.

Introduction

Puberty is a defining developmental stage of every child's life, both physically and psychosocially. Concerns about the normalcy of pubertal development and menstrual patterns are among the most common questions posed to every physician caring for children. This article reviews the primary physiologic changes in the hypothalamic-pituitary-gonadal (HPG) axis and in adrenal androgen and growth hormone (GH) production that underlie the normal pubertal milestones. Understanding of these changes allows interpretation of laboratory data in children suspected of having pubertal abnormalities.

Puberty is the developmental stage during which a child becomes a young adult, characterized by the maturation of gametogenesis, secretion of gonadal hormones, and development of secondary sexual characteristics and reproductive functions. *Adolescence* is used widely as a generally synonymous term for puberty, but the term often is used to convey an added connotation of cognitive, psychological, and social change.

Thelarche denotes the onset of breast development, an estrogen effect. *Pubarche* denotes the onset of sexual hair growth, an androgen effect. *Menarche* indicates the onset of menses and *spermarche* the appearance of spermatozoa in seminal fluid. *Gonadarche* refers to the onset of pubertal function of the gonads, which produce most of the sex hormones that underlie the pubertal changes in secondary sex characteristics. *Adrenarche* refers to the onset of the adrenal androgen production that contributes to pubarche.

The Hormonal Axes Underlying Puberty

The Hypothalamic–Pituitary–Gonadal Axis

Normal puberty results from sustained, mature activity of the HPG axis. (1). The major hormones of the HPG axis are shown in Figure 1. In response to a single gonadotropin-releasing hormone (GnRH), the pituitary gland releases two gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). GnRH is secreted by specialized neurons of the hypothalamus in a pulsatile fashion. Pituitary LH and FSH secretion consequently is pulsatile and can be sustained only in response to pulsatile GnRH signals. LH acts primarily on the specialized interstitial cells of the gonads to stimulate formation of androgens, and FSH acts primarily on the follicular/tubular compartment to stimulate formation of estrogen from androgen precursors, inhibin, and gametes. The function of the two compartments of the gonads is coordinated by paracrine regulatory mechanisms.

The HPG axis is active during three phases of development: fetal, neonatal, and adult, with puberty being the period of transition to mature function. Changes in GnRH secretion underlie the changing activity of the HPG axis. The sexually dimorphic patterns of sex hormone secretion during the prenatal and neonatal periods of HPG activity appear to play a role in programming sexually dimorphic patterns of behavior, metabolism, and neuroendocrine function in later life.

Abbreviations

ACTH:	adrenocorticotropic hormone
DHEAS:	dehydroepiandrosterone sulfate
FSH:	follicle-stimulating hormone
GH:	growth hormone
GnRH:	gonadotropin-releasing hormone
HPG:	hypothalamic-pituitary-gonadal
LH:	luteinizing hormone

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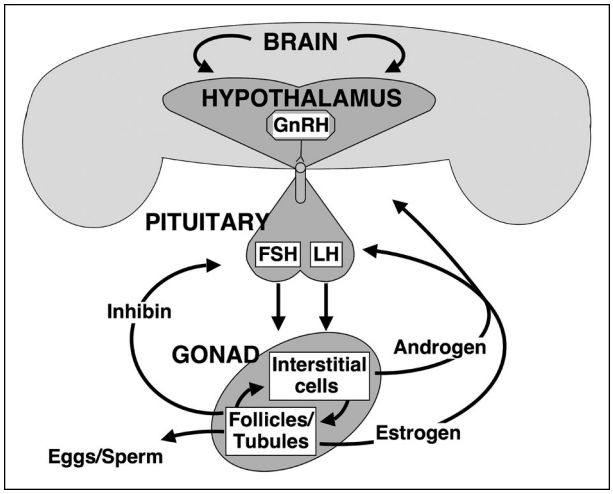

Figure 1. The hypothalamic-pituitary-gonadal axis. Hypothalamic neurons release gonadotropin-releasing hormone (GnRH) into the pituitary portal venous system, where it stimulates gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion. LH primarily stimulates specialized interstitial cells (theca cells in the ovary or Leydig cells in the testes) to secrete androgens. FSH primarily stimulates the ovarian follicle or seminiferous tubules to form estrogen, inhibin, and gametes (eggs or sperm). The interstitial and follicular/tubular compartments act cooperatively through paracrine mechanisms to form estrogen and to regulate sex steroid and gamete development. Sex steroids exert endocrine closed-loop negative feedback effects on GnRH and gonadotropin secretion. Inhibin exerts negative feedback on FSH secretion. In mature females, a critical estradiol concentration for a critical duration exerts a transient positive feedback effect to stimulate the LH surge that initiates ovulation.

