Normal Puberty

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KEYWORDS

• Luteinizing hormone • Follicle-stimulating hormone • Gonadarche • Puberty
• Gonadotropin-releasing hormone • Kisspeptin-neurokinin B-dynorphin neurons

KEY POINTS

- Puberty is characterized by gonadarche and adrenarche.
- Gonadarche represents the reactivation of the hypothalamic-pituitary-gonadal axis with increased gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone secretion following the quiescence during childhood.
- Pubarche is the development of pubic hair, axillary hair, apocrine odor reflecting the onset of pubertal adrenal maturation known as adrenarche.
- A detailed understanding of these pubertal processes will help clarify relationships between the timing of onset of puberty and cardiovascular, metabolic, and reproductive outcomes in adulthood.
- The onset of gonadarche is influenced by neuroendocrine signals, genetic variants, metabolic factors, and environmental elements.

INTRODUCTION

Puberty is the process through which reproductive competence is achieved.[1] Since ancient times, the importance of pubertal development has been recognized. Castration of animals and humans was known to interfere with the development of secondary sex characteristics and fertility. Indeed, some earlier cultures deliberately castrated men to create eunuchs to work with royalty, government, and religious institutions. Previously (and persisting in some cultures today), women were considered to be dangerous due to menstruation and menstrual blood; menstruating women were deliberately isolated. Subsequently, investigators during the twentieth century established the interrelationships of the hypothalamic-pituitary-gonadal (HPG) axis, isolated the various sex steroids, and discovered the necessity of pulsatile hormone secretion.[2,3]

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Endocrinol Metab Clin N Am 53 (2024) 183–194
https://doi.org/10.1016/j.ecl.2024.01.001 **endo.theclinics.com**

Genetic attributes, neuroendocrine interactions, and gonadal composition influence the onset and progression of puberty. Twin studies have established that the timing of puberty is highly heritable. The sex chromosome constitution of the embryo, XX or XY, determines whether the undifferentiated primordial gonads develop into ovaries or testes, respectively. By 5 to 6 weeks after conception, primordial germ cells migrate into the genital ridge. The environment of the developing gonads launches the developmental pathway directing primordial germ cells to eventually become oocytes or spermatogonia. Eventually, gonadal differentiation, whether ovary or testis, directs an individual's pubertal maturation archetype. During the transition from childhood to adulthood, children typically demonstrate a predictable sequence of hormonal and physical changes. Within the typical chronologic age ranges for pubertal development, individual variations regarding age at onset and tempo of pubertal development occur. Notably, in addition to genetic elements, metabolic, nutritional, environmental, ethnic, geographic, and economic factors influence the onset and tempo of pubertal development.[4]

GONADARCHE

Human puberty is characterized by 2 discrete physiologic processes, gonadarche and adrenarche. Gonadarche denotes the reactivation of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator characterized by increased pulsatile secretion of GnRH from the hypothalamus. Increased pulsatile GnRH secretion promotes pulsatile pituitary gonadotropin secretion which, in turn, stimulates the growth and maturation of the gonads accompanied by rising gonadal sex steroid secretion. Hence, HPG axis activity is fundamental to gonadarche, reproductive maturation, and fertility.

Gonadal sex steroids promote secondary sex characteristic development. In girls, increased gonadotropin secretion, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leads to increased ovarian estrogen secretion causing breast development, cornification of the vaginal mucosa, and uterine growth. In boys, increased LH and FSH secretion promotes increased testicular volume and testosterone secretion. This increased HPG axis activity culminates in folliculogenesis, ovulation, and menses in girls and spermatogenesis in boys.

Following the increased activity during the first few months of life known as the mini-puberty of infancy (see the following sections), the HPG axis becomes quiescent until increased pulsatile GnRH secretion launches the onset of gonadarche. Stimulatory and inhibitory impulses from higher hypothalamic and brain regions modulate hypothalamic GnRH secretion at the median eminence followed by transport through the pituitary portal blood system to the anterior pituitary gonadotroph cells. Acting on its cognate receptor, the GnRH receptor, GnRH stimulates gonadotropin secretion. The pituitary gonadotroph cells synthesize and secrete both LH and FSH. LH and FSH are glycoproteins with identical alpha subunits and distinct beta subunits that confer hormone specificity. Each GnRH pulse is intimately associated with a subsequent LH pulse. Pulse frequency is relatively constant in men with approximately 1 pulse every 90 to 120 minutes. In women, pulse frequency varies across the menstrual cycle with about 1 pulse per hour during the follicular phase and 1 pulse every 180 minutes during the luteal phase.

