Chapter 2
Normal Pubertal Physiology in Females

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Abstract The development of a female child into an adult woman is a complex process. Puberty, and the hormones that fuel the physical and psychological changes which are its hallmarks, is generally viewed as a rough and often unpredictable storm that must be weathered by the surrounding adults. The more we learn, however, about the intricate interplay between the endocrine regulators and the end-organ responses to this hormonal symphony, puberty seems less like chaos, and more of an incredible metamorphosis that leads to reproductive capacity and psychosocial maturation. Physically, female puberty is marked by accelerated growth and the development of secondary sexual characteristics. Secondary sexual characteristics are those that distinguish two different sexes in a species, but are not directly part of the reproductive system. Analogies from the animal kingdom include manes in male lions and the elaborate tails of male peacocks. The visible/external sequence of events is generally: breast budding (thelarche), onset of pubic hair (pubarche), maximal growth velocity, menarche, development of axillary hair, attainment of the adult breast type, adult pubic hair pattern. Underlying these external developments is the endocrine axis orchestrating the increase in gonadal steroid production (gonadarche), the increase in adrenal androgen production (adrenarche) and the associated changes in the reproductive tract that allow fertility. Meanwhile, the brain is rapidly adapting to the new hormonal milieu. The extent of variation in this scenario is enormous. On average, the process from accelerated growth and breast budding to menarche is approximately 4.5 years with a range from 1.5 to 6 years. There are differences in timing and expression of maturation based on ethnicity, geography, and genetics. Being familiar with the spectrum that encompasses normal development is
critical to identifying those rare cases when pathology is at the root of accelerated or absent pubertal signs, and for the frequent reassurance that young adults and their parents need to hear on the journey to womanhood.

**Keywords** Normal puberty • Endocrine axis • Hypothalamus • Pituitary • Ovaries • Adrenals • Hormones • Ovulation • Receptors • Tanner stages • Gonadotropins • Thelarche • Pubarche • Menarche • Reproductive capacity • Psychosocial maturation • Variations • Patterns of growth

**Overview of Normal Puberty**

The development of a female child into an adult woman is a complex process. Puberty, and the hormones that fuel the physical and psychological changes which are its hallmarks, is generally viewed as a rough and often unpredictable storm that must be weathered by the surrounding adults. The more we learn, however, about the intricate interplay between the endocrine regulators and the end-organ responses to this hormonal symphony, puberty seems less like chaos, and more of an incredible metamorphosis that leads to reproductive capacity and psychosocial maturation.

Physically, female puberty is marked by accelerated growth and the development of secondary sexual characteristics. Secondary sexual characteristics are those that distinguish two different sexes in a species, but are not directly part of the reproductive system. Analogies from the animal kingdom include manes in male lions and the elaborate tails of male peacocks. The visible/external sequence of events is generally:

- Breast budding (thelarche)
- Onset of pubic hair (pubarche)
- Maximal growth velocity
- Menarche
- Development of axillary hair
- Attainment of the adult breast type
- Adult pubic hair pattern

Underlying these external developments is the endocrine axis orchestrating the increase in gonadal steroid production (gonadarche), the increase in adrenal androgen production (adrenarche) and the associated changes in the reproductive tract that allow fertility. Meanwhile, the brain is rapidly adapting to the new hormonal milieu.

The extent of variation in this scenario is enormous. On average, the process from accelerated growth and breast budding to menarche is approximately 4.5 years with a range from 1.5 to 6 years [1]. There are differences in timing and expression of maturation based on ethnicity, geography, and genetics. Being familiar with the spectrum that encompasses normal development is critical to identifying those rare cases when pathology is at the root of accelerated or absent pubertal signs, and for the frequent reassurance that young adults and their parents need to hear on the journey to womanhood.
Control of the Hypothalamic–Pituitary–Ovarian Axis

The fetus, neonate, and prepubertal child are all capable of secreting gonadotropins and sex steroids in adult concentrations; however, the hypothalamus, anterior pituitary, and gonads (components of the HPO axis) carefully coordinate these functions with the female reproductive lifecycle (Fig. 2.1). Before birth, the development of the

![HPO axis diagram](image-url)
The hypothalamic–pituitary portal venous system begins at 9–10 weeks of gestation and is completed by 19–20 weeks with an associated increase in the gonadotropins and ovarian sex steroids that stimulate germ cell and follicular development [2]. The negative and positive feedback effects of the ovarian steroids on the hypothalamus and pituitary develop by mid-gestation and are critical to the functioning of the HPO axis. The characteristic pulsatile pattern of hypothalamic gonadotropin-releasing hormone (GnRH) secretion becomes apparent soon after birth, as the suppressive effects of the large amounts of maternal estrogen and progesterone from the placenta wear off [3]. Infancy is characterized by levels of gonadotropins and ovarian steroid levels which can be as high as those seen in reproductive-aged females—with a peak at 12–18 months—until the negative feedback systems become fully functional and the levels begin to drop to the lows of childhood [4]. Suppression of hypothalamic activity lasts until puberty, and is known as the “Juvenile Pause”; it is characteristic of all higher primates: Old World monkeys, apes, and humans [5]. This is in sharp contrast to other mammals, such as rodents, whose postnatal development of gonadotropin signaling develops without interruption [6]. This hormonal hibernation is theorized to be critical to human life history, allowing a prolonged childhood for socialization and brain development [7] (Fig. 2.2).