The HPG axis is established during the first trimester. Its activity in the second trimester contributes to the establishment of normal penile size and the inguinal-scrotal phase of testicular descent. (2)(3) In the latter half of pregnancy, activity is suppressed by the high estrogens elaborated by the fetoplacental unit.

The HPG axis promptly functions at a pubertal level in the newborn after withdrawal from maternal estrogens. This "minipuberty of the newborn" is subclinical, except for contributing to genital growth, acne, and transient thelarche in the neonate.

HPG function subsequently comes under gradual central nervous system restraint at the end of the neonatal period. The axis is relatively, but not absolutely, dormant throughout childhood, particularly in girls, who have slightly higher FSH concentrations than boys and a few ultrasonographically visible ovarian follicles as evidence of this effect. The HPG axis becomes increasingly active again in the late prepubertal period, as central nervous system restraint recedes, followed by an increasing tempo throughout puberty.

The gonads account for the most important circulating estrogen (estradiol) and androgen (testosterone). Gonadal function accounts for more than 90% of estradiol production in the female (50% in the male) and more than 90% of testosterone production in the male (50% in the female) (Fig. 2). (4)(5)

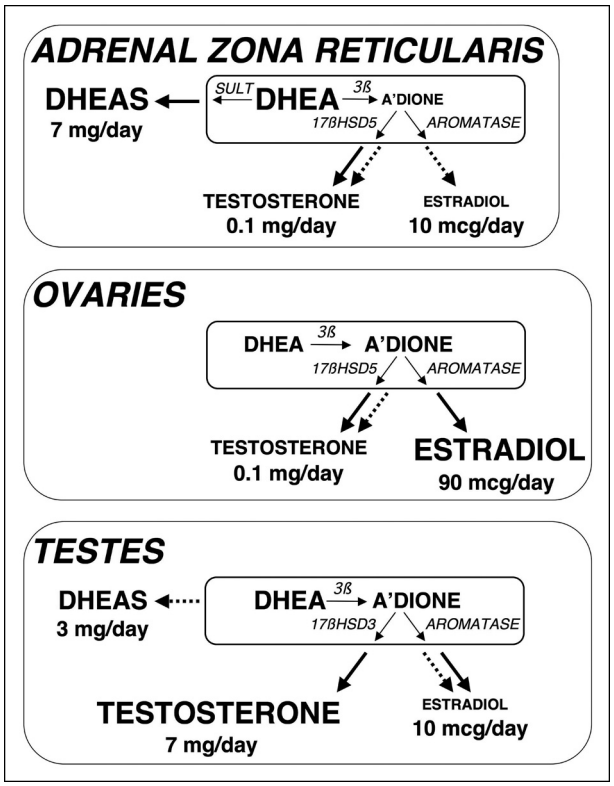

Figure 2. Simplified diagram of sex steroid production by the adult adrenal glands, follicular phase ovaries, and testes. Blood production rates shown are the sum of direct secretion (heavy solid arrows) and peripheral formation from secreted precursors (dotted arrows). Several key steroidogenic enzyme activities expressed in these glands, such as sulfotransferase (*SULT*), 3β-hydroxysteroid dehydrogenase (*3β*), aromatase, and 17β-hydroxysteroid dehydrogenase type 5 (*17βHSD5*), are also expressed in peripheral tissues such as liver, fat, and skin. Type 3 17βHSD (17βHSD3) is only expressed in testes. Peripheral conversion from secreted androstenedione accounts for 50% of testosterone in women, and about 10% of estradiol and DHEAS similarly arise from circulating precursors. Estrone, the intermediate in the pathway from androstenedione to estradiol, is not shown. DHEA=dehydroepiandrosterone, DHEAS=dehydroepiandrosterone sulfate, A'DIONE=androstenedione

Adrenarche, the "Puberty" of the Adrenal Gland

Adrenarche is actually a re-onset of adrenal androgen production. The fetal zone of the adrenal cortex elaborates large amounts of dehydroepiandrosterone sulfate (DHEAS), which is important as the major substrate for placental estrogen formation during pregnancy. This zone then regresses over the first several postnatal months.

