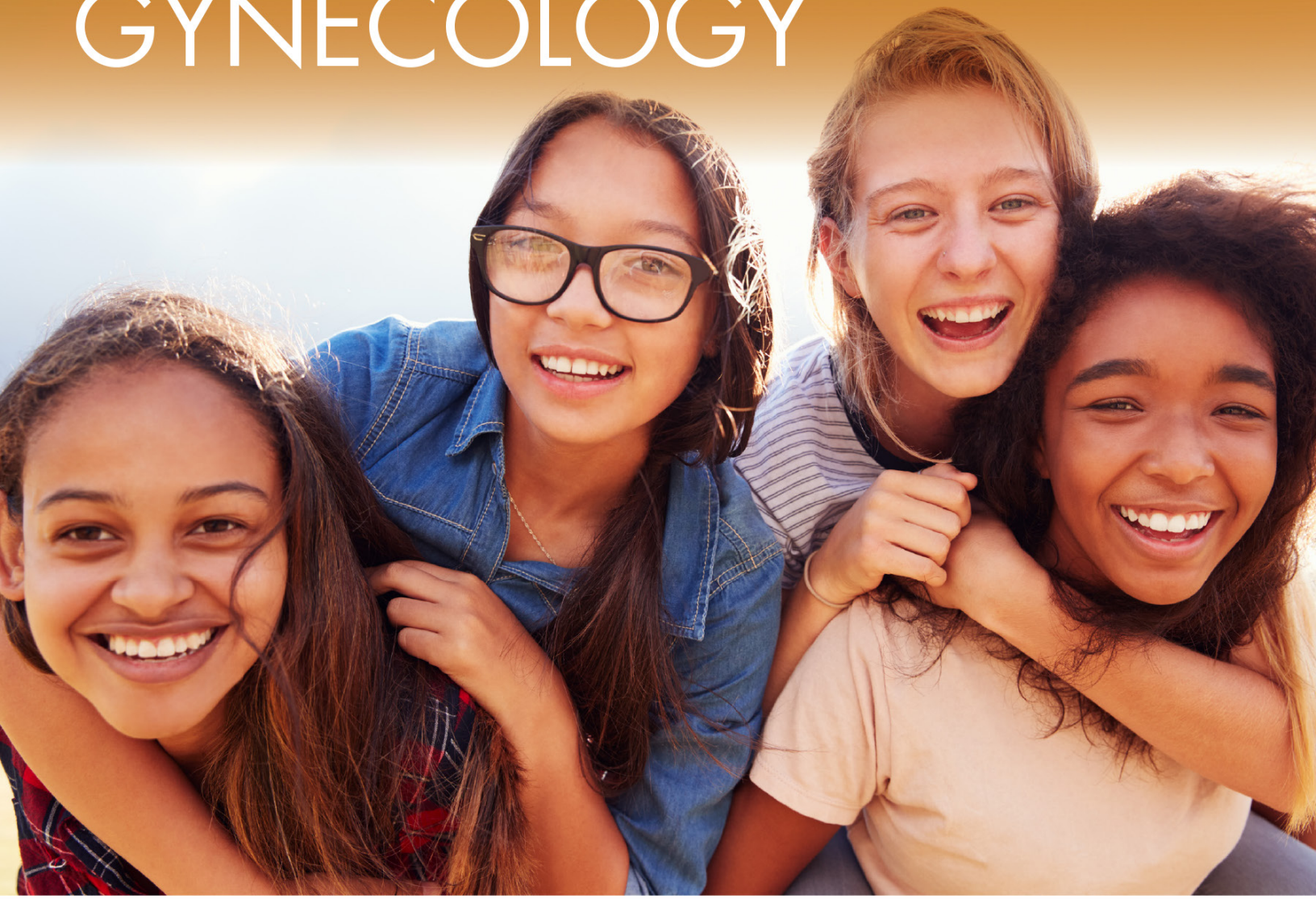
SECOND EDITION

SANFILIPPO'S TEXTBOOK OF PEDIATRIC AND ADOLESCENT GYNECOLOGY



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Sanfilippo's Textbook of Pediatric and Adolescent Gynecology

Second Edition

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Preface: We need the tools to get the job done

Where it all began—Prague, September 12, 1940: Rudolf Peter organized the first outpatient clinic for pediatric gynecology. In the United States, Goodrich Shauffler published the first pediatric gynecology (text) book in 1941. However, it was not until 1962 when there was further movement forward with the first faculty position predicated upon pediatric gynecology established at Charles University in Prague under the direction of Peter. Gynecology was now incorporated in pediatric educational curriculums.

In the United States and across the ocean, John Huffman at Northwestern collaborated with Vincent Capraro in Buffalo, New York, and Sir John Dewhurst in England to edit the book, *The Gynecology of Childhood and Adolescence*. Since that time, a number of books by authorities in the field have been published.

A number of us, serving as "Founding Fathers and Founding Mothers," organized the North American Society for Pediatric and Adolescent Gynecology (NASPAG) in 1986. Integral to the society was the *Journal of Pediatric and Adolescent Gynecology*, which I had the privilege of being affiliated with as the editor-in-chief from inception. The first issue included topics we continue to address and are included in this textbook, *viz.*, pubertal neuroendocrine maturation, molecular biology of steroid hydroxylase deficiency, and laparoscopy for chronic pelvic pain in adolescent women, as well as teen-parent programs, uterine and gonadal anomalies, and fertility in individuals with differences in sex development, to mention a few of the topics addressed.

We fast forward and see how expertise has expanded internationally. The Federation Internationale de Gynecologie Infantile et Juvenile (FIGIJ) has established educational forums all over the world (see Figure 0.1).