**Fig. 2.2** Variations in key reproductive functions over the lifetime. (Adapted with permission from Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility, 8th edition. Philadelphia: Lippincott Williams & Wilkins; 2010)
The arcuate nucleus in the medial basal hypothalamus is where the “hypothalamic pulse generator” resides. These specialized secretory cells rhythmically secrete GnRH into the pituitary portal plexus. GnRH is a decapeptide with a serum half-life of 2–4 min, which binds to receptors on anterior pituitary gonadotrophs which synthesize and store both of the glycoprotein gonadotropins: follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which act directly on the gonads to stimulate follicular maturation. Classic studies in the 1970s using oophorectomized rhesus monkeys demonstrated the importance of pulsatile vs. continuous GnRH infusion on HPO axis function. Gonadotropin secretion is actually suppressed by continuous infusion, whereas regular intermittent administration will lead to ovarian stimulation, maturation, and production of steroid hormones [8].

The changes seen in gonadal function over the reproductive life span reflect changing activity in the hypothalamic pulse generator, which in turn result from modulating levels of central inhibition. Although GnRH pulsatile activity can be detected in prepubertal children, the frequency and amplitude of these secretions are very low (and primarily occur during sleep), and do not result in gonadal steroid production [9]. The diphasic pattern of GnRH secretion, which is high in infancy, low in childhood, then high again as puberty progresses, was demonstrated in the absence of signals from the gonads. Studies of girls with Turner’s syndrome, and confirmatory studies of primates, debunked the earlier notions of a “gonadostat” as the locus of control for turning the hypothalamic pulse generator “back on” at the initiation of puberty [10]. Thus, gonadal steroids are critical to carrying out the changes associated with puberty, but are not essential to the initiation of the process.

There is a marked decrease in pituitary responsiveness to GnRH during the prepubertal childhood years, along with the reduction in amplitude and frequency of GnRH pulses from the hypothalamus (Fig. 2.3). Over the last few decades, several
key pathways have emerged as critical to the central nervous system inhibition controlling life cycle variation in the HPO axis:

- Gamma-aminobutyric acid (GABA)
- Neuropeptide Y (NPY)
- Glutamate
- Kisspeptins

GABA is an inhibitory neurotransmitter, which has been shown through primate perfusion studies to be inversely related to GnRH pulsatile secretion during puberty [11]. It is likely a key factor in the “brake” that is put on hypothalamic GnRH activity during childhood. Similarly, NPY—a hypothalamic neuropeptide associated with food intake and reproduction-related behaviors—appears to be a player in the neuroendocrine hold on GnRH secretion during prepuberty [12]. Glutamate has been shown to stimulate GnRH release and appears to play a role in the return of the pulsatile activity at puberty [13].

Kisspeptins have been shown to be a major component of the hypothalamic GnRH pulse generator system, discovered as a result of genetic studies in a family affected by hypogonadotropic hypogonadism and delayed puberty. Affected individuals were found to harbor homozygous inactivating mutations for GPR54 (encoded by the KISS1R gene), the G-protein coupled receptor through which kisspeptins act as neuropeptides [11, 14]. Neurons expressing kisspeptins (encoded by the gene KISS1) are located exclusively in the arcuate nucleus—which is known to be the location of the hypothalamic pulse generator—and GnRH-secreting neurons also express GPR54. Other evidence for the importance of kisspeptins in modulating HPO activity includes the finding of a young girl with central precocious puberty who had a mutation in the KISS1R gene that lead to prolonged activation [15]. Studies in primates also validate the importance of kisspeptin neurons and demonstrate their role in the negative feedback system involving gonadal steroids and the hypothalamus [16]. Although the exact mechanism is unknown, it is clear that the kisspeptin system is key to transducing signals from the internal and external environment that are used to initiate, in each individual, the process of puberty.

The Endocrine Mediators of Puberty

At the appointed time, induced by the still mysterious signal, nocturnal pulses of gonadotropin secretion become more pronounced, and LH begins to predominate over FSH. This occurs about 1 year prior to breast budding, which requires detectable levels of estradiol, brought about by the gradual increase in gonadotropin peak amplitudes. At the level of the hypothalamus, GnRH pulse frequency increases and begins to attain a diurnal, or daily, pattern [9]. GnRH pulses are inferred from measurement of serum LH (which has a half-life of 30 min compared to 300 min for FSH), and pulse frequency will eventually average out to approximately once an hour during a woman’s reproductive years, with significant variation over the course of the menstrual cycle [17].
During puberty there is a significant increase in the responsiveness of the pituitary to GnRH, due to regulation in the gonadotrope receptors and increased synthesis of gonadotropins. Subsequently, LH secretion peak amplitude increases and will eventually be 20–40 fold greater than levels seen in the prepubertal state. LH bioactivity then increases due to changes in glycosylation [18]. FSH secretion increases only two to threefold, and is held in check by the negative feedback at both the hypothalamus and pituitary from the rising estradiol levels coming from the ovaries. In addition to the key effects of GnRH pulse pattern and the gonadal steroids, other substances, such as inhibin A and B, activin, follistatin, and cytokines, all have an effect on modulating gonadotropin activity and creating the positive and negative feedback systems essential to a mature reproductive neuroendocrine axis (Fig. 2.1).

