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Editor

Female Puberty

A Comprehensive Guide for Clinicians

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We dedicate this to our families, friends, colleagues, and learners who have encouraged and inspired all of us in the writing of this book. This project could not have been completed without your dedication, love, and support.

Foreword

The subject of female puberty commands a particular level of expertise, and indeed it has been achieved with this publication, *Female Puberty: A Comprehensive Guide for Clinicians*. Its organization reflects the extensive experience of the exceptionally qualified clinicians who have shared their time and talent in the field of Pediatric and Adolescent Gynecology.

Each chapter provides concepts concisely conveyed, but at the same time each chapter is comprehensive in scope. Complex subjects such as details of the hypothalamic–pituitary–ovarian axis are provided in a readily understandable manner. Chapters neatly complement each other. Indeed, the information provided for clinicians will be part of mainstream discussions that involve the Menstrual Cycle as a vital sign. This text covers what is the best modus operandi when faced with virtually any type of pubertal aberration. Bullet points serve as reminders to clinicians of what the key concepts for the subject at hand are, once again facilitating for clinicians' salient points that need to be addressed.

It always aids clinicians to have some algorithm in mind when pursuing a specific topic; for example, Precocious Puberty is broken down into central and peripheral etiologies. Indeed, this is an excellent teaching tool as well as clinical convenience when one is trying to sort out the problem and identify the most appropriate diagnostic avenue(s) to pursue.

The multi-pronged approach to delayed puberty serves to remind clinicians of indeed what is the most probable etiology, i.e., constitutional delay. This is complemented by whether or not it is GnRH dependent and the implications of such. What are the "key historical points" to obtain? Once again, this is embarked upon and covered in a succinct manner.

Clinicians do not always understand the importance of "Extreme Exercise" and the potential effects on the fine-tuned central nervous system balance. Low body fat and lean body mass remain key factors in assessment. Does one "routinely consider" medications, i.e., glucocorticoids, opiates, psychotropics, phenothiazines?

Once again, here we are provided with the succinct path to promptly determine the underlying etiology of the problem: psychological considerations, referral to internet sources, and the resources go on and on.

A vote of congratulations for succinct, targeted knowledge provided by experts in the field is deserved. Kudos for such a fine accomplishment!

Pittsburgh, PA, USA Joseph S. Sanfilippo, M.D., M.B.A.

Preface

Female Puberty: A Comprehensive Guide for Clinicians is the first edition of what I hope will be many editions over the years to come. As Editor, I am honored to have had the opportunity to participate in the planning, initiation, development, writing, editing, and coordination of this project. This book addresses an area of need that will prove to be useful not only for Obstetrician Gynecologists, but also for Reproductive Endocrine Specialists, Pediatricians, Pediatric Specialists, Family Practitioners, and Allied Health Professionals.

Puberty is a topic that transcends all of these practitioner groups, and, because of careful planning and thoughtfulness with regard to the chapter contents herein, I believe this book addresses puberty comprehensively. From the basics to the complexities of puberty, encompassing psychosocial development to pubertal nuances in highly specialized populations, this book answers many questions and thoroughly reviews the literature to date.

In each chapter, the author has completed or is currently completing Pediatric and Adolescent Gynecology Fellowship Training in the Department of Obstetrics and Gynecology at Baylor College of Medicine in Houston, Texas. I am thrilled to have been able to involve each one of them in a special part of this book based on their areas of interest, focus of education, or research attention.

As authors, we hope to stimulate others' interest in this basic and yet complex topic of female puberty, with the goal of improving health care knowledge in order to address reproductive health problems in girls, adolescent females, and young women worldwide. We are especially excited to offer this book both in print as well as in an online accessible format. We encourage you to explore both options and to utilize this book for future reference for many years to come.

Houston, TX, USA — Jennifer E. Dietrich, M.D., M.Sc.

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Chapter 1
History and Trends of Pubertal Development in Females

Jessica C. Francis

Abstract Puberty represents the transition from childhood to reproductive maturity. This process is unique in humans and has been a subject of great interest for many years. We now know that there are many factors that contribute to normal and pathologic pubertal development. Some of the history and trends pertaining to pubertal development over time are outlined in this chapter.

Keywords Puberty • Genetics • Menarche • Nutrition • History • Trends

History

Puberty represents the transition from childhood to reproductive maturity. This is a process that occurs in all organisms, but there are certain aspects that are unique to human beings. Many intriguing changes have been documented over the years, but the mechanisms of these changes often remain a mystery. In this chapter we will review some of what is known about the history and trends of pubertal development.

Early Documentation of Noted Physical Changes

Various authors presented information regarding puberty as early as the 1930s, with emphasis on timing and progression of pubertal events. These early studies conducted in London were cross-sectional studies, which made it difficult to assess accuracy. Marshall and Tanner started documenting the physical changes that accompany

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puberty back in the 1960s, and their observations have stood the test of time, most likely due to their initial study design [1]. This was accomplished by conducting longitudinal studies documenting pubic hair and breast growth at 3-month intervals. They additionally noted linear growth and time of menarche. This information was compiled and compared with earlier studies to establish normative ranges for pubertal progression in adolescent females as well as males. These studies ultimately established a puberty staging system that is used to this day by clinicians worldwide to monitor pubertal progression. Additionally, they brought to light some variations in sequence of staging as well of duration of time spent in each stage. Perhaps even more important was the information provided regarding the relationship between timing of different pubertal events, which helped us to establish expectations for menarche based on development of secondary sex characteristics. This information has been useful not only in our patients who undergo normal puberty, but also in our patients who are being monitored for precocious or delayed pubertal progression. These studies were subject to inherent bias, based on the relatively homogenous population studied. However, no study is flawless, and we owe a great debt to Marshall and Tanner for bringing pubertal studies to the forefront of the research world, as a significant body of research has been published based on their initial observations.

As time has passed, and research strategies have become more sophisticated, we have been able to study larger, more heterogeneous groups of patients. Changes have been noted, but this does not necessarily reflect flawed early studies; more likely it represents ongoing environmental and genetic adaptations that are occurring at a population level.

Accepted Norms for Timing of Puberty

According to Marshall and Tanner's observations, the first signs of puberty appear between the ages of 8.5 and 13 years in 95 % of girls, and the first signs usually include either pubic hair or breast development. The breasts generally reach stage 5 (full maturity) between ages of 11.8 and 18.9 years, with a standard deviation of 1 year. The mean age at peak height velocity was noted to be age 12 years and the mean age at menarche was noted to be age 13 years. The interval from the first sign of puberty to completion of the pubertal process was reported to take anywhere from 1.5 years to greater than 6 years. Variations in sequence were also noted, and therefore there were many acceptable variations of normal also noted in this early landmark study [1].

Trends

Humans have a distinctly unique childhood phase between birth and puberty. Other species, including primates most closely genetically related to humans, complete growth prior to reproductive maturity. There may be some additional weight gain in

apes, but very little skeletal growth at the time of puberty. This indicates that there is something very unique about human puberty and how it changes as our environment also changes [2].

Genetic Factors

There is a considerable amount of research aimed toward establishing genetic links to normal puberty. At this point, we know that about half of the variance noted in timing of menarche is due to genetic factors [3]. We have also learned that the neuropeptide kisspeptin is a critical gatekeeper of pubertal development. This information was solidified over the past decade when it was confirmed by two independent research groups that mutation or deletion of part of this signaling pathway resulted in failed puberty and infertility in both humans and rats [4, 5]. Research is currently ongoing as to the exact mechanism of action of this particular neuropeptide, and this research will continue to give us information regarding normal puberty as well as pathologic progression of puberty. We have established several distinct causes of precocious and delayed puberty, but reliable genetic triggers for normal puberty have been more difficult to isolate and confirm, most likely because over time we have been able to document population wide variations in puberty that can be linked to environmental factors and this has been an area of intense research. There is also an emerging body of evidence that epigenetic factors often play a major role in the timing of puberty [6].