In this *Textbook of Pediatric and Adolescent Gynecology*, an effort has been made to provide easy access to a number of subjects:

- Establishing a pediatric and adolescent clinical and educational program designed for physicians in training
- Approach to transgender care in adolescents—a modus operandi for adolescents
- Fertility preservation—counseling, preservation of ovarian tissue as well as oocytes
- Obesity—what works and does not work
- Confidentiality in the age of electronic medical records
- Menstrual cycle as a "vital sign"—implications for clinical care
- Congenital anomalies—assessment and management both surgically and nonsurgically
- Common vulvovaginal problems clinicians are likely to manage
- Genital injuries—including acute care
- Dermatology—general and vulvovaginal

Figure 0.1 Pediatric adolescent gynecology sites across the world. (From http://www.figij.org/members/ with permission from Fédération Internationale de Gynécologie Infantile et Juvenile; accessed January 25, 2019.)

- Breast disorders—staging and assessment
- Polycystic ovarian syndrome—much new information
- Adolescent pregnancy—prevention and early gestation assessment
- Nutrition—designed to change your approach to counseling and follow-up
- Confidentiality—complex and challenging but extremely important
- An additional video section with further common procedures in pediatric and adolescent gynecology

The American Board of Obstetrics and Gynecology (ABOG) has established recognition of Adolescent Gynecology in developing a "Focused Practice" level of certification. Clinicians need to have a venue to be updated with progress in pertinent sectors of medicine germane to their clinical practice. What we have provided in this textbook serves to provide that foundation or complement your current state of knowledge. The education process needs to be ongoing, and thus entities such as the NASPAG, the ABOG, the Society for Adolescent Medicine, the American Society for Reproductive Medicine—Pediatric Adolescent Gynecology Special Interest Group, the American College of Obstetricians and Gynecologists—Committee on Adolescent Health Care, and the American Academy of Pediatricians—Section on Adolescent Health provide such a forum. We hope to meet your every expectation.

Welcome, Bienvenue, Wilkommen, Velkommen, Bem-vindo, Benvenuto, Bienvenido, Witam Cie, Croeso, Bengali, Shagatom, Aloha. Yokodo, Tuloy ka, Welkom, Shalom!

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Normal pubertal development and the menstrual cycle as a vital sign*

1

MEREDITH LOVELESS

Puberty consists of a complex interplay of hormonal and physiologic changes that result in sexual maturation and capability for reproduction.[1] This transition is an important phase of development accompanied by physical, social, and behavioral changes. Health-care providers play an important role during this time in monitoring that the process is occurring within normal parameters and providing evaluation if concerns in development arise. In most cases, the process of puberty occurs normally, although there is a broad variation of "normal" that may lead to anxiety in some patients and families. When the pubertal process does not occur within standards of normal, it may represent underlying health concerns and alert the health-care provider of the need for further evaluation and possible interventions. This chapter reviews the stages of normal puberty in females and provides guidance on abnormalities that may require investigation.

TIMING OF PUBERTY

Girls normally begin puberty between 8 and 13 years of age.[2] Thelarche is usually the first sign of puberty followed by pubarche; although 15% of girls will experience pubarche first.[3] Vaginal bleeding before thelarche does not typically represent menarche and should be evaluated. The physiologic mechanism for timing of puberty is not known. There are multiple factors that influence pubertal timing, including genetic, environmental, neuropeptides, energy balance, intrinsic factors, stress, and sleep; however, the key regulatory step for activation of puberty is unknown.[1] Sexual maturation declined rapidly during the first half of the twentieth century attributed to better nutrition as the Western world developed but has remained steady the latter part of the twentieth century. Age of menarche has declined minimally; however, age of thelarche appears to continue to decline.[4] There appears to be a trend toward earlier age to reach Sexual Maturation Rating (SMR) 2 but the age for SMR 3 and age of menarche remains steady.[5] Delayed puberty is defined as lack of pubertal development by an age that is 2–2.5 standard deviations beyond the population mean.[6] In the United States, lack of breast development (SMR 2) by age 13 and menses that has not started within 3 years of thelarche or by age 15 warrant evaluation.[6,7] Precocious puberty is defined as pubertal changes occurring prior to the age of 8 years, although the earlier onset of thelarche makes this age cutoff more controversial. Further discussion on the anomalies of puberty is included in Chapter 5.

It is plausible that the earlier onset of breast development is related to environmental factors. These factors are called *endocrine disruptors* and are environmental chemicals, dietary supplements, and/or medications that interfere with the endocrine system.[8] There is evidence from animal studies that endocrine disruptors affect pubertal timing, but studies in humans have been more difficult and are not currently well understood.[5] More research is needed to understand how medications, environmental agents, and nutritional deficiencies, as well as supplements, can impact pubertal timing. One environmental agent that was found to disrupt puberty in animals and is found in higher levels in children with higher adiposity is biphenol A (BPA). Found in plastic bottles and toys, it has been linked to having an estrogenic effect at low levels and to competing with endogenous estrogen for binding and antiandrogenic properties at higher levels.[9] Chemicals, pesticides, dioxins, polychlorinated biphenyls (PCBs), and flame retardants are present across the ecosystem and have been detected in humans.[9] Exposure to a broad mixture of environmental contaminants makes it challenging to determine if these substances are playing a role in pubertal timing and what that role is; however, growing evidence suggests there is environmental impact on pubertal timing.

Another important factor that may influence pubertal timing is obesity. Multiple studies show a correlation between increased body mass index (BMI) and early puberty.[5] The National Health and Nutrition Examination Survey III (NHANES III) collected pubertal data from 2300 U.S. children ages 8 years and up from 1988 to 1994. This data showed children with a BMI greater than the 85th percentile were strongly associated with earlier age of breast development and menarche, with menarche occurring at a mean age of 12.06 in obese girls compared to 12.57 in nonobese girls.[10] Additional studies suggest that rapid weight gain and early puberty followed by development of obesity, and metabolic syndrome lead to an overall increase in mortality that persists into adulthood.[5] Data have not shown obesity alone as the primary cause of earlier pubertal timing. Some studies suggest leptin, which is related to growth and pubertal development and affects appetite, adiposity, and energy regulation, may be a link associated with this finding.[4] It is also postulated that endocrine disruptors may act on adipocytes, thereby linking early puberty and obesity.[4]

* Thanks to Shawn Smith, Kimberley McClanahan, and Hatim Omar for their contributions from the first edition to this chapter.