The hypothalamic GnRH-secreting neurons are physically located within a network of neurons secreting 3 neuropeptides: kisspeptin, neurokinin B, and dynorphin. These neurons, labeled the kisspeptin-neurokinin B-dynorphin (KNDy) neurons, are located in close proximity to glial cells such as tanycytes, astrocytes, and ependymal cells.

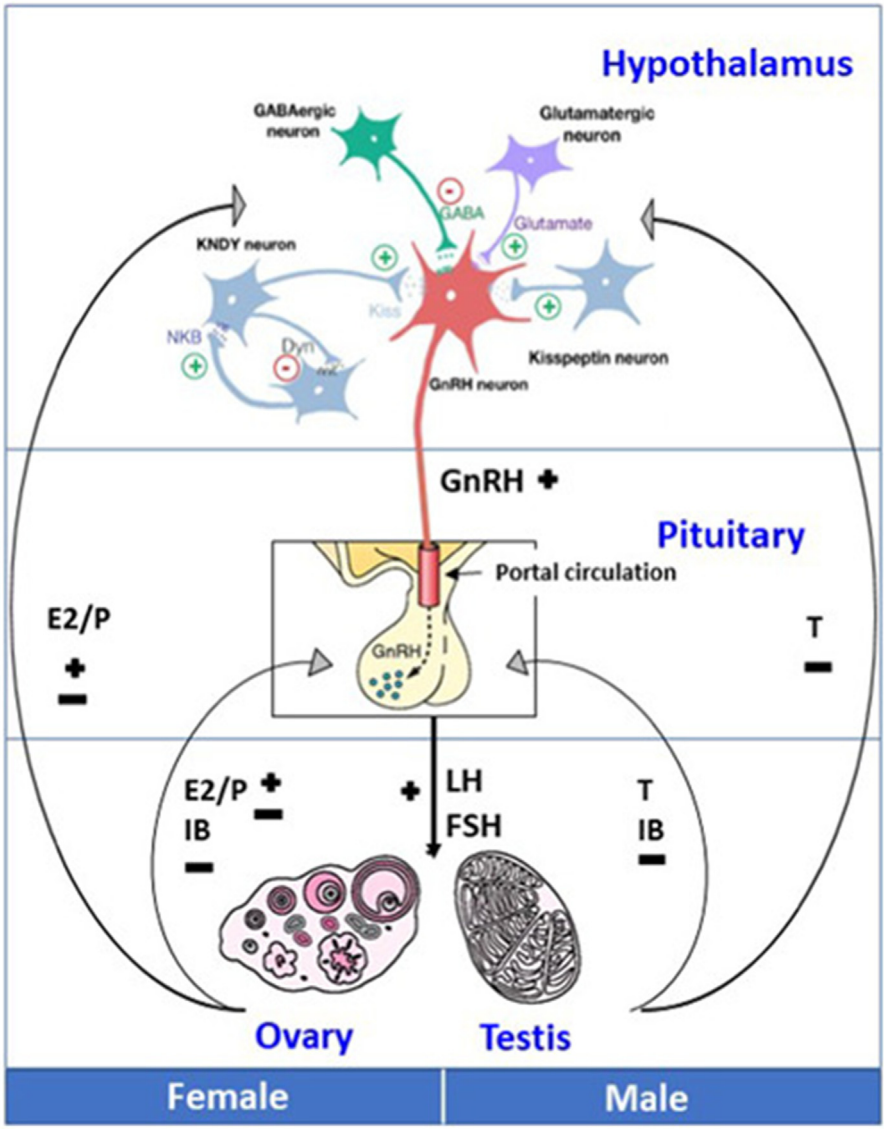

Fig. 1. Schematic representation of the hypothalamic-pituitary-gonadal axis. Kisspeptin, neurokinin B, and dynorphin along with other upstream signals govern hypothalamic GnRH neuron function. GnRH is secreted into the median eminence and travels via the pituitary portal circulation to the anterior pituitary where it stimulates LH and FSH production. These gonadotropins stimulate gonadal sex steroid secretion. Sex steroids provide a mix of negative and positive feedback on the pituitary and hypothalamus. IB provides negative feedback on the pituitary. Key: –, negative feedback; +, positive feedback. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; IB, inhibin B; LH, luteinizing hormone. (Reprinted with permission: Howard SR. Interpretation of reproductive hormones before, during and after the pubertal transition-Identifying health and disordered puberty. Clin Endocrinol (Oxf). 2021;95:702-15. https://doi.org/10.1111/cen.14578. PMID: 34368982.)