Environmental Factors

It is known that, historically, puberty will not occur until a mammal has achieved a size and level of development that would result in a high likelihood of reproductive success [7]. Therefore it stands to reason that factors affecting physical growth would then be factors affecting pubertal progression. Generally, due to ethical constraints in human research trials, studies regarding human nutrition are observational and may not be applicable to the general population. That being said, we have obtained valuable information regarding the effects of nutrition on puberty based on observational and indirect studies [8]. Menarche seems to correspond to physical size more directly than with chronologic age [9] and this correlates with evidence that girls are reaching menarche at an earlier age than in the past. Girls age 9 years today are more likely to have the stature of a 10- or 11-year-old girl 30 years ago. What we don't know at this point whether there is a lower age limit before which menarche is not feasible without being pathologic [10].

Observations regarding changes in the timing and progression of puberty provide us with indirect evidence that nutrition has an effect on timing of puberty and menarche. We do know that nutrition is not the only factor, based on the fact that historically, in socioeconomic classes where nutrition has not appreciably changed, the age

at menarche was still noted to be on the decline [11]. Alternatively, in geographic locations where nutrition has not changed over time, age at menarche also remained stable. This has been noted in some Inuit, Lapp, and East Indian populations [12]. Studies have been performed worldwide to evaluate nutrition effects on puberty over the past century, and in the USA it has been recorded that age at menarche differs significantly between groups of adolescents in close geographic proximity, but with dietary discrepancies. Dreizen et al. [13] reported a mean age of menarche of 12.4 years in areas where diet was adequate and a mean age of 14.5 years where diet was inadequate. Delayed skeletal maturation was also noted in these patients with inadequate nutrition, which is another marker of pubertal progress.

In developing countries, nutritional deficiency has historically been the most likely problem associated with changes in pubertal progression. In more developed nations, however, there has been a long trend of self-induced dietary restriction that results in delayed menarche. Dieting, intentional weight loss, and low body weight were noted to be associated with delayed menarche by Kennedy [14] and this continues to be an issue in our modern society.

While some females are intentionally losing weight because of issues associated with body image, some women have menstrual dysfunction simply related to their level of physical activity, regardless of intention to lose weight. Elite athletes and even young women who have recently initiated a strenuous exercise regimen may note changes in menstrual status as well as menarche. It is known that amenorrheic runners have a lower percentage body fat than normally menstruating runners [15]. Interestingly, it has also been noted that injuries preventing exercise in elite athletes who were previously amenorrheic will result in resumption of menses without any appreciable weight gain [16].

Nutrition does not solely affect the physical markers of puberty. There are also known effects of nutrition on pubertal hormones. In the 1970s and 1980s, several studies were published looking at the effects of nutrition on pubertal hormones. Historically, plasma gonadotropins were reported to be significantly lower in children with poor nutrition than in age-matched controls with adequate nutrition [17]. The mechanism of this interaction is unknown, but was still significant, as this caused limited stimulation of the ovary and delayed pubertal ovulation. It was found that if a nutritional deficiency were noted, available nutrients would be preferentially directed to organ systems of higher priority, namely the nervous system. The reproductive system is lower priority under these conditions, and therefore puberty will be delayed as reproductive maturity is slowed or halted [8].

Nutritional deficiency is not the only dietary issue affecting puberty. There is also evidence that obesity is influencing the timing and tempo of puberty. There has been a trend of increasing body mass index in children over the past century, most notably after the 1970s, and this trend is presenting in early childhood [18]. Another recent study indicated that girls with higher percent body fat, higher body mass index, and larger waist circumference at ages 5 and 7 years were more likely to exhibit earlier pubertal development at age 9 years [19]. While obesity is a measure of adiposity and is hard to directly correlate with developmental markers such as puberty, we do see changes in weight and that seem to reflect changes is puberty as well.

This correlation cannot be ignored and will continue to be evaluated over the years to come, as the obesity epidemic becomes even more prevalent in our young people.

It is also important to note that stress is a puberty accelerator. In many countries, divorce resulting in single parent families has rapidly escalated over time, and this has correlated with a reduction in the age of puberty onset in many countries [20]. Stress does not only come in the form of emotional stress, but also physical stress. There is a known correlation with stress in utero resulting in early puberty. This is seen most frequently in individuals who were nutritionally deprived in utero and have excessive caloric intake in childhood. This has been observed most consistently in immigrant but is likely to be seen in any population where deprivation is commonplace [21].

As our world continues to evolve, we anticipate that pubertal response to the environment will change as well. This may result in changes that help people adapt to the world, but these changes may also challenge society as well. There is a large body of literature that suggests for the first time in history the age of puberty does not match the age of psychosocial and societal maturity. This is posing problems in society that have not been present in the past. We know that in earlier societies, puberty was often occurring at a much younger age. This was not considered pathologic because this young age matched the age at which individuals were active members of their given society. This generally occurred in hunter-gatherer groups, and it was not until people began settling in large groups and colonies did we start to see negative effects of colonization that changed the timing of puberty. With colonization and settlement came overpopulation, disease, infection, and poor nutrition [21].

Conclusion

There have been many exciting findings in puberty research over the years, and research is ongoing. We hope that these recent advances will help us understand puberty in the context of recent changes compared to historical norms. This may ultimately result in evolving definitions of what is normal and what is pathologic in the realm of pubertal progression.

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Chapter 2
Normal Pubertal Physiology in Females

Hillary B. Boswell

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

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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