Early puberty has also been associated with higher rates of depression, anxiety, smoking, delinquent behavior, and early sexual experiences.[5] Chronic stress including a lower socioeconomic status has also been associated with early puberty.[5,10] It is difficult to determine if the consequences of obesity, such as bullying, stress from difficult social situations, or early puberty itself, are related to the link with mood and behavior changes.

HORMONAL CHANGES

Puberty is initiated and controlled by a complex relationship of multiple hormones. The regulatory steps to initiation of puberty are still unknown. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which signals the gonadotrophs in the pituitary to release gonadotrophins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Luteinizing hormone acts on the theca cells in the ovary to produce androgens, and FSH acts on ovarian follicles to produce estradiol, inhibin, and gametes. The interplay is called the hypothalamic-pituitary-gonadal (HPG) axis (Figure 1.1).[3] During the first 3 months of life, under the influence of maternal estrogen exposure in utero, LH and FSH levels are high. By age 6 months, LH levels are almost undetectable. While FSH levels decrease after the first 6 months, they can remain elevated until age 3–4 years.[3] At this point, the HPG axis remains quiescent until activation initiates puberty. The LH level is generally the most useful marker for assessing onset of puberty with elevated levels in childhood indicating central nervous system activity related to onset of puberty.[3] Levels of FSH may be found elevated with thelarche (which can be an isolated event), so they are not a reliable indicator of pubertal onset.[4] Estradiol and testosterone levels are low in prepubertal girls and rise with onset of puberty and should be consistent with laboratory reference levels for age. Leptin does not have a direct role in puberty initiation but likely influences GnRH secretion.[3]

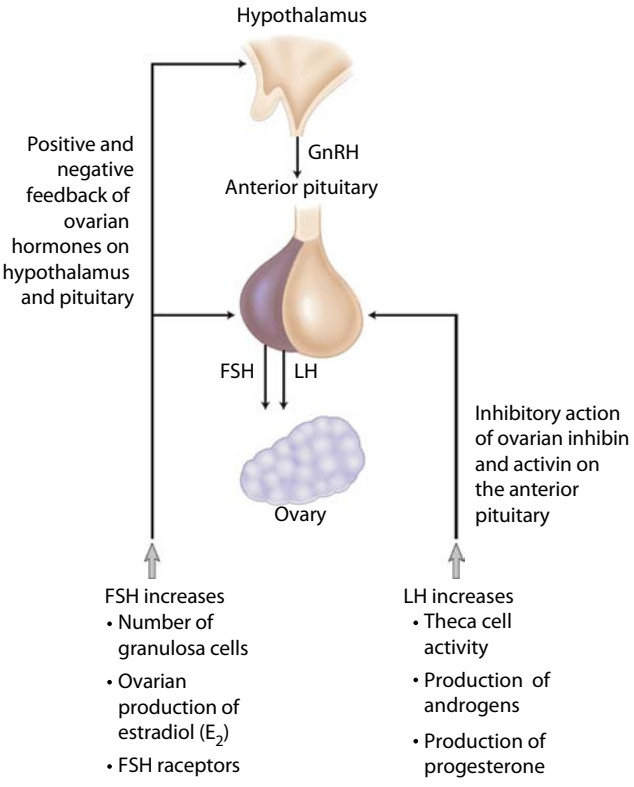


Figure 1.1 Hypothalamic-pituitary-gonadal axis. (With kind permission from Springer Science+Business Media: Normal timing of puberty, 2014, Boswell H. In: Dietrich JE, ed. *Female Puberty: A Comprehensive Guide for Clinicians*, New York, NY, p. 9.)

The action of multiple hormones in concerted fashion regulates linear growth in children and adolescents. Growth hormone is the primary growth-stimulating factor during prepubertal growth. Sex hormone augmentations of growth hormone secretion, as well as direct growth-stimulating effects of sex steroids, cause growth acceleration during puberty. Thyroid hormone also plays a key role in growth and development. The concerted actions of both growth hormone and thyroid hormone are largely responsible for skeletal growth. When growth is not occurring on a normal trajectory, evaluation for underlying endocrine etiology should be considered. Failing to appropriately assess a child's growth can often cause a missed or delayed diagnosis of a systemic illness.

GROWTH

The process of normal puberty includes growth, development of secondary sexual characteristics, and onset of menstruation. There is a wide age range in which girls will start the pubertal process. Multiple factors may influence the age at which puberty begins, including family history, environmental factors, underlying health conditions, and nutrition, among others. There are several guidelines to help determine if the child is progressing in a manner that falls within the norm. Growth spurt is typically the first indication of pubertal onset and typically occurs before the onset of secondary sexual characteristics. A longitudinal study reported an increase in both height and foot growth before the onset of secondary sexual characteristics, suggesting change in foot size may be an early marker for puberty.[11] The correct assessment and measurement of growth is an essential component of health supervision. When evaluating a child's growth, it is imperative to determine growth rate, rather than simply relying on a cross-sectional analysis of one measurement in time. Correct monitoring of growth requires careful plotting of data on growth curves. Growth curves are published by the Centers for Disease Control and Prevention and include percentile ranges for girls 2–20 years of age (Figure 1.2).[12] The BMI is an anthropometric index of weight and height combined with age and is a useful index in the evaluation of overall general health (Figure 1.3).[12] The BMI is calculated by dividing weight in kilograms by the square of height in meters. An important difference between using BMI in children and adults is the influence of changing levels of sexual maturity. For example, among patients with similar BMI, the patients with higher sexual maturation will have