Kisspeptin and neurokinin B appear to play major roles in GnRH secretion (Fig. 1). The KNDy neurons in the infundibular nucleus in the hypothalamus appear to comprise the major elements of the GnRH pulse generator. For more detailed discussion of the KNDy neurons, the reader is referred to another publication.[5]

PUBARCHE AND ADRENARCHE

Pubarche describes the physical development of pubic hair accompanied by increased apocrine body odor, acne, and axillary hair. Pubarche is the physical manifestation of adrenarche. Adrenarche, defined by rising dehydroepiandrosterone (DHEA) sulfate (DHEAS) concentrations, is characterized by increased secretion of C-19 steroids from the zona reticularis of the adrenal cortex. These C-19 steroids are categorized as "adrenal androgens" although binding to the androgen receptor is limited. These hormones include DHEA, DHEAS, androstenedione, testosterone, and the 11-oxyandrogens. Adrenarche may be evident prior to the onset of breast development in girls and testicular enlargement in boys.

The 11-oxyandrogens, 11β-hydroxyandrostenedione (11OHA4), and 11β-hydroxytestosterone (11OHT) are formed from androstenedione and testosterone in the adrenal cortex following 11β-hydroxylation by the enzyme 11β-hydroxylase. Extra-adrenal oxidation of 11OHA4 via 11β-hydroxysteroid dehydrogenase type 2 generates 11-ketoandrostenedione which serves as a substrate for reduction by aldo-keto reductase 1C3, yielding the active androgen 11-ketotestosterone (11 KT). Indeed, 11 KT appears to be the dominant bioactive androgen during both normal and premature adrenarche.[6] Longitudinal tracking of a small cohort of normal children demonstrated that 11OHA, 11 KT, and 11OHT increase across puberty.[7]

Despite expanded knowledge regarding adrenal physiology, the etiology for adrenarche remains unclear. Based on urinary steroid hormone profiling, adrenarche may be a gradual process beginning earlier than previously believed.[8]

SECONDARY SEX CHARACTERISTICS ASSOCIATED WITH PUBERTY

In the 1960s, Tanner and colleagues[9,10] followed the physical features associated with pubertal development of children living in an orphanage in the United Kingdom. They categorized puberty into 5 stages with stage 1 being prepubertal and stage 5 representing adult development. For girls, Tanner staging is used to describe breast and pubic hair development. For boys, Tanner staging is used to describe testicular volume, penile development, and pubic hair development. Tanner and his colleagues[9,10] also reported that the tempo of puberty varied between individuals. In general, breast development in girls and testicular enlargement in boys precede pubic hair development. The tempo for pubic hair development is faster such that genital and pubic hair development is synchronized during the later stages of puberty. Nevertheless, discordance between gonadarche and adrenarche may be evident in normal development.

Girls

For girls, increased ovarian estrogen secretion promotes breast development. The development of breast buds with increased areolar diameter is considered to be stage 2; greater enlargement of the breasts occurs in stage 3, accompanied by increased pigmentation of the areolae and nipples. During stage 4, the areolae are mounded above the breast tissue. Recession of the areola to the general breast contour represents breast stage 5. Estrogen also induces cornification of the vaginal mucosa,

uterine growth, and acquisition of an adult female body habitus. Palpation of the breast is essential to differentiate between breast tissue and lipomastia.

Menarche typically follows an anovulatory cycle and generally occurs 2 to 3 years after the onset of breast development. During the first year post-menarche, irregular menstrual cycles are common; cycles are typically 21 to 45 days. By 3 years post-menarche, cycles are typically 21 to 35 days. Lack of menses by 3 years post-thelarche or cycles greater than 90 days is abnormal and warrants further evaluation.