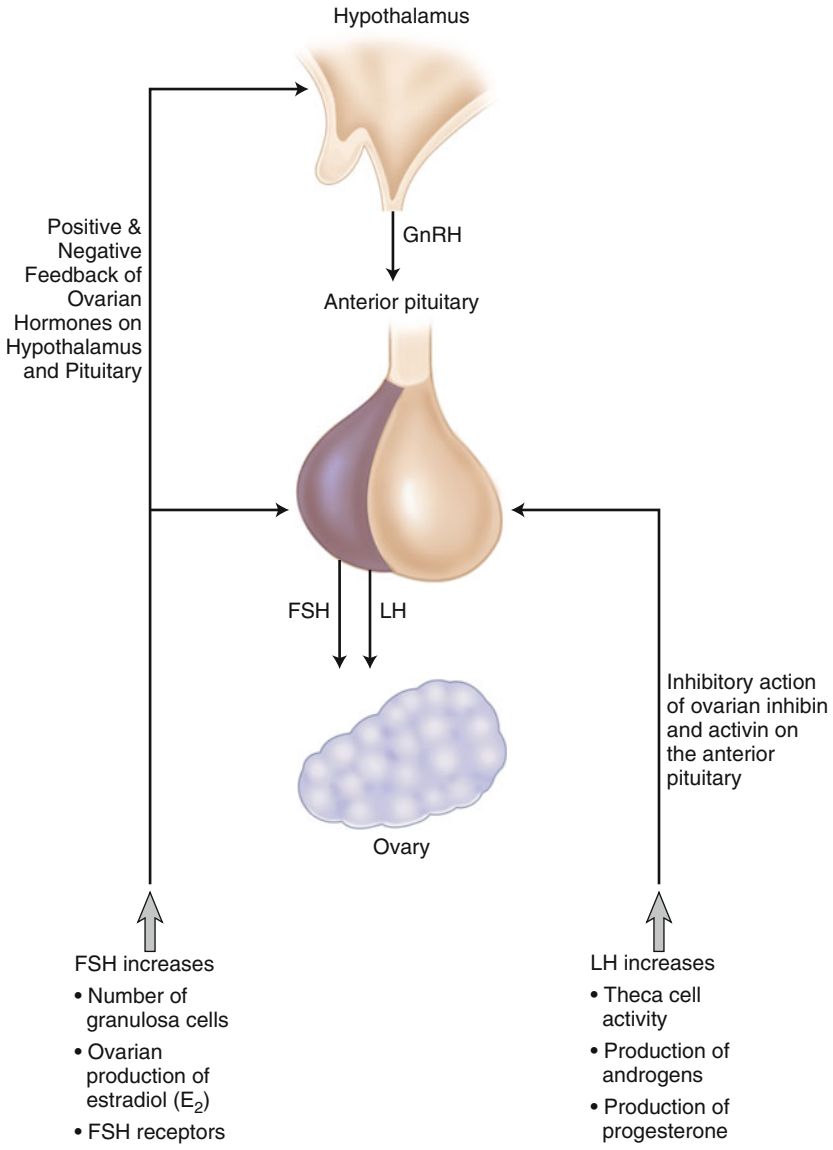


Fig. 2.1 HPO axis

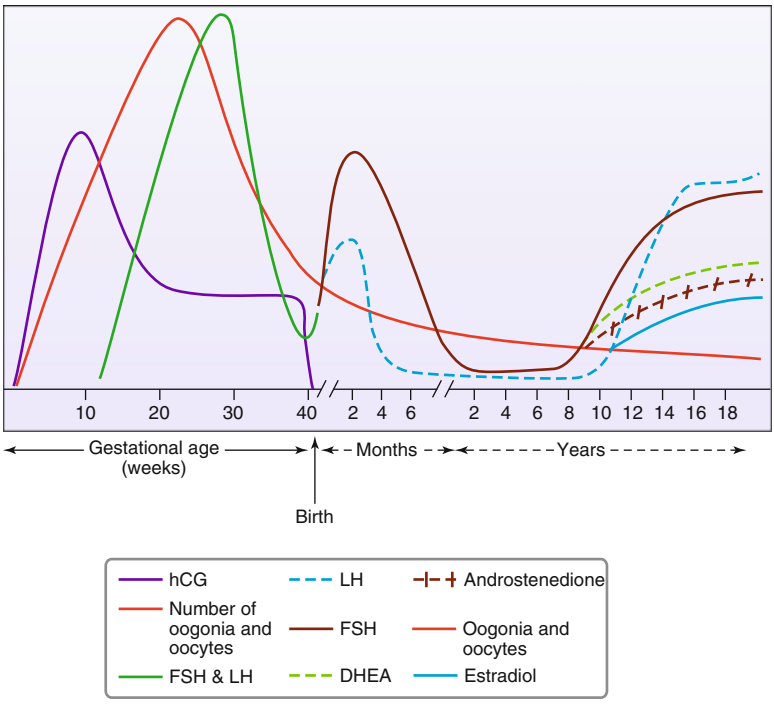


Fig. 2.2 Variations in key reproductive functions over the lifetime. (Adapted with permission from Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility, 8th edition. Philadelphia: Lippincott Williams & Wilkins; 2010)

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).

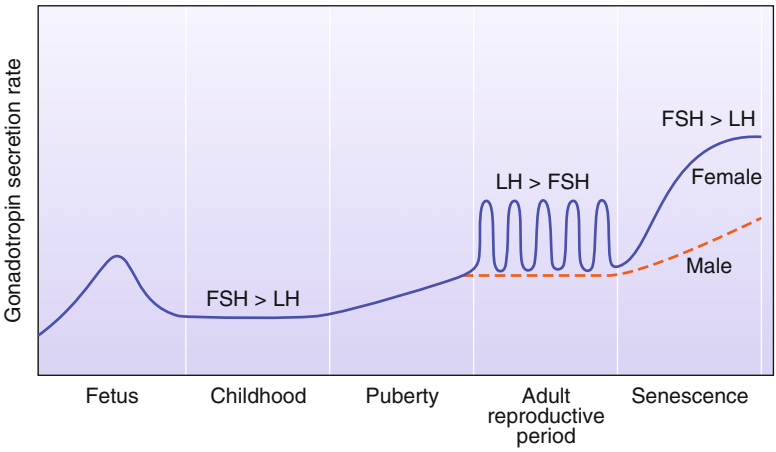


Fig. 2.3 Gonadotropin levels over the life span. (Adapted with permission from Emans SJ, Laufer MR, Goldstein DP. The Physiology of Puberty. Pediatric and Adolescent Gynecology. 5 ed. Lippincott Williams & Wilkins; 2005)

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 $KISS_1R$ gene), the G-protein coupled receptor through which kisspeptins act as neuropeptides [11, 14]. Neurons expressing kisspeptins (encoded by the gene $KISS_1$) 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 $KISS_1R$ 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 Δ5-3β-hydroxysteroid intermediates (17α-hydroxypregnenolone and dehydroepiandrostenedione, DHEA) and decreased production of Δ4-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 μg/dL or greater (approximately 5 μg/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 hypoadrenal 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 also 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

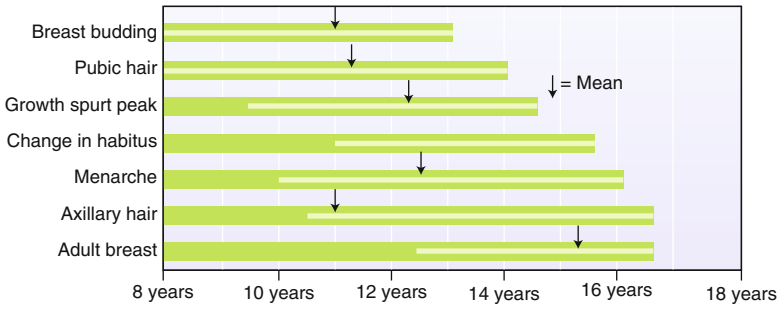


Fig. 2.4 Timeline of female pubertal milestones. (Adapted with permission from Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility, 8th edition. Philadelphia: Lippincott Williams & Wilkins; 2010)

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

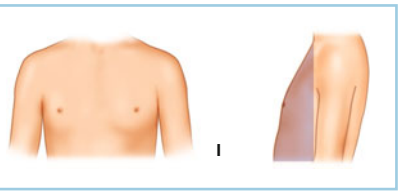
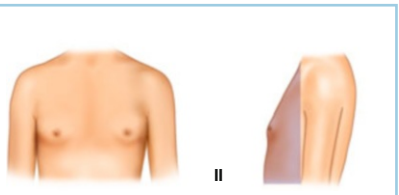
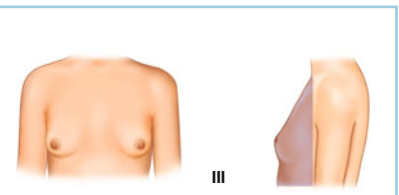
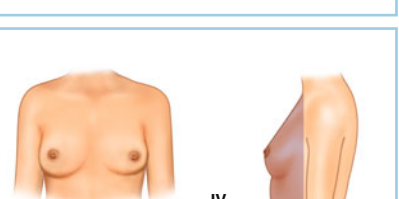
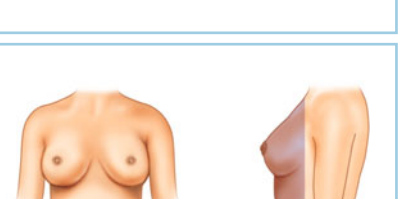
Tanner Stage1	Preadolescent	Only papilla is elevated	
Tanner Stage 2	Breast budding	Enlargement and widening of the areola and mound-like elevation of the breast and papilla	
Tanner Stage 3		Further enlargement of breast and areola with NO separation of contours	
Tanner Stage 4		Projection of the areola and papilla to form secondary mound above the level of the breast and further enlargement	
Tanner Stage 5	Adult Breast	Projection of the papilla only, as the areola recesses to the mature contour of the breast	

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)

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.