Adrenarche is the pseudopuberty of the adrenal gland that begins in mid-childhood as the zona reticularis of the adrenal cortex develops. (1) This zone has the capacity to form 17-ketosteroids, but not cortisol, in response to adrenocorticotropic hormone (ACTH), and DHEAS is the primary endpoint of this biosynthetic pathway. Consequently, although cortisol concentrations and the cortisol response to ACTH do not change from childhood to adulthood, DHEAS values gradually rise from mid-childhood until adulthood. This timeframe coincides approximately with the gonadal androgen production of true puberty, but adrenarche is an incomplete aspect of puberty that is independent of pubertal maturation of the HPG axis. The adrenal gland secretes more than 90% of DHEAS in children and women and more than 70% in adult men, while 50% of testosterone in the female and less than 10% of testosterone in the male is produced by the adrenal. (6) Adrenal androgen concentrations increase to a point sufficient to stimulate apocrine odor and mild acne after about 5 years of age and pubic hair growth after about 10 years of age (Table).

Interactions Between Pubertal Hormones and the Growth Hormone/Insulin-like Growth Factor-I Axis

Pituitary GH secretion increases during puberty in response to sex steroids. (1) This rise in GH causes a rise in insulin-like growth factor-I concentrations to peaks in late puberty that are above those of adults, sometimes in the adult acromegalic range. Half of the characteristic pubertal growth spurt is due to the direct effect of sex steroids on epiphyseal growth and half to GH stimulation. Conversely, in accord with the general principle that everything grows better with GH, GH is necessary for optimal gonadotropin effects on gonadal growth and sex steroid effects on secondary sex characteristics. For example, selective GH resistance is characterized by small testes and micropenis, poor breast and sexual hair development, and absence of a pubertal growth spurt. (12)

Regulation of the Onset and Progression of Puberty

There is no single "trigger" for puberty; rather, puberty results from a gradual increase in GnRH pulsatility that arises from maturation of central nervous system developmental programs that send inhibitory and stimulatory signals to GnRH neurons. (1) Puberty is associated with changing sensitivity of the neuroendocrine system to negative feedback by gonadal hormones. When GnRH secretory activity is low due to central nervous system inhibition in mid-childhood, it is inhibited by trace amounts of sex steroids. Increasing central activation during puberty permits sex steroids to rise to adult concentrations before exerting negative feedback effects.

The major GnRH-inhibitory systems are GABAergic and opioidergic; the major excitatory systems involve glutamate and kisspeptin, with glial cells facilitating GnRH secretion. Kisspeptin is a hypothalamic neuropeptide discovered in the search for the molecular basis of hypogonadotropic hypogonadism; it acts as an important signal for pubertal GnRH release via GPR54, a G-protein coupled receptor located on GnRH neurons.

It has been estimated that at least half of the varia-

Table. Typical Early Morning Pubertal Hormone Blood Concentrations

Group	LH (IU/L)	FSH (IU/L)	Estradiol (pg/mL)	TT (ng/dL)	DHEAS (μg/dL)
Prepubertal 1 to 5 yr	<0.3	<4.0	<10	<20	5 to 40*
Premenarchal females	≤12	1.0 to 12	<50	13 to 44	35 to 130
Postmenarchal females**	2.0 to 11	1.0 to 12	20 to 85	15 to 59	75 to 255
Adult men***	1.4 to 9.0	1.0 to 9.2	<60	300 to 950	100 to 460

DHEAS=dehydroepiandrosterone sulfate, FSH=follicle-stimulating hormone, LH=luteinizing hormone, TT=total testosterone
Conversions to SI units: estradiol×3.61=pmol/L, testosterone×0.0347=nmol/L, DHEAS×0.0271=μmol/L
Assay-specific ranges may vary.
*Prepubertal children 6 to 9 years of age may have adrenarchal DHEAS values up to approximately 70 μg/dL
**Early follicular phase values given; mid-cycle LH up to 85 IU/L, FSH up to 19 U/L, estradiol up to 350 pg/mL
***Pubertal males values are between and overlap with prepubertal and adult male values
Data from Bordini et al, (7) Mortensen et al, (8) Zimmer et al, (9) Mayo Clinical Laboratories, (10) Esoterix Laboratory Services. (11)

tion in the timing of puberty is genetically determined, and ethnicity is one such factor. (1)(13) Sex hormones, hormonally active environmental chemicals ("environmental disruptors"), (14) diverse somatic stimuli (including nutrition, the growth hormone/insulin-like growth factor system, thyroid hormones), and general health all affect the pubertal process.