Inhibins are glycoprotein dimers (an alpha subunit with either a βA or βB linked to it), which are produced mainly in the gonads and can function as peripheral markers of granulosa cell activity. They act to suppress FSH secretion and thus participate in the negative feedback within the HPO axis [19]. Levels of inhibin B are low or undetectable in prepubertal girls, but then increase sharply with puberty until the onset of regular ovulatory cycles, when levels start to decline. Similarly, levels of inhibin A are low or undetectable in prepubertal girls, but then rise steadily with puberty and reach adult levels after menarche. Inhibin B is produced largely by follicles in the early stages of development, and thus peaks during the follicular phase of the menstrual cycle, while inhibin A is largely produced by the corpus luteum and peaks during the luteal phase [20]. Measurement of inhibin B, together with other biomarkers, can be helpful in diagnosing disorders of puberty as well as following inhibin-secreting neoplasms (granulosa cell tumors).

As the ovaries mature, they become more adept at responding to and amplifying central signals, and release more steroid hormones for a given amount of gonadotropin. When estradiol and inhibin B levels become high enough to exert negative feedback on gonadotropin secretion, a cycle will develop and menarche can occur. A reproducible cycle length and other characteristics are established as ovulation occurs and the positive feedback system matures between ovarian estradiol production and central gonadotropin secretion [21]. Additionally, ovarian size increases as puberty progresses, due to increased stroma, the growth of individual follicles, and an increase in the number of follicles maturing. This adds to the concentration of gonadal peptides that act in paracrine and endocrine fashions to modulate gonadotropin secretion. Activin is structurally similar to inhibin but appears to act as a stimulant of FSH secretion, while inhibin (appropriately named) is an inhibitor of FSH secretion. Follistatin has a complex role in the feedback process, but in simple terms, binds activin and is a regulator of the inhibin–activin system [22].

Although independent of the maturation of the HPO axis, adrenarche—a marked increase in adrenal steroid production—occurs in conjunction with the onset of gonadal maturation and is critical to the appropriate development of several key pubertal hallmarks. In both boys and girls, the process begins at around age 6. Similar to the “reawakening” of the HPO axis after the quiescence of childhood, adrenarche reflects a regrowth of the zona reticularis, which was very active and large in the fetus [23]. The primary change leading to the increase in adrenal
androgen production by the hypothalamic–pituitary–adrenal (HPA) axis involves enhanced adrenal sensitivity to adrenocorticotropic hormone (ACTH). Adrenal steroidogenesis shifts towards production of $\Delta 5 \beta$-hydroxysteroid intermediates (17α-hydroxypregnenolone and dehydroepiandrosterone, DHEA) and decreased production of $\Delta 4$-ketosteroids (17α-hydroxyprogesterone, 17-OHP; androstenedione), without changing cortisol production [1]. The subsequent increases in circulating DHEA-sulfate (DHEA-S) signal the onset of adrenarche, which—along with other adrenal androgens—is necessary for the development of pubic and axillary hair, also known as pubarche. The rise in adrenal androgens also stimulates the development of the pilosebaceous unit in the skin—made up of a hair follicle and associated oil gland—and increases cortical bone density.

Adrenarche is characterized by DHEA-S levels of 40 $\mu$g/dL or greater (approximately 5 $\mu$g/dL in prepubertal children), and usually occurs about 2–3 years before the reactivation of the HPO axis is detectable. As with the initiation of gonadarche, the ultimate stimulus for the initiation of adrenarche is unknown. Studies actually suggest that adrenarche is not an abrupt “signaled” process, but in fact represents a gradual process ongoing since birth [23]. Given the temporal relationship between the two events, a causal link is tempting to imagine, however, the evidence does not support a link to date [24]. In fact, the two processes can occur independently. For example, in true precocious puberty, gonadarche precedes adrenarche and premature adrenarche does not induce premature puberty. In addition, children with hypo-adrenal disorders—such as Addison’s disease—will undergo gonadarche with appropriate adrenal supplementation. One final example includes patients with hypogonadotropic or hypergonadotropic hypogonadism who undergo adrenarche spontaneously.

While the exact mechanism that signals the start of puberty is unknown, body weight and other metabolic factors must play a key role in sending a message—likely via the hypothalamus—to initiate the process. The correlation between increased BMI and earlier initiation of puberty has been repeatedly shown, and the inverse relationship between malnutrition and optimal reproductive functioning is understood [25, 26]. Given the tremendous energy stores needed for both growth and reproduction—the ultimate purpose of successful puberty—it is logical that a peripheral signal of adiposity is central to the process. There is substantial evidence that leptin—secreted from adipocytes—is critical to the communication process between the peripheral somatic status and the centrally mediated initiation of puberty. For example, leptin-deficient rodents fail to enter puberty, while treatment with recombinant leptin reverses the failure [27]. In humans, adults with leptin deficiency (or nonfunctional leptin receptors) have all been reported to have severe hypogonadotropic hypogonadism [28].