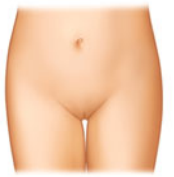
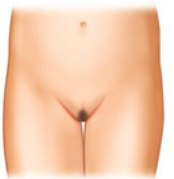
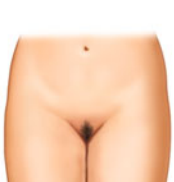
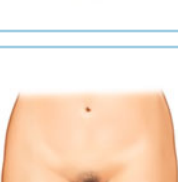
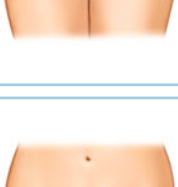
Tanner Stage1	Preadolescent	No discernable difference between vellus hair on the mons and anterior abdominal wall, no pubic hair	 I
Tanner Stage 2		Appearance of few, sparse, lightly pigmented hairs, with minimal curl on the labia	 II
Tanner Stage 3		Hair becomes darker, coarser and begins to spread over the junction of the labia	 III
Tanner Stage 4		Adult hair type emergens, 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

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

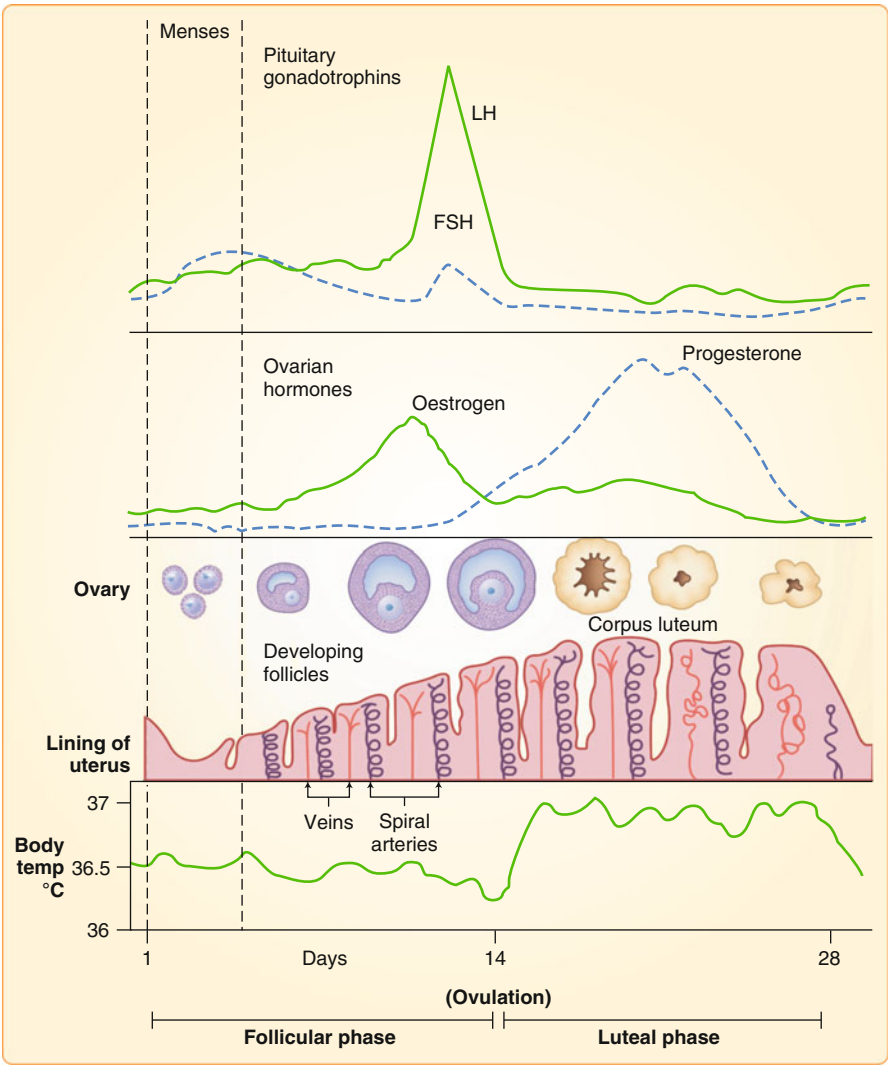


Fig. 2.7 Menstrual cycle. (Adapted with permission from Emans SJ, Laufer MR, Goldstein DP. The Physiology of Puberty. Pediatric and Adolescent Gynecology. 5 ed. Lippincott Williams & Wilkins; 2005)

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

Table 2.1 Timing of pubertal milestones in the US girls

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

Data from: Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997 Apr;99(4):505–12

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

Pubertal milestone	African American	Mexican American	Caucasian
Mean age in years			
Pubarche	9.5	10.3	10.5
Thelarche	9.5	9.8	10.3
Menarche	12.1	12.2	12.7

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

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 observes 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).

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 has 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 correlates 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 γ (PPAR-γ), 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 μL/dL were 80 % less likely to reach these pubertal milestones than girls with levels in the 2.1–4.9 μL/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 adrenache, 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.

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Chapter 3
Genetics of Puberty

Judith Sanchez

Abstract Genetics is an important determinant in the timing of puberty. Genes such as *KISS1* and *TAC3* were discovered while studying specific cases of idiopathic hypogonadotropic hypogonadism and are now believed to play a critical role in normal puberty. *MKRN3*, which was found while studying central precocious puberty, is the most recent addition to the list of genes responsible for puberty. Genome-wide association studies have also made breakthroughs in other genes, such as *LIN28B*, involved in the process of puberty. This chapter will discuss the aforementioned genes and their roles in normal puberty.

Keywords Genetics • Puberty • Leptin • Kisspeptin • *KISS1* • *KISS1R* • Neurokinin B • NKB • NKR3 • *TAC3* • *TACR3* • *MKRN3* • *LIN28B* • Single nucleotide polymorphism • Genome-wide association studies • Hypogonadotropic hypogonadism • Central precocious puberty • GnRH • Hypothalamus • Timing of puberty

Introduction

There are many factors that influence the timing of puberty including nutrition, socioeconomics, environment, and geography [1]. However, the most influential factor is likely genetics as evidenced by studies demonstrating similar age at menarche among mother–daughter, twin and sibling pairs [2]. Nonetheless, studies have shown that heritability can range anywhere from 50 to 80 % [2–4].

There have been many recent breakthroughs in the genetics of puberty, which will be discussed in this chapter. Many studies use menarche as a proxy for the initiation of puberty, although it is not the first sign of puberty. Thelarche is the first

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secondary sexual characteristic [5] and its timing is influenced by the same genetic effects as menarche, therefore making menarche a useful substitute in determining the timing of puberty [6, 7]. Additionally, age at menarche can be easily identified and recalled many years later [8] and as such, is often used in research studies to gain insight into the timing of puberty.