Pubertal and skeletal maturation appear to have common somatic determinants. Children generally enter puberty when they achieve a pubertal bone age. Pubertal stage normally correlates better with the bone age than with chronologic age. (15) Thus, for example, the onset of breast development normally occurs at a bone age of about 10 years and menarche occurs at a bone age of about 12.5 years, whether the child is 9 or 14 years of age.

Optimal nutrition is necessary for initiation and maintenance of normal reproductive function. The hypothesis that a critical amount of body fat is the weight-related trigger for pubertal development originated with the discovery by Frisch and coworkers that weight correlated with pubertal growth and menarche better than it did with chronologic age or height. (16) Early to mid-childhood may be a critical period for weight to influence the onset of puberty. (17) Suboptimal nutrition related to socioeconomic conditions is an important factor in the late onset of puberty in underdeveloped countries. Conversely, obesity is an important factor in advancing the onset of puberty in United States girls. (13)

Leptin, a hormone secreted by fat cells, appears to be an important link between nutrition and the attainment and maintenance of reproductive competence. (1) Leptin acts on the hypothalamus to reduce appetite and stimulate gonadotropin secretion. Leptin deficiency causes obesity and gonadotropin deficiency. Blood leptin concentrations rise throughout childhood and puberty to reach higher values in girls than boys. Attainment of a critical threshold appears to signal that nutritional stores are sufficient for mature function of the GnRH pulse generator and, thus, permits puberty.

Although prolactin and pineal gland hormones affect puberty in lower animals and can cause pubertal disorders in humans, neither has a clear role in normal human puberty.

Hormonal Changes of Normal Puberty

The first hormonal change of puberty is a sleep-related increase in the pulsatile release of LH by the pituitary gonadotropes. FSH is secreted in parallel but increases relatively less. At the beginning of puberty, a unique diurnal variation of pubertal hormones occurs, with little LH secretion during the day and a significant increase in pulsatile secretion during sleep (Fig. 3). (18)(19) In response to nocturnal LH secretion, the pattern of gonadal sex steroid secretion differs between the sexes: ovarian secretion of estradiol peaks in mid-day and testicular secretion of testosterone peaks promptly during sleep. In addition, girls' pubertal hormone secretion is subclinically cyclic from early puberty. As puberty progresses, LH secretion persists further into the daytime. After menarche, this diurnal variation no longer exists. Adult sex steroid concentrations, however, have a mild diurnal variation, being highest on awakening.

The two gonadotropins each act primarily on specific gonadal cell types. LH stimulates the interstitial cells of the ovaries (theca cells) to form androgenic precursors of estradiol and those of the testes (Leydig cells) to secrete testosterone itself. FSH acts on the sex cord derivatives of the ovary (granulosa cells) and testes (Sertoli cells) to stimulate gametogenesis and gonadal growth. In granulosa cells, FSH strongly stimulates aromatase to form estradiol from thecal androgens.

As the gonads become increasingly 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 and testosterone increases an average of 100 ng/dL (3.47 nmol/L) yearly to reach the lower adult range (Table). (20) These concentrations then gradually induce their effects. The hormonal increases culminate in positive feedback in girls, which refers to the female neuroendocrine system becoming capable of secreting a mid-cycle surge of LH when the ovary signals that it is prepared for ovulation via a critical and sustained level of estrogen secretion.

Estrogen stimulates the classic female target tissues: the female genital tract (eg, endometrial growth, cervical mucus secretion) and breasts. Androgen stimulates the classic male target tissues (eg, sexual hair and sebaceous gland). Both stimulate sexual drive and function. Both sex steroids account for the pubertal growth spurt, directly and indirectly via growth hormone. Both directly stimulate epiphyseal growth and epiphyseal maturation, which is indexed by bone age radiographs and peak bone mass accrual. (21) However, they differ in some of their effects on skeletal growth. Androgen is responsible for the wider bones (the laryngeal enlargement accounting for the pubertal voice change), while estrogen is ultimately necessary for epiphyseal fusion and is the more potent inhibitor of bone resorption. They also affect growth of a wide variety of other somatic tissues. During puberty, estrogen promotes lipogenesis and lower body