Leptin is secreted in a pulsatile manner with a diurnal pattern, and its levels are directly correlated with the amount of fat stored by the body [29]. Serum leptin levels are low in both prepubertal boys and girls, and then there is a striking sexual dimorphism that develops; in males, leptin increases until mid puberty, then decreases while levels progressively increase through puberty in females. This is consistent with the finding that estrogens induce leptin gene expression while
androgens suppress its production. The effect of leptin on the HPO axis occurs at multiple sites, with stimulatory effects at the hypothalamus—which has the highest concentration of the most active isoform of the leptin receptor—and inhibitory effects at the gonads [30].

Data supports the idea that a minimum level of leptin is necessary, but not sufficient by itself, to signal the reactivation of the HPO axis that allows puberty to unfold. As leptin levels increase with continued accumulation of adipose tissue over time, the signal is sent to the CNS that adequate energy stores exist to undertake the adult processes of development. Consistently normal levels of leptin are needed to maintain ovarian function and fertility. Clinically, patients with anorexia nervosa who develop amenorrhea due to hypothalamic suppression (which generally occurs by the time the patient is 70% of ideal body weight) have significantly lower leptin levels than healthy controls, and the leptin levels correlate with percentage of body fat [31]. Other disorders of hypothalamic amenorrhea, such as exercise-induced and functional amenorrhea, are also associated with decreased leptin levels [32]. Conversely, disorders associated with obesity and the resultant increased leptin levels are marked by an acceleration of pubertal onset and ovarian dysfunction related to anovulation. One study in Caucasian girls aged 8–13 years (monitored over a 4-year period) showed a direct correlation between the elevated leptin levels of obesity/overweight and early initiation of puberty: a 1 ng/mL increase in serum leptin lowered the age at menarche by 1 month [33].

Following adrenarche, gonadarche, and the associated rise in steroid hormones and leptin, the distal end of the endocrine processes that define puberty involves activation of the growth hormone and insulin-like growth factor (ILGF) axis. Growth hormone (GH) is secreted from the anterior pituitary somatotropes, in response to hypothalamic pulsatile release of growth hormone-releasing hormone (GHRH). Peripheral factors reflecting nutritional status also affect GH release: ghrelin stimulates and somatostatin inhibits GH release from somatotropes [34]. GH secretion peaks during puberty, then steadily decreases with advancing age. The rate at which levels of GH rise during puberty is the most important determinant of growth velocity, with those having the most frequent and high amplitude GH pulses achieving the greatest growth velocity [35].

GH binds to receptors in the liver, which respond by producing and secreting ILGF, which has wide ranging effects throughout the body on growth and differentiation. Additional metabolic activities of GH include affecting salt and water balance, increased lipolysis, stimulation of protein synthesis and insulin antagonism. ILGF-1 enhances anabolic and stimulatory properties of ACTH, thyroid stimulation hormone (TSH), and FSH/LH at the level of the ovary. IGF-I levels are very low at birth, then rise at the time of puberty to their peak, then decline to their steady state by around age 20 [36].

While the rising levels of GH and ILGF-1 are the primary drivers of the pubertal growth spurt, the gonadal steroids also play a key role. In children with central gonadotropin-dependent precocious puberty, treatment with a long-term GnRH analog (leading to suppression of the gonads) leads to decreased GH and ILGF-1 levels during treatment [37]. Conversely, in girls with Turner’s syndrome, treatment
with exogenous steroids leads to improved height velocity and advanced bone age, compared to controls [38]. Thus, precocious puberty and the associated rising steroid levels can cause a premature growth spurt, even in the absence of the normal pubertal increase in GH via the activation of the growth hormone axis.

**End Organ/Organism Responses to the Pubertal Process**

The biologic purpose of female puberty is to develop traits to attract males and attain reproductive readiness. To that end, the secondary sexual characteristics of humans mature into their adult form (female breasts and hair patterns), internal and external reproductive organs become functional, the skeleton grows to accommodate childbearing and a shift in body composition, and the brain—marinated in estrogen—undergoes profound remodeling of neuronal circuits related to socialization and behavior. The first sign of puberty in most adolescent girls is the pubertal growth spurt or acceleration of growth, followed, or sometimes preceded by, breast budding (thelarche), the appearance of pubic hair (pubarche), and finally, the onset of menses (menarche). This pattern has tremendous variety in timing and pace, depending on the individual’s underlying genetics, environmental exposures, and social circumstances. For most adolescents, pubarche follows thelarche, but in a minority of girls the sequence is reversed and pubarche precedes thelarche. Whichever sign arrives first, they progress in tandem. On average menarche occurs after the peak growth has passed, about 2.6 years after the onset of puberty. In total, the processes of accelerated growth, thelarche, pubarche, and menarche require about 4.5 years to complete, with a wide range of 1–6 years [39] (Fig. 2.4).

The pubertal growth spurt is dependent upon the increasing GH and ILGF, as well as the rising levels of ovarian steroid hormones. A significant amount of the eventual adult height is gained during puberty; 16–18 % [40]. The peak height velocity is usually attained about 6 months prior to menarche and the mid stages of breast and

![Timeline of female pubertal milestones.](image)

Fig. 2.4 Timeline of female pubertal milestones. (Adapted with permission from Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility, 8th edition. Philadelphia: Lippincott Williams & Wilkins; 2010)
public hair development [41]. Girls’ peak height velocity generally occurs between the ages of 9 and 14, and averages 9.0 cm/year, compared to 10.3 for boys [42]. The height differential between males and females results from the earlier onset of the growth spurt (by about 2 years) in girls vs. boys who achieve more growth even before they experience peak velocity. There is still growth that occurs, but it is generally only 2–3 in. during the 2 years following menarche [43]. Skeletal proportions also change, as the extremities rapidly increase in length while the vertebral column is slower to grow. Ultimately, the process of puberty will work to limit adult height, as the gonadal steroids at high levels lead to epiphyseal closure of the long bones.