For girls, development of pigmented coarse hairs along the labia majora is classified as pubic hair stage 2. During pubic hair stage 3, the hair becomes darker and coarser spreading over the pubic symphysis. Tanner stage 4 pubic hair development is characterized by an inverse triangle spreading to the medial aspects of the thighs for Tanner stage 5. Apocrine odor may precede or accompany the development of pubic hair. Associated findings include axillary hair, acne, and oiliness of the skin and hair. The pubertal growth spurt normally occurs concomitantly with the onset of breast development peaking during mid-puberty with only 4 to 6 cm of linear growth occurring after menarche.

Boys

For boys, increasing testicular and adrenal androgen secretion contributes to the development of secondary sex characteristics. To assess testicular volume, palpation or orchidometer use is essential. At stage 2, the testes are approximately 4 to 5 mL in volume with the longest axis being approximately 2.5 cm. The volume of the mature human testis is approximately 20 to 25 mL. At genital stage 3, further growth of the testes has occurred; the length and diameter of the penis has increased. Spermatozoa (spermaturia) can be found in early morning urine samples beginning during genital stage 3. Nocturnal sperm emissions may also begin around this time. At genital stage 4, penile size has increased, and the scrotal skin has become darkened.

In boys, pubic hair stage 2 consists of sparse pigmented hair at the base of the penis. For pubic hair stage 3, the hair is longer, darker, and extends over the junction of the pubic bones. For pubic hair stage 4, the extent of hair has increased, but has not yet achieved the adult male escutcheon typical of stage 5. Additional secondary sexual characteristics in boys include axillary hair, increased size of the larynx, deepening of the voice, increased bone mass, and increased muscle strength. Terminal hair begins to develop in androgen-dependent regions on the face and trunk approximately 3 years after the appearance of pubic hair. Timing, density, and distribution of facial and body hair vary considerably.

Approximately 50% of normal boys experience gynecomastia, usually in mid-puberty. This is attributed to the ratio of circulating concentrations of estradiol to testosterone being relatively high. In most instances, gynecomastia resolves spontaneously by 16 years of age.

Voice break is another marker of pubertal progression in boys. Among healthy Danish boys, voice break occurred at the mean age of 13.6 years and was moderately correlated with other male pubertal milestones including testicular enlargement, axillary odor, pubarche, axillary hair, and peak height velocity.[11] The pubertal growth spurt in boys, with an average height velocity of 9.5 cm per year, occurs around the end of Tanner genital stage 3 and the beginning of Tanner stage 4.

ONTOGENY OF GONADOTROPIN-RELEASING HORMONE NEURONS

Gonadarche and reproductive competence depend on GnRH neuron development. In the human fetus, GnRH neurons initially develop in the olfactory placode outside the central nervous system. Subsequent influence of growth factors, adhesion molecules,

and diffusible guidance cues (both attractive and repulsive) direct the migration of the GnRH neurons. During this migration, the GnRH neurons are accompanied by olfactory-derived axons, olfactory epithelial sheath cells, and blood vessels toward the cribriform plate. Upon reaching the hypothalamus, the GnRH neurons disperse to their final locations, sending projections to the median eminence to release GnRH into the hypophyseal portal vasculature.[12] The precise origin and particular factors responsible for the specification and differentiation of GnRH neuron precursors remain enigmatic. Investigation of genetic variants associated with disordered puberty has provided insights regarding the development of human GnRH neurons. The anosmia/hyposmia phenotype of some genetic variants associated with congenital hypogonadotropic hypogonadism (CHH) reflects the close associations of the developing olfactory system and GnRH neurons. Normal function of the HPG axis is ultimately dependent on the meticulous spatio-temporal orchestration of the migration and function of the GnRH neurons.

MINIPUBERTY

With the availability of more sensitive hormone assays, Forest and colleagues[13] described a transient period of increased HPG axis activity in early infancy. Following the low gonadotropin concentrations at birth, gonadotropin concentrations were found to rise in both boys and girls within weeks of birth. This transient gonadotropin secretion has been labeled “minipuberty.” In the immediate neonatal period, low gonadotropin concentrations are attributed to hypothalamic-pituitary suppression by placental estrogen secretion. Upon interruption of placental estrogen exposure, gonadotropin secretion increases.