Leptin and Puberty

A girl's weight has long been associated with age of menarche. During the industrial revolution, the age of menarche decreased as overall nutrition and weight increased. Frisch and Revelle [9] even suggested a "critical weight" of 48 kg for menarche to occur. In the early 1990s, with the discovery of leptin and its effect on weight it was a natural segue way to begin its link to puberty.

Leptin is required for normal puberty as defects in this gene (*LEP*/*LEPR*) result in hypogonadism; however, it is more likely a permissive factor [10]. Studies have shown no association between the leptin gene and age of menarche [11, 12]. It was initially hypothesized that leptin contributed to puberty by affecting kisspeptin, an important regulator of the reproductive axis that will be discussed below, as leptin receptors are highly expressed in the hypothalamic arcuate nucleus, including on kisspeptin neurons [13–16], and leptin administration to leptin-deficient mice induces puberty and increases *KISS1* expression [13]. However, *LepR* knockout mice, in which leptin receptors were selectively deleted from kisspeptin neurons, had normal puberty and fertility suggesting that leptin's action on kisspeptin neurons is not needed for puberty [17]. Further studies have proven that leptin signaling in kisspeptin neurons arises after completion of puberty [18] therefore, suggesting that leptin's contribution to puberty is likely not related to genetics.

Kisspeptin: More Than Just a *KISS1*

KISS1R (then known as *GPRF54*) was first considered important to puberty by de Roux et al. [19] and associates while studying one particular family in late 2003. A 20-year-old young man was referred to their clinic in Paris for delayed puberty; signs included microorchidism, micropenis, short stature, and delayed bone growth. The patient's pedigree revealed that three out of four of his brothers and one out of three of his sisters had a similar phenotype. (The affected sister manifested her hypogonadism with partially developed breasts and had only had one menstrual period at age 16 years.) The patient's parents were first cousins and had had undergone normal puberty. The affected males had low levels of testosterone and the affected female had low levels of estradiol. All affected family members had low levels of gonadotropins and a blunted response to a gonadotropin-releasing hormone (GnRH) stimulation test. A genome-wide analysis was performed and gene

mapping revealed that a homozygous deletion error of the *KISS1R* gene located on the short arm of chromosome 19 (19p3) was responsible for these familial cases of idiopathic hypogonadotropic hypogonadism (IHH) [19].

At this time, little was known about the *KISS1R* gene other than that it encoded a G protein-coupled receptor that responded to the *KISS1* gene-derived protein kisspeptin [20, 21]. *KISS1* was known as a tumor metastasis suppressor gene that encoded the protein initially named metastatin [22]. (The term kisspeptin is now preferred over metastatin with the discovery that its role extends far beyond the suppression of tumor metastasis. Similarly KISS1R is now used instead of GPR54 [23]. All of the terms however pay homage to Hershey, Pennsylvania where the *KISS1* gene was first discovered [22].) Kisspeptin was known to play a role in cellular motility [20] and proliferation [20, 21] as well as controlling the migration of trophoblast cells [24]. *KISS1* mRNA is found most commonly in the placenta and in the brain (where it had been localized to the hypothalamus and basal ganglia) [25]. Because of kisspeptin's known activity, it was initially proposed that the kisspeptin/KISS1R complex played a role in the migration of GnRH neurons similar to the pathophysiology responsible for anosmic hypogonadotropic hypogonadism, better known as Kallman's syndrome [19]. However, this was soon proven wrong.

A large Saudi Arabian family presented to Seminara and her associates [26] in Boston seeking treatment for infertility. Similar to the family studied by de Roux et al., there was again consanguinity as three pairs of first cousins had married and reproduced. Of their combined 19 offspring, six (four men and two women) suffered from IHH. Genetic testing again implicated a homozygous variant of the *KISS1R* gene in the affected family members. The variant was responsible for loss of function of KISS1R and was not found in any of the 260 unaffected, unrelated chromosomal controls nor was it found to be homozygous in any unaffected family members. Seminara et al. [26] and her group then engineered knockout mice lacking the *KISS1R* gene. The knockout mice were functionally similar to the patients with IHH, which was demonstrated by their lack of sexual maturation and low levels of gonadotropins. Most notable among the knockout mice was the finding of normal levels of GnRH neurons in the hypothalamus thereby debunking the previous migration theory suggested by de Roux. The new theory was that the kisspeptin/KISS1R complex regulates the release of GnRH at the level of the hypothalamus acting as a gatekeeper for puberty [26].

Animal studies supported this new hypothesis as kisspeptin demonstrated to be a powerful stimulant of GnRH secretion after being bound to the KISS1R receptor [27]. Low doses of kisspeptin infusion resulted in a significant release of GnRH in both rats and monkeys [27, 28], and the expression of *KISS1* and *KISS1R* in the hypothalamus dramatically increased at the time of puberty [27, 29].

In 2008, soon after these breakthroughs, an adopted 8-year-old girl presented to an endocrinology clinic in Sao Paulo for evaluation of precocious puberty. She had Tanner stage 4 breasts which had been slowly developing since birth and Tanner stage 2 pubic hair; her bone age was 11 years according to the Greulich and Pyle method. Estradiol levels were elevated, gonadotropin levels were prepubertal and she did not respond to a GnRH stimulation test. Imaging of her pelvis and head was

normal. She was treated for idiopathic central precocious puberty with a GnRH analogue and responded appropriately. Sequencing of the patient's genomic DNA revealed a heterozygous variant in the *KISS1R* gene. This variant was not found in any of the 150 unrelated, unaffected controls or the 53 unrelated controls with idiopathic central precocious puberty. Functional analysis revealed that this variant caused decreased sensitization of the KISS1R receptor which resulted in a prolonged activation response to kisspeptin and an increased amplitude pulse of GnRH. An autosomal dominant activating mutation of *KISS1R* was found to be causing the patient's central precocious puberty [30].

These landmark studies demonstrate that kisspeptin and its receptor play an important role in activating the pulsatile secretions of GnRH that signal the beginning of puberty. Further research has evaluated the interaction between kisspeptin and other peptides active in the arcuate nucleus of the hypothalamus. See Fig. 3.1.

Neurokinin B and *TAC3*

Neurokinin B (NKB) is a member of the tachykinins family, a cluster of excitatory neurotransmitter peptides [31, 32]. NKB and its receptor NKR3 are encoded by *TAC3* and *TACR3* genes, respectively [33, 34].

In 2009, Topaloglu et al. [35] and associates studied nine consanguineous Turkish families who had multiple members affected with IHH. Using genome-wide analysis, they found that loss-of-function mutations of the *TAC3* or *TACR3* genes were responsible for these familial cases of IHH. Further analysis revealed that heterozygous carriers were unaffected; the variants were also not detected in 100 unrelated unaffected controls, suggesting an autosomal recessive disorder. All patients with homozygous *TAC3*/*TACR3* mutations had delayed puberty and showed signs of hypogonadism. Laboratory studies revealed low levels of sex steroids, prepubertal levels of gonadotropins, and a blunted response to a GnRH stimulation test. The affected females had primary amenorrhea and no spontaneous breast development. The affected males had micropenis and cryptorchidism. These findings suggest that the NKB system is essential for the activation of puberty [35].