In addition to gaining height and growth, accretion of bone mass during adolescence is critical to attaining adult skeletal characteristics. At least half of peak bone mass and total body calcium is achieved by age 17–19, stimulated by GH, estrogen, and adrenal steroids [44, 45]. In girls, approximately 9–12 months after peak height velocity is attained, the peak velocity in bone mineral accretion occurs, generally coinciding with menarche [46]. As body size grows, composition also changes, as the female pattern of body fat appears on the upper arms, lower abdomen, back, and buttocks. During childhood, increases in BMI reflect mostly lean mass, while after age 16 increases are due to gained fat mass [47]. Bone health is determined by many factors: genetics, calcium/vitamin D status, general health and nutrition, life-style choices (e.g., tobacco), body weight and BMI, exercise—especially weight-bearing, medications and hormonal status. Given that the preponderance of bone mass is acquired during early adolescence, the window for influencing this important component of future health is relatively short.

The visible changes of puberty involve the maturation of the secondary sexual characteristics, and are most frequently staged using the system developed by Marshall and Tanner in 1969 [48]. Also known as the Sexual Maturity Rating (SMR), there are five stages of breast and pubic hair development described for girls, from the prepubertal stage 1 to the adult stage 5 (Figs. 2.5 and 2.6). It is not uncommon for initial breast budding to be unilateral, or for asymmetry to occur between the right and left breasts, which often is corrected or much less noticeable as development continues. Similarly, breast and pubic hair development are not necessarily synchronous, as they are driven by different though closely related hormonal systems (gonadal and adrenal steroids, respectively).

While skeletal changes, breast and pubic hair development are evident over time, changes to internal reproductive organs remain hidden. The ovaries increase in size during the prepubertal years and begin to demonstrate follicular growth. The vagina is roughly 4 cm at birth and grows to 7–8 cm in late childhood. The uterus is approximately 2 cm in an infant with a larger cervix compared to the corpus. By menarche the corpus/cervix ratio is 1:1, and the corpus continues to develop as it becomes more functional, to reach the adult ratio of 3:1 [43]. The most dramatic and socially significant event of puberty is the result of sustained levels of estrogen leading to endometrial stimulation and eventual shedding. Menarche occurs about 2.5 years after the peak of the growth spurt and the initiation of puberty [48]. In this classic Tanner study, most girls had attained stage 4 breast (62%) and pubic hair (63%) development by the time they experienced menarche. In that same study, the
average time from the start of breast development to menarche was 2.3 years, but the range was large: 0.5–5.75 years. An earlier or later onset of puberty was not associated with shorter or longer intervals between milestones, and likely represents the complex interplay between genetics and environment that results in an individual’s expression of the pubertal process.

Fig. 2.5 Tanner stages of female pubertal breast development. (Created from data in Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969 Jun;44(235):291–303)
<table>
<thead>
<tr>
<th>Tanner Stage</th>
<th>Preadolescent</th>
<th>Adult hair type emergens, covers mons pubis, but does not extend to the thighs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanner Stage 1</td>
<td>No discernable difference between vellus hair on the mons and anterior abdominal wall, no pubic hair</td>
<td></td>
</tr>
<tr>
<td>Tanner Stage 2</td>
<td>Appearance of few, sparse, lightly pigmented hairs, with minimal curl on the labia</td>
<td></td>
</tr>
<tr>
<td>Tanner Stage 3</td>
<td>Hair becomes darker, coarser and begins to spread over the junction of the labia</td>
<td></td>
</tr>
<tr>
<td>Tanner Stage 4</td>
<td>Adult hair type in the classic female pattern</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 2.6** Tanner stages of pubic hair pubertal development. (Created from data in Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969 Jun;44(235): 291–303)
The cycles immediately following menarche are usually anovulatory and can be heavy or unpredictable. This can last for several years before the HPO axis matures in the later stages of puberty and the normal monthly menstrual cycle commences [49]. The exact mechanism underlying the preovulatory GnRH surge critical to the control of the menstrual cycle is still not fully understood. As puberty progresses, the HPO axis develops an estrogen positive feedback system where the rising gonadal steroids in the late follicular phase triggers a surge in LH and FSH which then leads to oocyte release. In the past, clomiphene citrate (an estrogen agonist–antagonist) was used to determine if the positive feedback system had developed: when it is given to pre- and peri-pubertal girls, it will result in a further suppression of gonadotropin levels, while in late puberty and adults, it leads to a rise in gonadotropins and ovulation (thus its continued use as a fertility agent) [50]. Menstrual regularity, reflecting ovulation, increases quickly after menarche, with 65 % of girls experiencing ten or more periods in the first year post-menarche and 90 % by 3 years [51, 52].