Over the first few years of life, sexual dimorphism in gonadotropin concentrations has been noted. Boys have higher LH concentrations than girls; LH concentration typically peak between 2 and 10 weeks of age and decline by 4 to 6 months of age. Testicular testosterone secretion occurs with testosterone concentrations typically peaking around 1 month of age followed by a decline to prepubertal concentrations by 7 to 12 months of age.

Girls have higher FSH concentrations, which may remain elevated until 2 to 4 years of age. One longitudinal study involving healthy full-term infant girls demonstrated 2 gonadotropin peaks in early infancy with 1 peak occurring around days 15 to 27 and a later peak occurring at days 164 to 165.[14]

As noted earlier, the human HPG axis manifests an on-off-on pattern (**Fig. 2**). The biological basis and rationale for transient post-natal HPG axis activity during the first few months of life are enigmatic. At birth, the brain is still plastic with ongoing development. Most axon and synapse formations are completed during the first year of life. Does this transient HPG axis activity imprint areas in the brain to influence future patterns of gonadotropin secretion? Do neonatal gonadal hormones affect future fertility, gender identity, sexual orientation, behaviors, and risk for autism spectrum dysfunction? Data are accruing regarding patterns of hormone secretion during the first 6 months of life. Nevertheless, the factors that initiate and terminate this transient HPG axis activity and maintain the quiescence of the HPG axis until the onset of puberty remain indeterminate.

GONADARCHE AND GONADS

Ovaries

Ovaries are responsible for hormone secretion, oogenesis/follicular maturation, and ovulation. For women, reproductive capacity is determined during gestation when

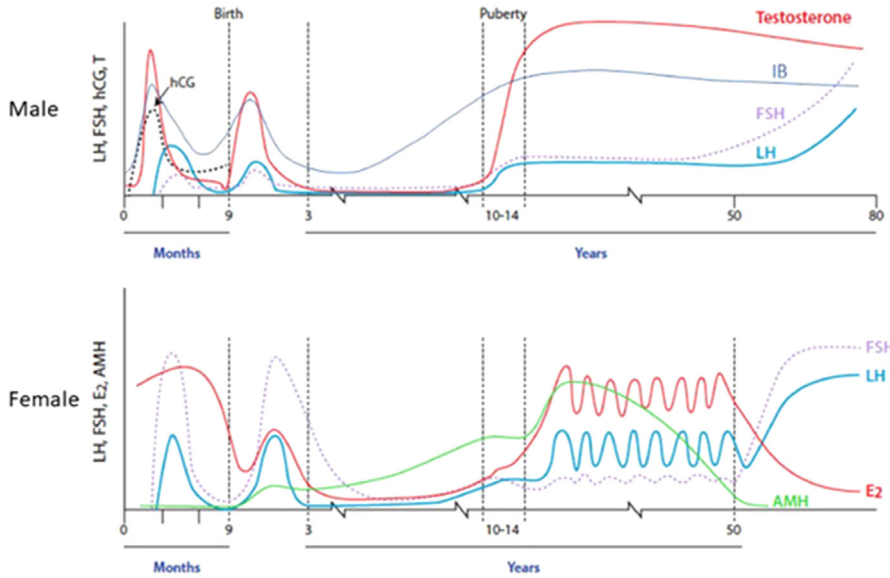

Fig. 2. The hypothalamic-pituitary-gonadal (HPG) axis during fetal and postnatal life. Circulating concentrations of gonadotropins, sex steroids, and inhibin B during the prenatal, immediate neonatal, prepubertal, pubertal, and adult time periods in boys and men (top panel). Gonadotropins, estradiol, and anti-Müllerian hormone during the same time period in girls and women (lower panel). AMH, anti-Müllerian hormone; E_2, estradiol; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; T, testosterone. (Reprinted with permission: Howard SR. Interpretation of reproductive hormones before, during and after the pubertal transition-Identifying health and disordered puberty. Clin Endocrinol (Oxf). 2021;95:702-15. https://doi.org/10.1111/cen.14578. PMID: 34368982.)

primordial follicles develop. Primordial follicles contain a small primary oocyte within a single layer of squamous granulosa cells. At birth, approximately 500,000 to 1 million primordial follicles are present. During the prepubertal years, primordial and preantral follicles predominate. Nevertheless, small gonadotropin-independent antral follicles can develop.