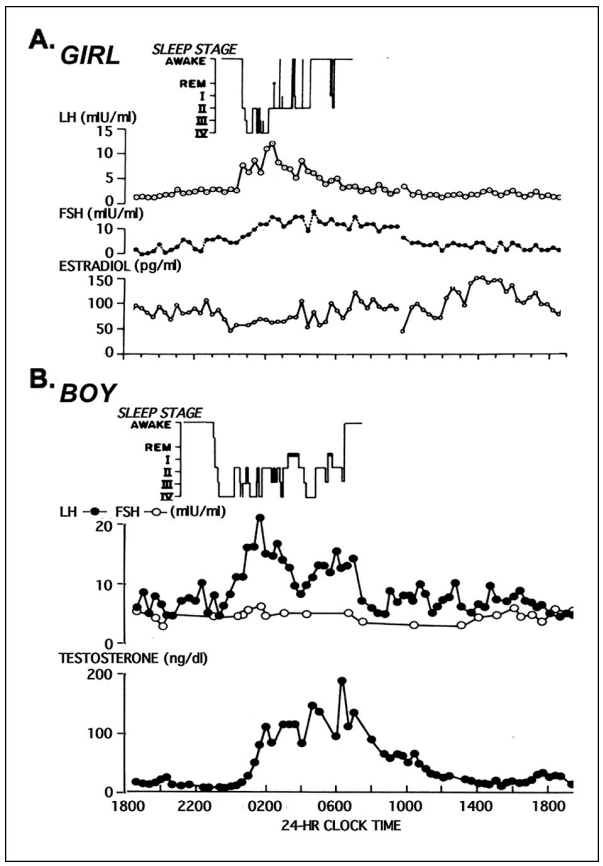

Figure 3. Pubertal hormone rhythms. In an early pubertal girl (top panel), luteinizing hormone (LH) secretion is minimal during waking hours. Pubertal LH pulsations promptly begin with sleep onset and wane with sleep offset, followed several hours later by increased ovarian estradiol secretion that peaks mid-day. Reprinted with permission from Boyar et al. (18) Copyright 1976, The Endocrine Society. In an early pubertal boy (bottom panel), daytime LH values are low, with minimal testosterone secretion. Pubertal LH pulsations begin promptly with sleep onset and cease with sleep offset; testosterone secretion occurs primarily during sleep, beginning about 2 hours after LH increases and waning on awakening. Reprinted with permission from Judd et al. (19) Copyright 1974, The Endocrine Society. Panels are modified by aligning times. This figure demonstrates the clinical importance of considering diurnal and pulsatile hormone secretion in evaluating pubertal status. First, because of diurnal rhythmicity, daytime hormone values during early puberty are not representative of the 24-hour production of pubertal hormones, as indicated for LH in this girl (breast stage 3) and for testosterone and gonadotropins in this boy (stage 2). Second, because of the episodic pulsatile nature of gonadotropin and sex steroid secretion, hormone values may differ markedly within 1 hour. The gonadotropin concentrations were determined by early-generation radioimmunoassays, and the baseline values are higher than those obtained by current assays.

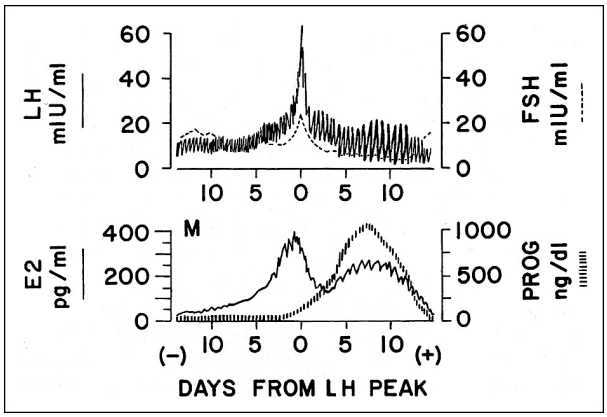

Figure 4. Diagram of average gonadotropin and sex steroid concentrations during the normal menstrual cycle. The data are centered in reference to days before (–) or after (+) the day of the mid-cycle surge of luteinizing hormone (LH). The gonadotropin concentrations are typical of polyclonal radioimmunoassay, and the baseline values are about twice as high as those obtained by current monoclonal assays. M=menses begin, E2=estradiol, PROG=progesterone. Reprinted with permission from Rosenfield et al. (1)

fat distribution. In contrast, androgens generally are lipolytic, although they favor the development of visceral fat stores, and promote muscular development. The similar increase of body mass index during puberty in girls and boys, thus, is due to differences in body composition, with a higher percent being body fat in girls and lean body mass in boys. (22)