The mature HPO axis involves complex interactions between the CNS and the developing ovarian follicle, leading to cyclic ovulation and the menstrual cycle (Fig. 2.7). Look to Chap. 4 for a more detailed description of the ovulatory and menstrual process. In brief, the cycle itself involves three phases:

1. Follicular
2. Ovulatory
3. Luteal

During the early follicular phase, pulsatile GnRH from the hypothalamus stimulates FSH and LH from the pituitary. FSH receptors are expressed in increased numbers on the granulosa cells of the ovarian follicle and aromatizing activity to convert androgen precursors to estradiol is evident. Estradiol further increases the number of granulosa cells surrounding the follicle to amplify the FSH effects. LH stimulates ovarian theca cells in the ovarian stroma to produce androstenedione, testosterone, and estradiol as substrate for the granulosa cells and developing follicle. At the level of the ovary, a dominant follicle is usually evident by day 5–7. The rising estradiol level stimulates the glandular cells of the uterine stroma, leading to endometrial proliferation. FSH begins to decline during the mid-follicular phase, as inhibin (produced by granulosa cells in parallel with estradiol) rises, affecting gonadotropin release. The dominant follicle continues to respond to FSH, due to the high number of receptors there. LH receptors begin to increase within the dominant follicle and the steroid pathway becomes diverted to initiate production of 17-hydroxyprogesterone and progesterone which leads to the gradual luteinization of the granulosa cells. As mentioned previously, the exact mechanism underlying the signals for ovulation are still a mystery, however following the LH surge, the dominant follicle ruptures and the oocyte is expelled to be picked up by the fallopian tube in hopes of meeting with a sperm.

During the luteal phase of the cycle, the corpus luteum continues to produce progesterone and estrogen, which in turn stimulates the secretory phase in the uterine endometrium, characterized by coiling of the glands, increased vascularity in the
stroma, and rising glycogen within the epithelial cells. By 8–9 days following ovulation, the endometrium is mature, and if fertilization does not occur, it begins to regress. Without a rise in placental human chorionic gonadotropin (HCG), the corpus luteum also begins to involute, and progesterone and estrogen levels begin to decline. The mechanism behind luteolysis, which generally occurs after 14 days following ovulation in the absence of HCG, is still unclear, but involves inhibin A secretion and decreased steroidogenesis. As the progesterone and estrogen levels
decline, the endometrium undergoes necrotic changes leading to menstrual bleeding. During the late luteal phase, FSH begins to rise again, to initiate new follicular development and prepare for a new cycle.

The Onset and Timing of Puberty

Although the exact signal leading to the initiation of puberty is still a mystery, there are many factors that are known to influence this complex process:

- Genetics (for more detail, please see chapter on genetics of puberty)
- Health status
- Body weight, composition, BMI, nutrition
- Social factors
- Geographic factors
- Environmental exposures

For example, a family history of early puberty increases an individual’s risk for precocious onset, and timing of menarche correlates with that of her mother and sisters [1]. It is estimated that roughly half of the phenotypic variation in timing of puberty and menarche in girls in developed countries is due to genetic factors [53]. Living closer to the equator, at lower altitudes, in an urban setting and having mild obesity all predispose to an earlier onset of puberty in comparison to those in northern latitudes, higher altitudes, rural settings, and low BMI. Differences also appear along racial and ethnic lines, independent of other factors. In recent years, evidence exists supporting the role of certain environmental toxins as “endocrine disruptors,” with possible wide-ranging effects on many reproductive functions.

Recently, the trend towards declining age of puberty in the United States and other countries has caused concern in the general public [52]. A close review of the data, however, does not support a tremendous change in timing of puberty, but rather an adjustment to current social standards and environmental factors. JM Tanner (famous co-developer of the above-cited pubertal staging system) first brought the trend to light, noting that the average age of menarche in Scandinavian countries during the early 1800s was 16–17, drastically different from the 12 to 13 noted in modern studies [39]. In his classic study of English girls (upon which the staging system is based), the mean age at menarche was 13.46 years with a range of 9–16 years [48]. Critics note his historical data were based on small samples of girls in orphanages, and likely did not represent the population as a whole [54]. Other historic records from ancient Rome to medieval Europe are more in line with an average age of menarche around 13. Tanner also reviewed available data from countries around the world, and there was a trend towards later onset of puberty in association with poorer nutrition and economic standards.

In 1997 a study was published evaluating the age of menarche and appearance of secondary sexual characteristics in over 17,000 girls seen in pediatric offices across the USA [55]. Conclusions drawn from this work included a fall in the average age of menarche: 12.75 years in 1960 to 12.5 years in the 1990s, and that the appearance
of secondary sexual characteristics was occurring earlier than previously reported, especially in African American girls. Table 2.1 illustrates the marked racial differences, with African American girls generally experiencing the first signs of puberty between ages 8 and 9, while Caucasian American girls by age 10. However, thelarche and/or pubarche can occur in African American girls as early as age 6 and in Caucasian American girls as early as age 7. Challenges to the validity of the study include the fact that hundreds of different observers were responsible for obtaining the data and determination of pubertal staging—especially early breast development in obese patients—can be challenging. Also, the study did not evaluate any children over age 12. Despite these limitations, the study brought awareness to providers and the lay public about the high prevalence of pubertal processes occurring in young girls across the United States.

Studies analyzing data from the National Health and Nutrition Examination Survey (NHANES) observed a 2.3 month decrease in the average age of menarche when surveys for the years 1988–1994 and 1999–2002 were compared [56]. Significant racial/ethnic differences were again noted (Table 2.2).