As would be anticipated, prepubertal ovaries are smaller than pubertal ovaries. Prepubertal ovaries show increased density of primordial follicles, less well-defined corticomedullary junction, and less commonly identified tunica albuginea compared to pubertal ovaries.[15] The prepubertal ovary contains a population of aberrant oocytes within primordial follicles. These oocytes are apparently eliminated prior to gonadarche because they are absent from the pubertal ovary. Factors governing the initial progression from primordial to primary follicles in the peri-pubertal ovary are poorly defined. Available data suggest that FSH and other factors influence oocyte chromatin and epigenetic factors such as histone methylation to advance oocyte development.[16]

Upon gonadarche, ovarian volume increases achieving maximum volume between menarche and age 16 years. FSH is essential to promote granulosa cell aromatase expression for the transition from primary to preantral follicles and estrogen synthesis. Among regularly cycling 16-year-old non-obese Danish girls, transabdominal ultrasound revealed the median ovarian volume to be 6.78 cm^3 with a median of 10 follicles (2.0–7.9 mm) per ovary.[17] Polycystic ovary morphology may be detected in healthy

adolescent girls and is generally not associated with decreased ovulatory rate, hyperandrogenism, or metabolic abnormalities in this age group.

Testes

Sertoli cells, the first somatic cell type to differentiate in the embryonic testis, coordinate the differentiation of other testicular cells such as germ cells and Leydig cells. During embryonic testis development, fetal Sertoli cells aggregate surrounding the primordial germ cells, gonocytes, to form the testicular cords which will eventually develop into the seminiferous tubules in the adult testis. Throughout gestation and the neonatal period, Sertoli cells proliferate until terminal differentiation to adult Sertoli cells occurs at gonadarche.

By midgestation, most germ cells undergo transition to prespermatogonia. Spermatocytes, spermatids, and spermatozoa are absent from testes both during minipuberty and the prepubertal years. Despite circulating testosterone concentrations in the pubertal range during minipuberty, spermatogenesis fails to occur because Sertoli cells lack expression of the androgen receptor. Upon gonadarche with increased gonadotropin secretion, exponential increases in spermatogonia and testicular volume are apparent.

Two distinct populations of Leydig cells exist in mammals. Following birth, the fetal Leydig cells involute. With the onset of gonadarche, adult Leydig cells apparently derived from distinct stem cell progenitor cells arise.[18] Additional details regarding testicular development can be found elsewhere.[19]

FEEDBACK AT THE HYPOTHALAMUS AND PITUITARY

Sex Steroids

In males, LH promotes testicular testosterone synthesis and secretion. Testosterone circulates predominantly bound to sex hormone–binding globulin. Testosterone binds directly to the cytosolic androgen receptor. In some target tissues, such as the male genital skin and the prostate, testosterone is converted by the enzyme 5-alpha reductase to the more potent androgen, dihydrotesterone. Testosterone can also be converted to estradiol by the aromatase enzyme. Testosterone enables negative feedback inhibition of LH secretion by suppression of GnRH secretion via hypothalamic kisspeptin neurons and direct action on pituitary gonadotropes. Gonadotropin concentrations are typically not elevated in patients with complete androgen insensitivity. Measuring gonadotropins and testosterone during early infancy can help diagnose CHH in boys who present with micropenis.[20]

In females, LH promotes theca cell androstenedione synthesis followed by androstenedione diffusion to granulosa cells where FSH-stimulated aromatase converts it to estrogens. In females, sex steroid feedback affecting GnRH pulse frequency is essential to the menstrual cycle and involves both negative and positive feedback actions of ovarian steroids at both the hypothalamic and pituitary levels.

Gonadal Peptide Hormones

Anti-Mullerian hormone (AMH) is a homodimeric disulphide-linked glycoprotein member of the transforming growth factor-β family. Sertoli cells of the developing male fetus secrete AMH to promote in utero regression of the Mullerian ducts. With the onset of gonadarche, rising testosterone concentrations suppress Sertoli cell AMH production. In contrast, AMH concentrations are low in the developing female fetus. In the adolescent and adult woman, AMH is secreted by primary follicles and appears to negatively regulate the recruitment of resting follicles into active follicles. Thus, AMH

limits the number of follicles maturing at any specific time point. Low AMH concentrations in girls with Turner syndrome or primary ovarian insufficiency suggest low follicular reserve.[21] High AMH concentrations in adolescent girls with irregular menses and hyperandrogenism suggest polycystic ovary syndrome.[22] Variable AMH assays and inconsistent AMH concentrations impede its usefulness in girls who are cancer survivors.[23]