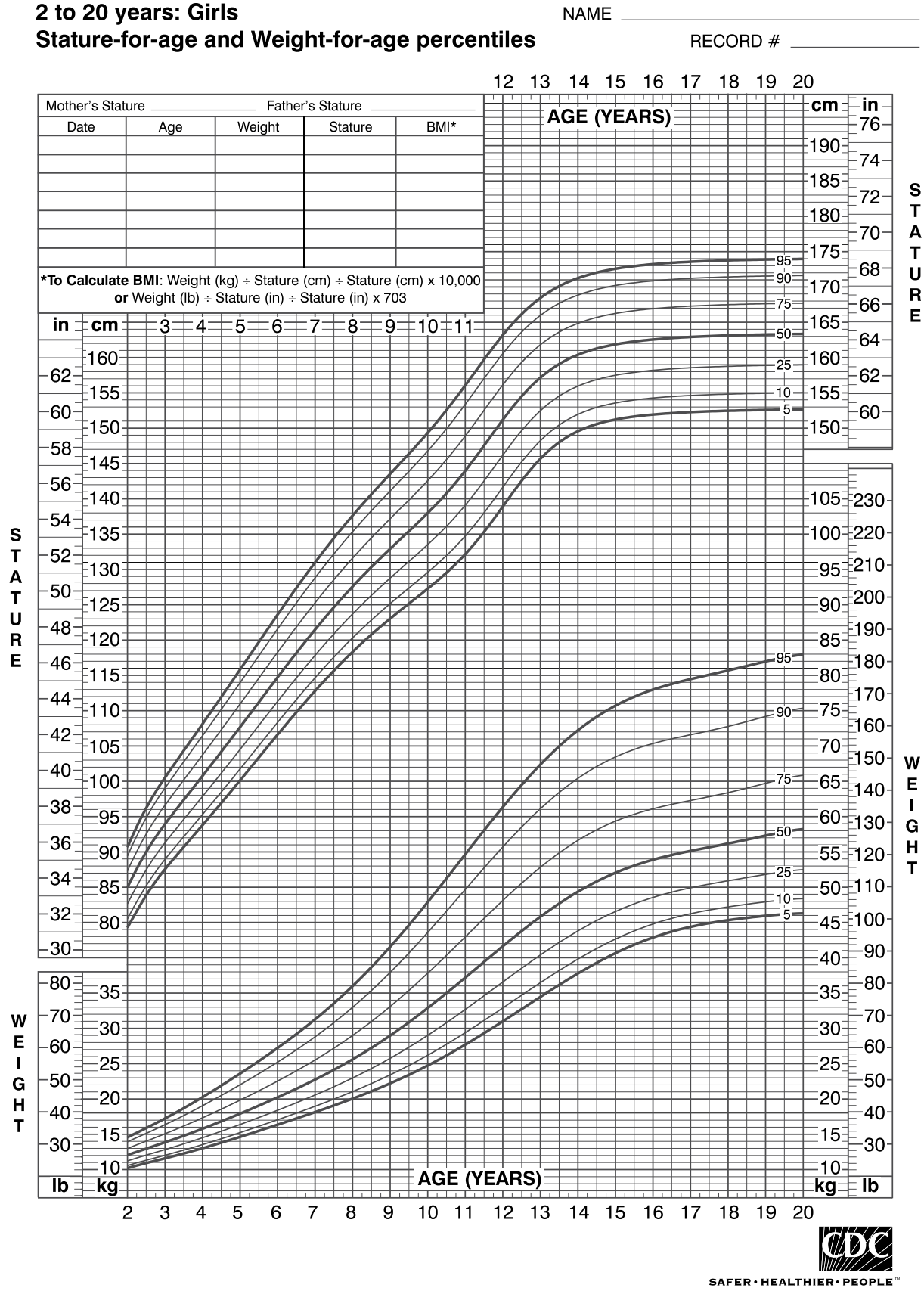


Figure 1.2 Growth chart for monitoring of growth in girls aged 2–20 years, developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, May 30, 2000 (modified November 21, 2000). (From https://www.cdc.gov/growthcharts/data/set2clinical/cj41c072.pdf.)