### Table 2.1 Timing of pubertal milestones in the US girls

<table>
<thead>
<tr>
<th>Pubertal milestone</th>
<th>African American girls</th>
<th>Caucasian girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thelarche</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>8.9</td>
<td>10.0</td>
</tr>
<tr>
<td>Age 6 (%)</td>
<td>6.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Age 12 (%)</td>
<td>98.9</td>
<td>96.0</td>
</tr>
<tr>
<td>Pubarche</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>8.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Age 6 (%)</td>
<td>9.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Age 12 (%)</td>
<td>98.8</td>
<td>92.2</td>
</tr>
<tr>
<td>Menarche</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>12.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Age 6 (%)</td>
<td>2.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Age 12 (%)</td>
<td>62.1</td>
<td>35.2</td>
</tr>
</tbody>
</table>


### Table 2.2 Racial differences in timing of pubertal milestones in the United States

<table>
<thead>
<tr>
<th>Pubertal milestone</th>
<th>African American</th>
<th>Mexican American</th>
<th>Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pubarche</td>
<td>9.5</td>
<td>10.3</td>
<td>10.5</td>
</tr>
<tr>
<td>Thelarche</td>
<td>9.5</td>
<td>9.8</td>
<td>10.3</td>
</tr>
<tr>
<td>Menarche</td>
<td>12.1</td>
<td>12.2</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Data from: Anderson SE, Must A. Interpreting the continued decline in the average age at menarche: results from two nationally representative surveys of U.S. girls studied 10 years apart. J Pediatr 2005 Dec;147(6):753–60
The marked differences in the onset of puberty between different ethnicities and races, most likely reflects genetic variation (Tables 2.1 and 2.2). Studies consistently demonstrate African American girls to be younger than their Hispanic or Caucasian counterparts when experiencing pubertal milestones and these differences remain after adjustment for BMI and social/economic variables [57, 58]. Metabolic and endocrine differences may be responsible for the increased susceptibility of African American girls to undergo early puberty. For example, African American girls have been found to have an increased insulin response to a glucose challenge compared to Caucasian girls, which leads to increased levels of free ILGF-1, which is critical to skeletal growth and maturation [59].

The trend towards earlier pubertal development has generally been attributed to improved nutritional status and the associated increases in body weight and composition at earlier ages in developed countries over the last century. As BMI has increased, age at menarche and appearance of secondary sexual characteristics have dropped, suggesting a critical body mass that must be achieved to trigger puberty. This concept is also supported by what we know about leptin and other peripheral mediators of somatic status and their influence on maturation. Many studies support the association between a higher BMI and an earlier onset of puberty [25, 60, 61], and review of the NHANES data shows that a girl in the 85th percentile for BMI is twice as likely to experience menarche than a girl at the 50th percentile with the same age and race [56]. The link between increased BMI and earlier onset of pubertal milestones is as yet unclear, and it may be due to a direct effect of body mass on the timing of puberty, or it may also involve other exposures than the obesity epidemic of modern society, such as environmental toxins that disrupt normal endocrine function [62].

The theory of a critical body mass necessary for menarche was put into practice by Frisch in the 1970s, who developed a nomogram predicting the age of menarche based on height and weight for girls between the ages of 9 and 13, based on her observation that a minimum body fat percentage of about 17% was needed for menses to start and about 22% body fat was needed to maintain a regular cycle [63, 64]. Athletes such as gymnasts, ballet dancers, and runners with reduced body fat often experience delays in maturation and menarche [65]. Adipose tissue also contributes to estrogen production through the aromatization of androgens in fat cells, thus low body fat may contribute less overall estrogen impacting pubertal development. Despite all of these observations, the theory of a critical weight necessary for menarche remains controversial and has been criticized as an oversimplification of a highly complex process [66]. In fact, weight and percentage body fat at the time of menarche is widely variable across individuals, and the Frisch nomogram was shown by Gonzalez and Villena to be coincidental rather than causative [67]. While there is certainly an effect of extreme conditions relating to body weight and composition in the timing and onset of puberty, the process of maturation and related changes in metabolism are likely more influential on adolescent and adult body composition than the other way around.

Socioeconomic factors, life-setting, family size and sibling order/sex, and even parental education have all been found to correlate with pubertal timing. In general, girls from families with higher incomes, education, and socioeconomic factors experience menarche at an earlier age than girls from families with lower status [68].
Urban setting also appears to correlate with an earlier menarche than being raised in a rural environment [69]. High quality nutrition and reduced anxiety or family strife are additionally suggested as reasons for this differential. Girls adopted from developing countries who are raised in affluent societies have a higher occurrence of early and precocious puberty [70, 71], possibly due to the “catch-up” growth that these children undergo when transitioned to a privileged environment from one of deprivation [72]. Although the underlying mechanisms are unclear, the timing of puberty and its developmental milestones are acutely tuned to what each girl is experiencing both externally and internally.