Gianetti et al. [36] reported in 2010 that mutations in the NKB pathway are a relatively common cause of hypogonadism and occur in more than 5 % of patients with IHH. The patients studied by Gianetti and his associates demonstrated a broad range of phenotypes. Fifteen of 16 males with *TACR3* variants had micropenis and two had cryptorchidism; none of the females had spontaneous thelarche or menarche. Seven males and five females with *TAC3* or *TACR3* variants were assessed after their treatment (most commonly hormone replacement therapy with a sex steroid) was discontinued. Six males demonstrated evidence for reversibility of their hypogonadism; three males showed significant increase in testicular volume while on androgens and two achieved fertility while off therapy. Four females with *TAC3* mutations had spontaneous menses and two of them conceived spontaneously without fertility treatment. The evidence for reversibility and spontaneous activity of the reproductive axis posttreatment contrasted with the severe hypogonadism

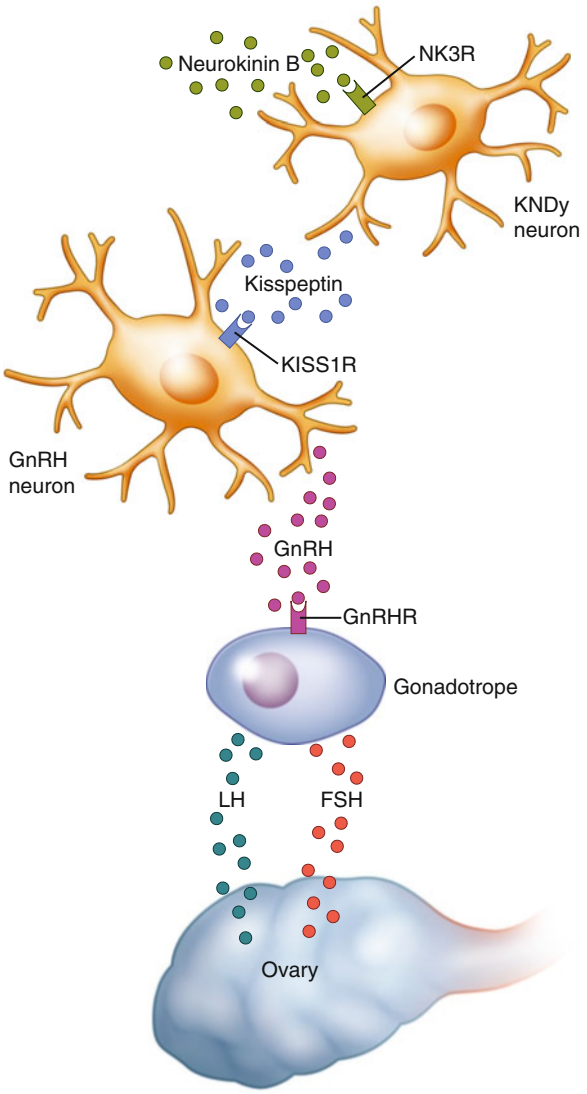

Fig. 3.1 KNDy (kisspeptin, neurokinin b (NKB), and dynorphin) neurons release kisspeptin and NKB which are integral in activating GnRH neurons to begin the pulsatile secretions that signal the beginning of puberty

demonstrated in early neonatal life suggest that the NKB/NKR3 complex may play different roles throughout reproductive development [36]. Pulsatile GnRH infusions to adults with *TAC3* and *TACR3* gene mutations restored serum LH and testosterone secretion in males and resulted in ovulation, pregnancy, and a normal birth in a female in a study by Young et al. [37]. These data in combination with Gianetti's study suggest that mutations in *TAC3* and *TAC3R* result in deficiencies at the level of the hypothalamus and not the anterior pituitary gland or gonads.

Approximately 40 patients with *TAC3* and *TACR3* mutations have been reported to date, with a worldwide distribution and a diverse racial mix [35–38].

These reports implicate the NKB/NKR3 complex as an essential component for the onset of puberty and the control of gonadotropin secretion [32]. The mechanism by which mutations in the NKB pathway cause GnRH deficiency and IHH are not yet clear [39]. However, it is known that NKB is expressed in the same neurons that express kisspeptin, in the arcuate nucleus of the hypothalamus [40–42]. As almost all of these neurons also express estrogen and progesterone receptors, they likely play an important role in the feedback of these steroids on GnRH neurons making them an important component not only of puberty, but also continuing reproductive function [40]. Additional studies are needed to elucidate the precise role of the NKB on the gonadotropic axis.

MKRN3: The Brake on Puberty?

Abreu et al. [43] recently discovered *MKRN3* may be another important factor in the genetics of puberty. While studying 15 different families affected by central precocious puberty, a link to *MKNR3* was found using whole-exome gene sequencing. A loss of function mutation in this gene was found to be responsible for a familial form of central precocious puberty. *MKRN3* is a paternally expressed, maternally imprinted gene which encodes the makorin RING-finger protein 3 [44]. *MKRN3* is an intronless gene located on chromosome 15q11.2 [45] and is involved with ubiquitination and cell signaling [46]; however, its full function or how its mutation causes central precocious puberty is not yet well understood [43].

Another aspect of Abreau and associates' study included determining *Mkrn3* mRNA levels in the arcuate nucleus of the hypothalamus of mice [43]. Genes such as *Kiss1* and *Tac2*, which are known to be important for the onset of puberty, are also expressed in the hypothalamic arcuate nucleus of the mouse [47]. Levels of *Mkrn3* were found to drastically decrease at the same time that *Kiss1* and *Tac2* began to increase expression indicating the onset of puberty [48, 49].

A defect in *MKRN3* leading to puberty being turned on too early (central precocious puberty) and the decrease in expression in mice at puberty suggest that *MKRN3*, in contrast to other genes like *KISS1* and *TAC3* which turn puberty "on," inhibits puberty [43].

LIN28B and Other Genes

Genome-wide association studies have gained popularity since the completion of the Human Genome Project as they are able to identify single nucleotide polymorphisms associated with a disease and usually have a very large sample size (up to hundreds of thousands).

He and associates [50] performed the first genome-wide association study for age at menarche on 17,438 women (2,287 from the Nurses' Health Study and 15,151 from the Women's Genome Health Study), which identified two significant

loci. One grouped in or near the *LIN28B* gene at 6q21 and the other at 9q31.2. Other independent genome association studies confirmed the *LIN28B* gene to be associated with age at menarche [50–53] and the locus at 9q31.2 was also confirmed by Perry and associates [52].

Ong et al. [51] found *LIN28B* was also associated with 0.12 years earlier menarche, earlier breast development in girls, earlier voice breaking and more advanced pubic hair development in boys, a faster tempo of height growth in girls and boys, and shorter adult height in women and men [51] (earlier menarche is associated with shorter height which has been suggested is due to earlier exposure to estrogen and therefore earlier closure of epiphyseal plates [54]) Another common genetic variant in *LIN28B* was linked with earlier puberty and a prolonged increase in BMI during adolescence and early to mid-adulthood in women only [55]. Perry et al. also found a genetic association between age at menarche and both height and BMI. Both height [54] and weight [56] have been previously correlated with menarche. Sulem also found *LIN28B* to be associated with increased BMI and earlier menarche [52, 53], which is interesting given the association between BMI and age at puberty found in population studies [56].