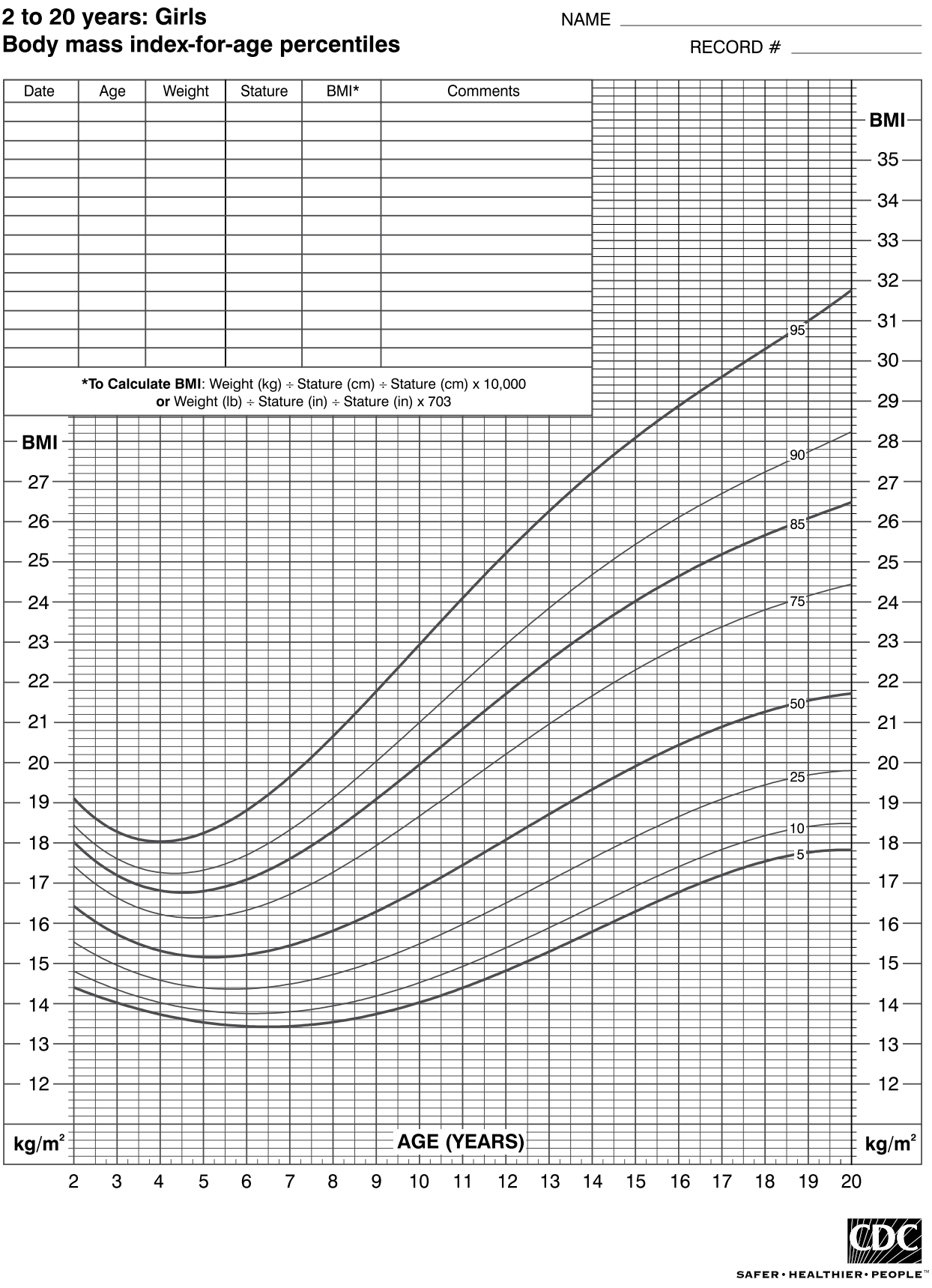


Figure 1.3 Chart for assessing body mass index (BMI) in girls aged 2–20 years, developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, May 30, 2000 (modified October 16, 2000). (From https://www.cdc.gov/growthcharts/data/set1clinical/cj41c024.pdf.)

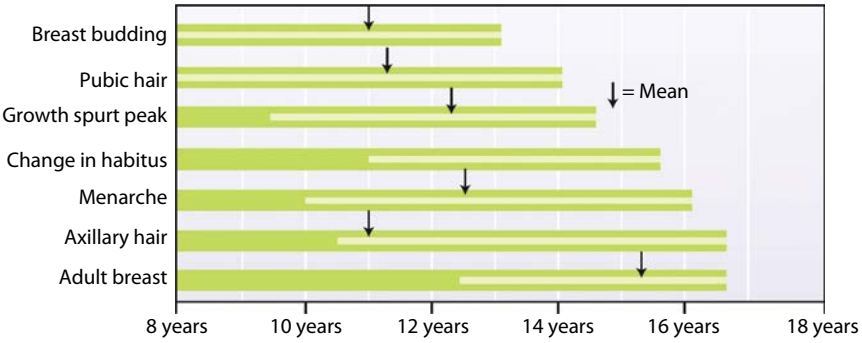


Figure 1.4 Timeline of female pubertal milestones. (Adapted with permission from Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; With kind permission from Springer Science+Business Media: Normal timing of puberty, 2014, Boswell H. In: Dietrich JE, ed. *Female Puberty: A Comprehensive Guide for Clinicians*, New York, NY, p. 16.)

a lower percentage of body fat. The importance of including BMI in routine evaluation of growth is to screen for underweight or overweight children and adolescents with respect to age and height. In children and adolescents, a BMI for age greater than 95% is defined as overweight and between 85% and 95% as at increased risk for obesity. Some growth charts have been developed that allow for the variation in growth pattern of a specific medical condition (e.g., Trisomy 21 or gonadal dysgenesis). These charts represent the standard growth for that condition, thereby allowing a child to be compared against standards in his or her own cohort. Many electronic health records will maintain the growth charts within the electronic system, which is a useful tool and allows multiple providers to see growth patterns over time.

PUBERTAL EVENTS

The process of puberty occurs through a series of coordinated events that follow a usually predictable timeline; however, events may overlap or vary slightly in their order (Figure 1.4).

PUBERTAL GROWTH

During puberty, males and females experience the greatest growth velocity, besides that seen during infancy. This growth can be conveniently divided into three stages[13]:

1. The nadir that occurs just before the growth spurt
2. The stage when the adolescent is experiencing the maximum growth velocity
3. The final stage when growth velocity decreases, which occurs before epiphyseal fusion

It is important to remember, especially when examining patients during this period of rapid growth, that although growth is described in centimeters per year, this represents the average growth for that year, and velocity may change throughout this time period. A good marker for following growth of an adolescent through puberty is the peak height velocity (PHV). In girls, PHV ranges from 6 to 10 cm/year, usually coinciding with SMR breast stage 2–3.[3] During puberty, girls will gain an average of 25 cm. For some, this growth velocity is doubled compared with preadolescent rates. The adolescent growth spurt occurs on average 2 years earlier in females compared with males. Thus, for a temporary period, girls may be taller than many boys of the same age.[14–16]

CHANGES IN BODY COMPOSITION

During the rapid growth of puberty, not only is there growth in all tissues, but there are also significant changes in body composition. Girls will experience an increase in percentage of body fat. Body shape changes as the increased body fat is distributed in the lower body to a gynecoid or pear-shaped distribution. The skeleton also undergoes a great amount of growth, not only in length but also in density. Each bone begins with a primary center of ossification and will go through many stages of enlargement and shaping. The adult form is reached when epiphyses ossify and fuse with the main body of the bone. All of these changes are evident on radiographics, as the calcium content of the bone is opaque. The sequence of the changes in bone is the same in all individuals; thus, using radiographs to evaluate skeletal bone age in comparison to chronological age is an excellent clinical tool. The photographic atlas of Greulich and Pyle is the most commonly used resource to compare radiographs of the hand with standards of maturation in a normal population.[17] Growth and puberty are 99% complete by the time bone age reaches 17 years.[3]

BONE DENSITY

Adolescence is an important time for bone density accrual. A longitudinal study demonstrated that during the 4-year adolescent period of peak linear growth, more than 35% of total body bone mineral and 27% of bone mineral at the femoral neck was laid down.[18] This corresponds to as much bone mineral as most adults lose during their remaining life.[1] Many factors can affect the accretion of bone mineral, including genetic factors, ethnicity, body mass, level of physical activity including weight-bearing activity, dietary calcium and vitamin D intake, smoking,

and dietary intake of certain products including carbonated beverages. Obtainment of peak bone density requires a high calcium intake, and recommendations for calcium and vitamin intake during this period are 1200 mg calcium and 400 IU vitamin D daily.[19] Estrogen is a key mediator for bone density accrual in females, so disorders that lead to a hypoestrogenic state can negatively impact bone density, such as female athlete triad, anorexia, and conditions resulting in hypothalamic hypogonadism.