While there is evolutionary pressure for pubertal timing to respond to environmental realities (such as plentiful food or available mates), the effects of exposure to environmental chemicals affecting puberty represent an unintended consequence of modern industrialized society. Endocrine-disrupting chemicals (EDCs) are substances in the environment, food, or consumer products that interfere with hormone biosynthesis, metabolism, or action and result in a change from normal metabolic, homeostatic, or reproductive functions. The mechanisms involved are numerous and include estrogenic, androgenic, thyroid, peroxisome proliferator-activated receptor \( \gamma \) (PPAR-\( \gamma \)), retinoid, steroidogenic enzymes, neurotransmitters, and many other highly conserved pathways in humans and wildlife [73]. The offending agents are a large class of molecules involved in industry, agriculture, plastics, fuels, etc. and are widely present in the environment. While we know that many of these agents have hormonal activities and can affect pubertal processes in vivo and in vitro, we do not yet know what constitutes safe or unsafe exposure levels or the different outcomes when exposure occurs during different life stages.

Two types of exposures that are known to affect the pubertal process include lead and organohalogen chemicals. In a cross-sectional survey of 1,706 girls aged 8–16 (1988 through 1994), increased blood levels of lead was associated with a decreased likelihood for either pubarche or menarche, but not thelarche. Girls with lead levels in the range of 5–21.7 \( \mu \text{L/dL} \) were 80 % less likely to reach these pubertal milestones than girls with levels in the 2.1–4.9 \( \mu \text{L/dL} \) range [74]. Lead has been shown to affect the HPO axis by altering serum gonadotropin levels in adults, and likely has similar actions in children and adolescents [75]. While the dangers of lead have been recognized for several decades with significant public health resources spent to eliminate or minimize exposure—especially in children—most other EDCs are not recognizable by the general public. Polybrominated biphenyls (PBBs) have been associated with early thelarche in girls breastfed by mothers exposed to high levels through drinking milk from cows given contaminated feed [76]. These same girls had an earlier onset of menarche compared to girls who were not breastfed by mothers with elevated PBB levels. Phthalates have also been associated with premature thelarche [77]. While it is tempting to assign blame to EDCs for the downward trend in age of pubertal milestones or the increased incidence of infertility given the congruence of these phenomena with the increase in production of environmental toxins, the data is as yet lacking to support these suspicions. Large, longitudinal studies designed to evaluate the affects of various levels of exposure during different points in development are needed to truly understand the role of EDCs in reproductive disruption.
While there is debate about the degree to which puberty has accelerating in the modern age, there are undisputable repercussions to an extended period of reproductive readiness. An earlier entrance to puberty, especially when coupled with a late graduation to menopause, increases the risk for several disease states. There is an overall increased cardiovascular risk, due to the association between early puberty and increased BMI, insulin resistance, and blood pressure when compared to later maturing girls [78]. A recent large cohort study confirmed that an early age at menarche is indeed associated with cardiovascular disease and related mortality [79]. Several studies have demonstrated that early menarche is a risk factor for breast cancer, substantiating the theory that the longer the breast is exposed to estrogen, the higher the chance that genetics or epigenetics will falter as the mammary tissue undergoes its complex metaplastic changes monthly, and then dramatically with each pregnancy [80]. A large study in Norway that included over 58,000 women confirmed that early age at menarche, late age at first birth, low parity, and later menopause are all associated with an increased risk of breast cancer [81]. In addition to the concept of prolonged estrogen exposure, several investigators are exploring the idea that puberty is a time of elevated susceptibility of the breast to carcinogens (such as endocrine disruptors and estrogen-mimicking agents) that could lead to a higher risk of cancer later in life [82].

While the effects of an earlier puberty on disease risks generally are not apparent for decades, the impact of puberty on the individual, her family, and society can be immediately challenging. A lengthy discussion of the functional and psychological development of the adolescent brain is beyond the scope of this chapter, but a brief synopsis may help elucidate a confounding characteristic: risk-taking behavior. Teenagers act more impulsively and appear to disregard consequences, leading to a higher incidence of accidents, suicides, unsafe sexual practices, and even criminal activity [83]. Traditionally, this has been explained as a “race care with bad brakes,” likening the adolescent body to a high-performance machine that is carelessly driven. Recent research, however, using functional MRI and other modalities, suggests the reality is more complicated, and that an imbalance between a heightened sensitivity to motivation coupled with immature cognitive control, is what leads to risk-taking behavior [84]. Furthermore, this risk-taking behavior is theorized to be an evolutionary adaptation for social creatures, who need to develop increased novelty and sensation seeking in order to leave the safe and familiar juvenile home and strike out into adulthood [85]. Admittedly, in our current society where the juvenile state extends well into our early 20s this coincidence with risk taking and puberty may be much less adaptive.

Conclusion

Frequent complaints and concerns during puberty can be understood as normal features of this amazing developmental period, and a medical provider’s understanding and sensitivity to what an adolescent girl is experiencing can greatly ease her
anxiety about many common conditions. For instance, acne can occur as a result of adrenarche, and is often easily treated with topical treatments or in conjunction with a dermatologist, so teaching patients about this can alleviate concerns. Furthermore, anovulatory bleeding is very common in the first year following menarche: reassurance and expectant management is often helpful for patients and families. Finally, a rapid growth spurt, breast asymmetry, and other awkward adjustments to a developing body can lead to the wide spectrum of body dimorphic disorders, so it is critical that providers assess how a teenage patient feels about her body. Like so many other mundane female realities, we realize that the process of puberty retains many mysteries, the improved understanding of which will certainly help ease the transition from girl to woman.

References

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