However, these two genes (*LIN28B* and 9q31.2) only explain 0.60 % of variation in age at menarche [50]. Elks et al. [57] performed further genome association studies and were able to identify an additional 30 genes. A meta-analysis of 32 genome-wide association studies in over 87,000 women was performed [57]. *LIN28B* and 9q31.2 were the most significant loci; however 30 new variants, or single nucleotide polymorphisms, were identified. Among these new loci were four genes previously associated with childhood obesity (in or near *FTO*, *SEC16B*, *TRA2B*, and *TMEM18*), three in or near other genes implicated in energy homeostasis (*BSX*, *CRTC1*, and *MCHR2*), and three in or near genes implicated in hormonal regulation (*INHBA*, *PCSK2*, and *RXRG*) [57].

The strongest novel menarche signal was found downstream of *INHBA*, which encodes the protein subunit inhibin beta A. Heterodimers of inhibin beta A and the inhibin alpha subunit form the female reproductive hormone inhibin A [58]. Inhibin A is produced by granulosa cells in the ovary and levels increase dramatically during puberty [59, 60]. Inhibin A is involved in negative feedback regulation by inhibiting production of follicle-stimulating hormone (FSH) by the pituitary and secretion of GnRH from the hypothalamus [61]. Conversely, homodimers of inhibin beta A ultimately form the hormone activin A, which stimulates pituitary FSH production and also exhibits a wide range of biological activities, including the regulation of cellular proliferation and differentiation [62].

Conclusion

Overlap between the genes regulating puberty, height, weight, and now reproductive hormones have been identified by the studies discussed in this chapter. An important area of future research will further clarify their role in the complex matrix responsible for the initiation of puberty.

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Chapter 4
Psychology and Neurobiology of Puberty

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Abstract Puberty is derived from the Latin word pubertas, which means adulthood. It represents the transition from childhood to adulthood and is characterized by physical maturation and attainment of fertility. Adolescence and puberty are not exchangeable terms. Puberty usually marks the beginning of adolescence and is a 3–4 year process where hormonal and physical changes cause an individual to reach sexual maturity. In females, the signal for maturity is the first menstrual period. Adolescence represents that time frame where social and psychological growth transform a dependent child into a functionally independent young adult; it encompasses puberty and can take up to a decade for full maturation to occur. The psychology of puberty is closely intertwined with the physiologic changes that take place as a female undergoes maturation. Physiologic changes are initiated by hormonal surges from the brain to the gonads (ovaries) which secondarily produce hormones that stimulate peripheral entities such as the breast, hair, and sexual organs. The attainment of the milestones of development is a process in which females undergo thelarche (breast development), pubarche (sexual hair development), menarche (onset of menstrual cycle), and the growth spurt. The neurobiology of puberty is a complex topic on which there is an abundance of information. The goal of this chapter is to provide basic information concerning the physiology; also the mental and behavioral characteristics surrounding this phase of life will equally be examined.

Keywords Developmental psychology • Hormonal changes • Growth curve • Bone development health • Adolescent sexuality • Thelarche • Adrenarche • Menarche • Psychosocial interactions • Early puberty • Mid-puberty • Late puberty • Adolescent

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Introduction

Puberty is derived from the Latin word pubertas, which means adulthood. It represents the transition from childhood to adulthood and is characterized by physical maturation and attainment of fertility. Adolescence and puberty are not exchangeable terms. Puberty usually marks the beginning of adolescence and is a 3–4 year process where hormonal and physical changes of the body cause an individual to reach sexual maturity. In females, the signal for maturity is the first menstrual period. Adolescence represents that time frame where social and psychological growth transform a dependent child into a functionally independent young adult; it encompasses puberty and can take up to a decade for full maturation to occur.

Overview

The psychology of puberty is closely intertwined with the physiologic changes that take place as a female undergoes maturation. Physiologic changes are initiated by hormonal surges from the brain to the gonads (ovaries) which secondarily produce hormones that stimulate peripheral entities such as the breast, hair, and sexual organs. The attainment of the milestones of development is a process in which females undergo thelarche (breast development), pubarche (sexual hair development), menarche (onset of menstrual cycle), and the growth spurt. The neurobiology of puberty is a complex topic on which there is an abundance of information. The goal of this chapter is to provide basic information concerning the physiology; also the mental and behavioral characteristics surrounding this phase of life will equally be examined.

Hypothalamo-Pituitary-Ovarian System

The organs at play in the female reproductive system include the brain (hypothalamus, pituitary gland), ovaries, fallopian tube, and uterus which together form the hypothalamo-pituitary-gonadal axis (Fig. 4.1). All organs in this axis communicate and do not act independently. The hypothalamo-pituitary-ovarian (HPO) system is well developed at the time of birth and is in fact intact by 12 weeks of gestation [1, 2]. Negative feedback of hypothalamic-pituitary gonadotropin is first acquired in fetal life by midgestation [1–3]. When development is normal, the feedback mechanism ensures that the process of puberty is beautifully orchestrated at the appropriate time.

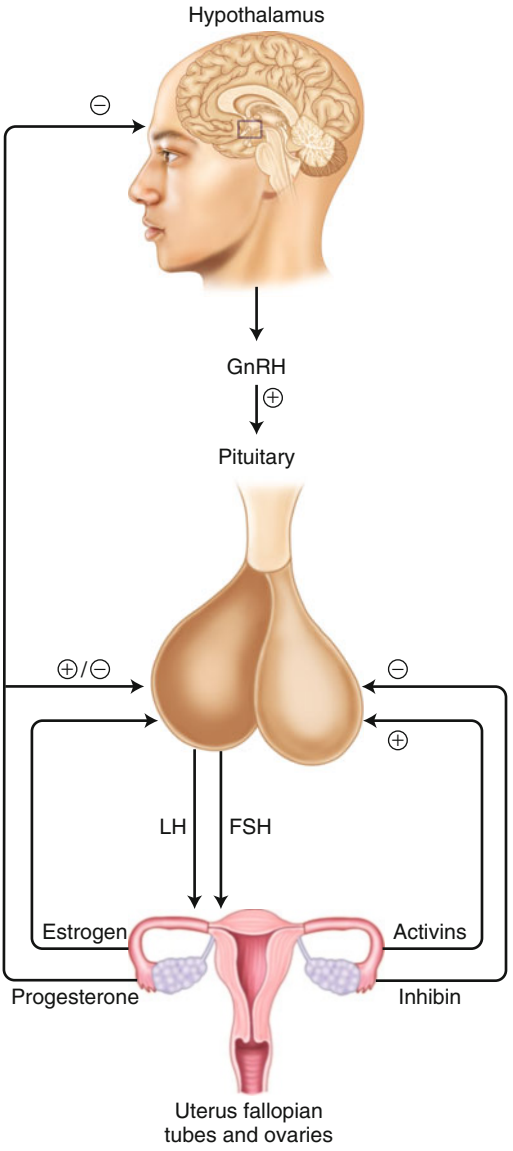

Fig. 4.1 Hypothalamic-hypophyseal-gonadal axis

Gonadotropin Releasing Hormone

The hypothalamus is an essential brain structure in the process of puberty and it produces the neurohormone, gonadotropin releasing hormone (GnRH), a 92 amino acid precursor protein encoded on the short arm of chromosome 8 with a half life of 2–4 min in vivo [4]. GnRH is responsible for the release of the gonadotropins,

follicle stimulating hormone (FSH), and luteinizing hormone (LH) from the anterior pituitary gland. The arcuate nucleus which lies within the tuberal hypothalamus contains the greatest number of GnRH-producing neurons [5, 6].