SLEEP

Sleep regulation changes during sexual maturation. Teens tend to want to stay up later and sleep in later than younger children. The changes that occur during puberty include a significant decline in non-rapid eye movement (NREM) sleep, melatonin release is later, and circadian rhythm patterns change. Teens and parents often express concern about daytime sleepiness despite adequate overall sleep time, and this may be attributed to the decrease in NREM sleep.[20] The American Academy of Sleep Medicine recommends teenagers 13–18 years of age should sleep 8–10 hours per 24 hours on a regular basis to promote optimal health.[21] The American Academy of Pediatrics published a policy statement in 2014 with recommendations to delay school start times to 8:30 a.m. or later to optimize sleep in students.[22] The report explains that there is a substantial body of research demonstrating that delaying school start times is an effective countermeasure to chronic sleep loss and has a wide range of potential benefits for students regarding physical and mental health, safety, and academic achievement.[22]

BRAIN DEVELOPMENT

Structurally, the brain undergoes changes during puberty that largely affect the frontal and prefrontal cortex. The frontal cortex is responsible for executive function tasks, so teen's tasks involving oculomotor abilities and problem-solving have been shown to improve during adolescence; however, reaction time to assess emotional-related material declines during this time.[1,23,24] Studies have shown the prefrontal cortex is responsible for forward planning and regulatory control of emotional behavior and continues development into the early 20s.[1,25] The definition of adolescence as defined by the World Health Organization (WHO) focuses on ages 13–19 years but has been extended by several organizations into the early 20s in conjunction with timing of brain maturation.[26]

SECONDARY SEXUAL CHARACTERISTICS

Objective measures to evaluate pubertal physical changes allow the clinician to better monitor the normal rate of development. The standard universal system in use today was initially described by Tanner in 1969 and is currently known as the Sexual Maturity Scale (SMS).[3] Activation of the HPG axis leads to production of sex steroids, estrogen and androgens from the ovaries. The effect of estrogen includes breast development, estrogenization of the vagina and growth of female internal reproductive organs, body fat deposition, and linear growth. Androgens secreted by the adrenal gland contribute to body odor and the growth of pubic and axillary hair. Previous studies focused significantly on differences by ethnic background, but now these ages need to be considered carefully, because the pure lines of racial origin are not as clear as in the past.

Thelarche

When evaluating the breast, it is important to include palpation of the breast tissue and visual inspection of the areola, papilla, and breast tissue. Palpation is an important tool to differentiate breast tissue from adipose tissue in overweight females. Age of onset of breast development can be influenced by ethnicity, and mean age of onset is 8.8, 9.3, 9.7, and 9.7 years for African American, Hispanic, white non-Hispanic, and Asians, respectively.[27] In African American and Mexican American girls, breast development may occur up to a year earlier than in other ethnic cohorts and can be normal in the 7th year of age.[4]

SMR is used to describe breast development (Figure 1.5).[28] In SMR stage 1 or the preadolescent stage, there is only elevation of the papilla. Stage 2 progresses to elevation of the breast and papilla as a small mound. Stage 3 represents further enlargement and elevation of breast and areola with no separation of their contours. Projection of the areola and papilla to form a secondary mound above the level of the breast is stage 4. Finally, stage 5 represents the mature stage, which is projection of the areola and papilla due to the recession of the areola to the general contour of the breast. The initial breast tissue in the earlier stage of growth can be unilateral, which may persist for 6–9 months. Knowing this can not only provide reassurance to patients and families, but also may avoid unnecessary diagnostic tests. Historically, menarche occurred 2–2.5 years after thelarche; however, the correlation of age of onset of breast development and menarche has changed in the last decade and therefore is less predictive than it once was.[5,18,29]

Pubarche

Pubarche is the physical findings of growth of pubic and axillary hair. Pubarche is caused by adrenarche, which is the increase in adrenal androgens, principally dehydroepiandrosterone (DHEA) and androstenedione.[1] Mean onset of pubic hair in nonobese girls is 11.57 years and 11.39 years in obese girls. Pubarche begins at a mean age of 10.65 in non-Hispanic black, 11.6 years in non-Hispanic white, and 11.63 in Mexican American girls.[29] As with breast development, SMR is used to describe pubic hair development (Figure 1.6).[28] When examining pubic hair, it is important to make note of the distribution of the hair. For example, from the prepubertal stage 1 to stage 2, pubic hair begins to grow along the labia; as maturity continues, growth occurs over the mons pubis; and finally at stage 5, growth has occurred on the medial thigh. During the progression through the SMR, the hair becomes more pigmented, coarser, and curlier. There is no SMR for axillary hair. However, a gross scale of 1 (no hair) to 3 (adult pattern of hair) is sometimes used. There is an increase in the activity