Inhibin B, a member of the transforming growth factor-β family, is secreted by Sertoli cells in males and granulosa cells in females. Inhibin B is a glycoprotein heterodimer consisting of an inhibin alpha-subunit and an inhibin beta-B subunit. Inhibin B downregulates pituitary FSH synthesis. Inhibin B increases during minipuberty, remains low during childhood, and increases with gonadarche. In adult males, inhibin B reflects Sertoli cell mass and spermatogenic capacity.

Insulinlike peptide 3 (INSL3) is secreted by Leydig cells. During fetal life, INSL3 plays an important role in abdominal testicular descent. INSL3 secretion follows a similar pattern to LH with elevation during minipuberty, low concentrations during childhood, and rising again at gonadarche.

Gonadal peptide hormones can provide information regarding gonadal function. Low AMH and inhibin B concentrations in phenotypic boys are consistent with congenital anorchia or CHH. Inhibin B tends to be higher among boys with constitutional delay compared to those with CHH. Nevertheless, overlap between these groups occurs. The overlap in INSL3 concentrations limits its value in distinguishing individuals with CHH.

GENETICS OF PUBERTY

As noted earlier, the timing of puberty is heritable, with epidemiologic data indicating that genetic regulation accounts for 50% to 80% of the variation at age of pubertal onset. Age at puberty is associated with risk regarding long-term health outcomes such as breast cancer, cardiovascular disease, and osteopenia/osteoporosis. Large genome-wide association studies have identified genes that are associated with age at menarche in girls and age at voice break in boys. Over 1000 independent genetic signals associated with age at menarche were identified in multi-ancestry genetic analyses in approximately 800,000 women. These analyses implicated 660 genes in pubertal timing.[24]

SECULAR TRENDS TOWARD EARLIER PUBERTY

Over the past few decades, observations have suggested that puberty is starting at younger ages. Clinical studies examining ages at the onset of puberty depend on the criteria used to indicate puberty. For girls, age at the onset of breast development and age at menarche are conventional markers of puberty in girls. For boys, age at voice change has been used as a marker.[25]

Several longitudinal studies including the Breast Cancer and the Environment Research Program have noted a decrease in the age at the onset of breast development and a smaller decrease in the age at menarche.[26,27] The onset of breast development was assessed both through observation and palpation; however, gonadotropin concentrations were not included in these studies. Most of these studies have suggested that thelarche now occurs earlier than in the 1960s;[28] however, the age of menarche has remained relatively stable over recent decades, resulting in a longer interval between thelarche and menarche.[29] Several factors have been implicated as potential contributors to this earlier onset of puberty including obesity both in boys and girls,[30,31] environmental factors,[32] stress and perinatal growth,[33] and

epigenetic factors. Internationally adopted girls seem to be at a higher risk of developing precocious puberty.[34] Environmental factors include exposure to substances which may mimic and/or antagonize endogenous sex steroid action, synthesis, or degradation, termed endocrine-disrupting chemicals (EDCs), many of which (like phthalates and phenols) are found in common household products.[32] Exposure to EDCs may occur by direct absorption through the skin, inhalation, or ingestion, and the effects can be cumulative due to consistent or repeated use of these products as well as potential joint effects of exposure to multiple chemicals across different chemical classes.

SUMMARY

Our understanding of the physiology of pubertal development, both in males and females has expanded over the past decades. Genetic, environmental, nutritional, and metabolic factors can influence the onset and tempo of puberty. Important findings include augmented knowledge of HPG axis function, discovery of the kisspeptin system, and the role of KNDy neurons in regulating hypothalamic GnRH secretion.

CLINICS CARE POINTS

- Genetic, metabolic, nutritional, environmental, ethnic, geographic, and economic factors influence the onset and tempo of pubertal development.
- The expansion of knowledge regarding how the timing and tempo of puberty relate to adult health status is important and should be further explored.
- An improved understanding of gametogenesis will enable successful fertility preservation for prepubertal children affected with disorders that would impact future fertility.

DISCLOSURE

The authors have nothing to disclose.

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