The menstrual cycle arises from cyclic maturation of ovarian follicles that result in cyclic changes in sex hormones, particularly estradiol and progesterone, which entrain cyclic changes in gonadotropin concentrations (Fig. 4). The biologic goal of this monthly variation is to select and nurture one dominant follicle to the point of ovulation for potential fertilization. A normal average 28-day cycle consists of two phases: the follicular phase (variable in duration, averaging 14 days at maturity) and the luteal phase (14±1 SD days), with the latter occurring only in ovulatory cycles. The follicular phase begins with the onset of menses and culminates in the mid-cycle LH surge, which induces ovulation from the follicle. The empty follicle forms the corpus luteum, initiating the luteal phase. Progesterone increases steadily to be sustained at very high levels for several days, along with lesser but substantial increases in estradiol. Progesterone and estradiol secretion from the corpus luteum maintain the endometrial layer of the uterus in preparation for potential pregnancy. If pregnancy does not occur, with its resultant increase in human chorionic gonadotropin,

the corpus luteum life span is exhausted, which results in withdrawal of female sex steroids, followed by endometrial sloughing and menstrual flow.

Assessment of pubertal hormone concentrations requires reliable hormone assays in addition to consideration of the diurnal changes of early puberty and cyclic changes in girls. Although early pubertal children have greater average hormone concentrations than prepubertal children, their values still are much less than those of adults (Table). (7)(8)(9)(10)(11) The widely available, older generation of polyclonal antibody-based radioimmunoassays for gonadotropins do not possess sufficient sensitivity and specificity for optimal diagnosis of pubertal disorders. The modern multichannel platform assays available in many community hospitals are generally adequate for these purposes, as indicated by sensitivities of 0.1 to 0.15 U/L for LH and FSH. These platform assays are also reliable for DHEAS assays. On the other hand, platform assays are very unreliable for measuring testosterone and estradiol at the relatively low values that are normal for pubertal children and women. The practitioner should not order these tests unless provision can be made to assay them by accurate methodology, preferably in consultation with a pediatric endocrinologist. (23)

Daytime pubertal hormone concentrations may not indicate the early stages of puberty accurately because of diurnal and cyclic variations (Fig. 3). For this reason, GnRH-stimulated values may be necessary to diagnose pubertal disorders. A peak LH value greater than approximately 4.0 U/L in response to GnRH or GnRH agonist testing has been suggested as indicative of the onset of puberty. (24)(25)

***Part II of this article, which deals with the clinical aspects of puberty, will be published in the July issue of* Pediatrics in Review.**

Summary

All of the following are based on strong research evidence:

- The neuroendocrine control of puberty follows the hierarchy of most other hormone systems: hypothalamic-pituitary-target gland (ie, gonads).
- The exact mechanisms that awaken the HPG axis from its childhood quiescence remain unknown, but new neuroendocrine pathways have been recognized.
- Pubertal hormones not only bring about the maturation of secondary sexual characteristics and reproductive capacity, but they have important neuroendocrine effects and somatic effects on growth and body composition.

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PIR Quiz

Quiz questions also available online at http://pedsinreview.aappublications.org.

1. Which of the following statements about normal puberty in children is *true*?

   A. Bone age correlates better with pubertal development than chronologic age.
   B. Gonadotropin-releasing hormone (GnRH) secretion in response to negative feedback from sex steroids is constant throughout life.
   C. Growth hormone secretion is the sole determinant of the pubertal growth spurt.
   D. Menarche is the first stage of puberty in girls.
   E. Normal pubertal development is unrelated to nutritional status.

2. Which of the following statements *best* describes adrenarche?

   A. Breast development becomes evident in girls.
   B. Hypothalamic production of adrenocorticotropin hormone increases.
   C. Maternal estrogens are withdrawn, causing neonatal acne.
   D. Spermatozoa begin to appear in seminal fluid.
   E. The adrenal gland increases production of dehydroepiandrosterone sulfate.

3. Which of the following is the primary action of luteinizing hormone?

   A. Secretion of follicle-stimulating hormone.
   B. Secretion of GnRH from the pituitary gland.
   C. Stimulation of gametogenesis in the testes.
   D. Stimulation of the gonads to produce androgens.
   E. Stimulation of the ovarian follicle to produce estrogen.

4. At which of the following phases of the menstrual cycle is the concentration of progesterone the highest?

   A. The beginning of the follicular phase.
   B. The beginning of the luteal phase.
   C. The end of the luteal phase.
   D. The middle of the follicular phase.
   E. The middle of the luteal phase.

HealthyChildren.org Parent Resources from AAP

The reader is likely to find material to share with parents that is relevant to this article by visiting this link: http://www.healthychildren.org/English/ages-stages/gradeschool/puberty/Pages/default.aspx.

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