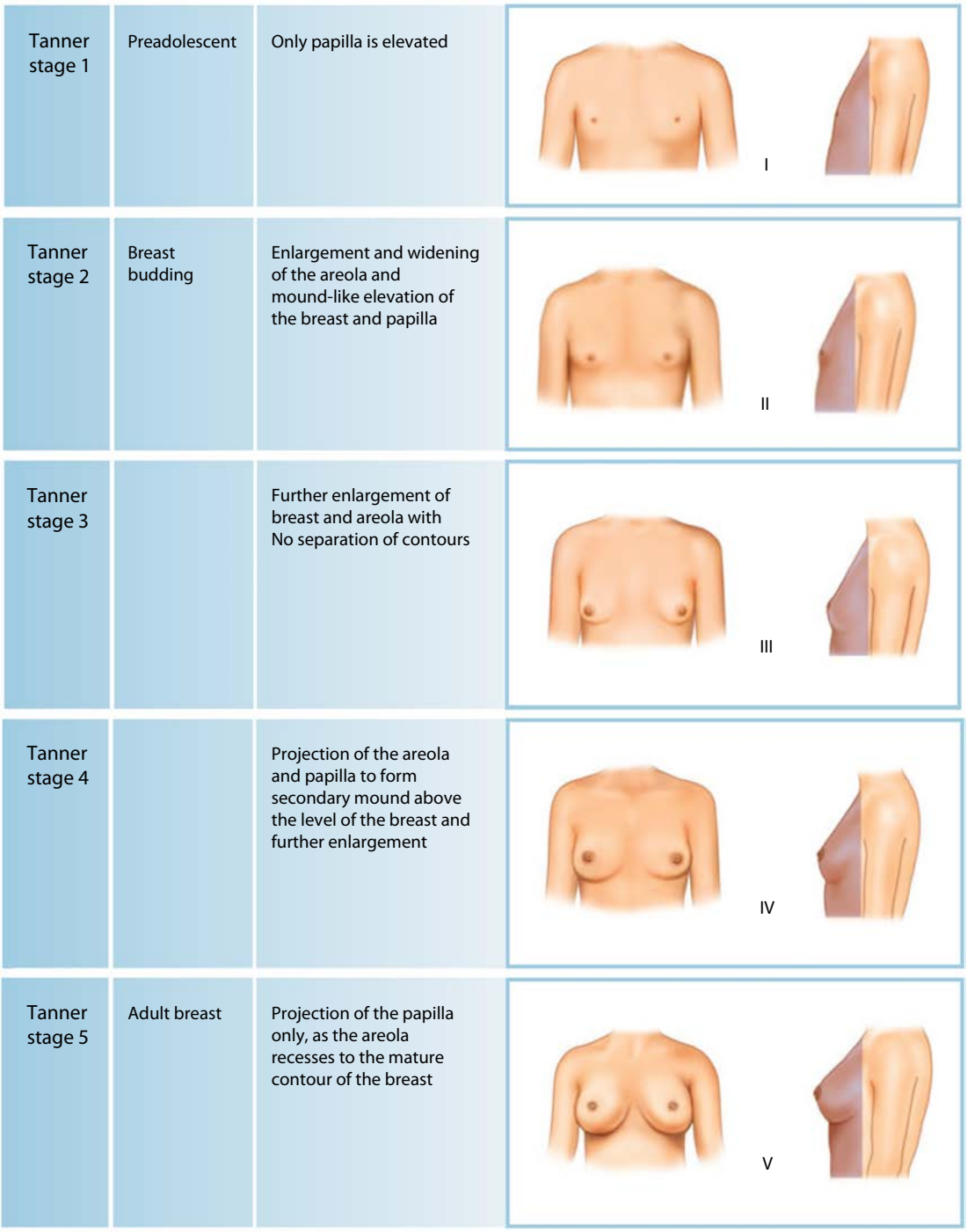


Figure 1.5 SMR staging: female breast development. (With kind permission from Springer Science+Business Media: Normal timing of puberty, 2014, Boswell H. In: Dietrich JE, ed. *Female Puberty: A Comprehensive Guide for Clinicians*, New York, NY, p. 18.)

of glandular tissue, specifically sebaceous glands and merocrine sweat glands. During the initial appearance of pubic and axillary hair, the apocrine glands begin to function.[14]

Premature pubarche is precocious development of axillary and pubic hair caused by premature adrenarche, which is the early increase of adrenal DHEA. Pubarche is considered early or premature when it occurs prior to the age of 8 years in girls. It affects up to 15% of girls and may be considered a normal variant, so the true definition of premature pubarche is not well defined.[2,29] This is more common in girls than in boys, especially in African American girls. Risk for premature adrenarche is increased in small-for-gestational-age infants and has been described as an early marker for development of polycystic ovarian syndrome (PCOS).[30,31] Girls with premature adrenarche have a higher rate of metabolic syndrome, including being overweight, having insulin resistance, and having dyslipidemia.[1,32]

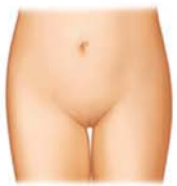
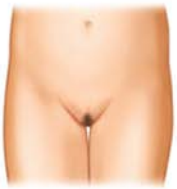
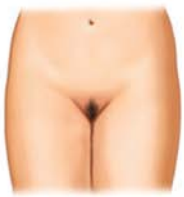
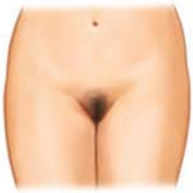
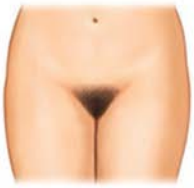
Tanner stage 1	Preadolescent	No discernable difference between vellus hair on the mons and anterior abdominal wall, no pubic hair	 I
Tanner stage 2		Appearance of few, sparse, lightly pigmented hairs, with minimal curl on the labia	 II
Tanner stage 3		Hair becomes darker, coarser and begins to spread over the junction of the labia	 III
Tanner stage 4		Adult hair type emerges, covers mons pubis, but does not extend to the thighs	 IV
Tanner stage 5	Adult hair pattern	Adult hair type in the classic female pattern	 V

Figure 1.6 SMR female pubic hair development. (With kind permission from Springer Science+Business Media: Normal timing of puberty, 2014, Boswell H. In: Dietrich JE, ed. *Female Puberty: A Comprehensive Guide for Clinicians*, New York, NY, p. 19.)

Menarche

Menarche is often considered the final pubertal milestone. As the HPG axis matures, it leads to the production of estrogen and low levels of androgens from the ovaries, establishing a hormonal feedback loop. Under the influence of estrogen, the uterus will grow, and the endometrial lining will become thickened. When ovulation occurs, there is a surge in progesterone, coupled with a fall in estrogen levels. In the absence of pregnancy, this will trigger the shedding of the endometrial lining and menstrual cycle. Initial menstrual cycles may not all be ovulatory. Menses requires several components, including intact HPG axis, structurally normal end organs (ovaries and uterus), and good overall health. When the body is under stress, the HPG axis does not function normally and results in disruption of menses, making it an excellent marker for overall health. The American College of Obstetricians and Gynecologists (ACOG) Committee on Adolescent Health, endorsed by

the American Academy of Pediatrics (AAP), published a committee opinion advocating the use of the menstrual cycle as a vital sign. They encourage asking about last menstrual period and menstrual patterns at each comprehensive or preventive care visit. By including an evaluation of the menstrual cycle as an additional vital sign, clinicians reinforce its importance in assessing overall health status for patients and caregivers.[7]

To use menses as a vital sign, we must understand what normal menstrual function is. The median age of menarche is 12–13 years across well-nourished populations in developed countries.[7] In the past 30 years, there has not been a change in median age of menarche according to NHANES, except among the non-Hispanic black population, which has a 5.5-month earlier median age at menarche than it did 30 years ago.[7,32] Menarche typically follows pubertal onset by 2–2.5 years; however, this historical guide is not always a consistent rule. While the mean age for onset of menarche remains stable, the duration between puberty and menarche varies. Girls starting puberty at age 9 have an average of 2.7 years to menarche, while those starting puberty at age 13 years have an average of 0.7 years to menarche.[1,33] Once menarche has started, the expected interval is every 21–45 days, with a cycle that lasts 7 days or less (see reference[7]). Immaturity of the HPG axis during early years after menarche may result in anovulatory cycles and an irregular pattern; however, 90% of cycles will be within the range of 21–45 days.[33,34] While a long interval due to anovulation is not uncommon in adolescents, it is statistically uncommon for girls to remain amenorrheic for more than 3 months (the 95th percentile for cycle length) and should prompt evaluation.[7] Patients should be encouraged to record their menstrual bleeding to help providers determine if the pattern is within normal limits. This can be made easier with a paper diary or apps that are readily available for this purpose. Adolescent girls may seek medical attention for cycle variations that fall within normal range or be unaware that their bleeding pattern is abnormal and may be attributed to significant underlying medical issues.[7] When the health-care provider inquires as to onset of menses and date of last menstrual period and their bleeding pattern, they have the opportunity to identify patterns that may require evaluation.[7] Providers who care for adult patients may also educate them regarding what is considered normal in adolescents, which may allow them to seek care when menstrual abnormalities are present in their daughters.

Abnormalities in timing of menarche are also a useful marker of overall health. Typically, menarche will occur within 2–3 years after breast budding, characteristically at SMR stages 3–4, and is rare before SMR 3.[35] The process from accelerated growth to menarche is 4.5 years, but the range is between 1.5 and 6 years.[33] Evaluation should occur if menarche has not occurred within 3 years after thelarche, by age 15 with secondary sex characteristics, or by age 14 with signs of hirsutism or evidence for excessive exercise or eating disorder. When abnormalities in the menstrual pattern are found, investigation for underlying causes based on careful history, physical exam, and appropriate imaging and laboratory studies should be undertaken or referral made to a specialist if that is not within the provider's scope of practice.[7]

An abnormal bleeding pattern can also represent underlying health concerns. The typical menstrual flow in adolescents is an interval of 32.2 days with a range of 21–45 days and a flow that lasts 7 days or less requiring 3–6 pads or tampons per day. Menstrual flow requiring a change of sanitary products every 1–2 hours, frequent flooding or soiling, and prolonged bleeding exceeding 7 days are consistent with excessive menstruation (see reference[7]). Teaching adolescents to evaluate the amount of flow using a visual tool such as the pictorial chart may be beneficial. Abnormal uterine bleeding, its causes, and its management are reviewed in Chapter 14.

CONCLUSION

Using the menstrual cycle as a vital sign gives clinicians an important tool to monitor overall health in female youth. Growth, pubertal timing and progression, and the onset of menarche can all provide reassurance of overall health when progressing in a normal fashion but can alert the provider to potential underlying health issues when the process is not proceeding normally. In some cases, abnormality in pubertal development and menses can be the first clue to an underlying health problem, so the practitioner must consider a broad differential, including nongynecological conditions, when abnormalities are encountered. Educating patients and caregivers about normal puberty and menstruation can provide anticipatory guidance so they can seek appropriate evaluation if problems arise. Using the menstrual cycle as a vital sign by checking last menstrual period and menstrual pattern at each visit is a quick and effective diagnostic tool in the care of young women.

REFERENCES

1. Finlayson CA, Styne DM, Jameson, JL. Endocrinology of sexual maturation and puberty. In: Jameson JL, ed. *Endocrinology: Adult and Pediatric*. 7th ed. Philadelphia, PA: Saunders/Elsevier; 2016:2119–29.
2. Herman-Gidden ME, Slora EJ, Wasserman RC et al. Secondary sex characteristics and menses in young girls seen in office practice: A study from the Pediatric Research in Office Settings network. *Pediatrics*. 1997;99(4):505–12.
3. Wolf RM, Long D. Pubertal development. *Peds Rev.* 2016;37(7):292–300.
4. Biro FM, Greenspan, LC, Galvez MP. Puberty in girls of the 21st century. *J Pediatr Adolesc Gynecol.* 2012;25:289–94.
5. Walvoord EC. The timing of puberty: Is it changing? Does it matter? *J Adolesc Health*. 2010;47(5):433–9.
6. Abitol, L, Zborovski, S, Palmaert, M. Evaluation of delayed puberty: What diagnostic tests should be performed in the seemingly otherwise well adolescent? *Arch Dis Child*. 2016;101:767–71.