Studies have found that initially there is episodic release of GnRH in the neonatal and fetal periods and in response, FSH and LH are elevated. It is important to note that in females, FSH levels are usually greater than LH levels at this stage [2, 6]. At around 6 months of age, this process becomes downregulated and eventually dormant during childhood where GnRH secretion is minimal and intermittent, and subsequently, mean LH and FSH levels are low [7]. From the quiescent state of childhood, pulsatile release of GnRH begins with the onset of puberty and initially is expressed only during sleep. Upon establishment of functional menstrual cycles, the pulsatility prevails throughout the 24 h period [2, 8–10]. With the onset of puberty, GnRH levels increase, the levels of LH and FSH rise and once the normal menstrual cycle is subsequently established, LH secretion levels predominate that of FSH. This preferential inhibition of FSH during the reproductive years results from increasing levels of both estradiol and inhibin [7, 11].

Two main hypotheses (theories) exist regarding the mechanism of the onset of puberty. The first is the hypothalamic maturation theory which hypothesizes that the childhood downregulation of GnRH is due to central inhibition. The nature of this central inhibition is still unclear, however, gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the nervous system has been implicated in this process. It is thought that a critical factor in the onset of puberty is the disinhibition of GnRH-producing neurons from GABA [2, 11–13]. The second is the gonadostat theory which hypothesizes that the regulating system for gonadotropins is very sensitive in childhood which keeps the concentration of sex steroids low. During sexual maturation, this gonadostat becomes desensitized to steroid feedback and the shift in sensitivity permits gonadotropin secretion [2, 13]. Both theories agree that the onset of puberty is largely due to the upregulation of GnRH which occurs as a result of multiple complex series of events between hypothalamic oscillators, target cells, neuropeptides, neurotransmitters, and neurosteroids [14–17]. The overall process is controlled by multiple genetic and environmental factors. Several gene mutations have been identified in delayed or absent puberty and are estimated to account for approximately 30 % of individuals with disorders of puberty [18].

The suprachiasmatic nucleus of the hypothalamus (SCN) commonly known as the central circadian pacemaker is known to communicate with the arcuate nucleus, which is often described as the GnRH pulse generator; these hypothalamic oscillators are crucial in the upregulation of GnRH [19]. Target cells within certain reproductive organs (pituitary, ovaries, oviducts, uterus) have been described as possessing autonomous clocks, which contribute to the timing of events in reproductive physiology [20]. In addition, neuropeptides, neurotransmitters, and neurosteroids all underlie the onset of pubertal processes and can either act as stimulants, inhibitants or in some cases, both, depending on the timing.

This paragraph briefly mentions some of the key players that have been identified in the process of pubertal onset and is in no way inclusive of all entities involved in this poorly understood intricate process. The most potent identified activator of GnRH neurons is Kisspeptin, a neuropeptide encoded by the gene Kiss1, and whose

secretion is regulated by Neurokinin B [5, 17, 18, 21]. Studies undertaken reveal that kisspeptin is involved in virtually all aspects of reproduction from the initiation of puberty to the daily control of reproduction. Inactivation of the kisspeptin receptor causes hypogonadotrophic hypogonadism. Neuropeptide Y (NPY) is also a neuropeptide that acts as a neurotransmitter in the brain. It has been implicated as the hypothalamic brake in the absence of estrogen (before puberty) working with GABA, but once puberty starts it has been noted to stimulate pulsatile release of GnRH and in the pituitary potentiates the response to GnRH [13, 22]. An example of a peripheral player is Leptin, a protein hormone mainly produced in adipose tissue that has receptors in the hypothalamus; some noted on cell bodies on NPY neurons [23]. Serum leptin levels are proportional to fat stores in the body, and are thought to play a central function in the metabolic control of puberty. Circulating levels of Leptin have been noted to rise during the pubertal transition in females. Anorexia is associated with amenorrhea and females with this condition have lower levels of circulating Leptin and gonadotropins. In addition, individuals deficient in Leptin fail to initiate puberty which further solidifies the importance of Leptin in the process of puberty [23–26]. Adrenarche, a process which occurs prior to puberty may play a role in the maturation of the hypothalamic-hypophyseal-gonadal axis. It causes the elevation of the neurosteroid dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) which has been implicated in the upregulation of GnRH [27].

Gonadotropins, Follicle Stimulating Hormone, and Luteinizing Hormone

Pulsatile release of GnRH causes activation of the GnRH receptors in gonadotrope cells of the anterior pituitary which leads to the secretion of Gonadotropins, FSH, and luteinizing hormone (LH). They belong to the family of glycoprotein hormones (in conjunction with thyroid stimulating hormone [TSH] and human chorionic gonadotropin [HCG]). These specific protein hormones are structurally similar to gonadotropins as they consist of two peptide chains: a common alpha chain and a unique beta chain which confers biologic activity. Nonetheless, the gene for universal alpha subunit of LH, FSH, TSH, and HCG is located on chromosome 6, while the beta subunit gene specifically for LH and FSH is located on chromosome 19 and 11 respectively [28–30]. The gonadotropins are also referred to as sex hormones as their target organs are the gonads (ovaries or testes), where together they act synergistically and regulate many aspects of gonadal function in both males and females such as normal growth, sexual development, and reproductive function.

The female ovaries have a dual function: production of germ cells and steroidogenesis, but the ability to function requires the interplay of hormonal stimulation, in addition to the ability to respond or sense hormones. LH provides the androgen substrate for estrogen synthesis; it targets the theca cells of the ovary where androgens are produced via the process of steroidogenesis. These androgens are converted into estrogen by adjacent granulosa cells via the enzyme aromatase (CYP19),

a member of the cytochrome P450 superfamily. Receptors for LH exist on the theca cells at all stages of the cycle but only appear on the granulosa cell after the follicle matures under the influence of FSH and estradiol usually in the middle to late follicular phase. LH acts synergistically with FSH to help follicular maturation, and later plays a role in promoting follicular degradation. In addition, LH also assists with follicular rupture via prostaglandin synthesis to bring about ovulation. After release of the mature ovum from the follicle, it stimulates progesterone synthesis by the corpus luteum [31–33].

FSH primarily stimulates the growth of ovarian follicles and targets the granulosa cells of the ovary which results in estradiol production. It enables maturation of the follicle by activating enzymes essential to estrogen production, including aromatase, and ultimately stimulating LH receptors on granulosa cells. The ovarian steroids and other protein complexes produced by the ovaries in response to LH and FSH such as activin, inhibin, insulin-like growth factor, and progesterone exert feedback on the hypothalamus and on the pituitary generating the cyclic pattern of gonadotropin release characteristic of the female reproductive system [34, 35].

The menstrual cycle which will be described in detail in a later section is an attestation to the feedback mechanism. For ovulation to occur normally, which is essential in normal reproduction, there must be proper stimulation of gonadotropin release. The amplitude and frequency of the GnRH pulse varies throughout the menstrual cycle and specifically, there are two distinct modes of GnRH secretion, namely the pulsatile and surge mode. Pulsatile GnRH release drives tonic gonadotropin and regulates folliculogenesis; this tonic mode accounts for the low but pulsatile release of LH. The surge mode generates the preovulatory LH surge which triggers ovulation. In the female, pulsatile secretion is negatively regulated by estrogen and/or progesterone, and surge release is positively regulated by estrogen [6, 36].

Menstrual Cycle

Unlike males, the reproductive capacity of a female is intermittent and each female is born with a finite number of ova in the ovary. Much of the germ cell maturation occurs during intrauterine life. Primordial germ cells migrate from the entoderm of the yolk sac to the genital ridge in the second month of gestation and begin to multiply at a rapid rate. Within the genital ridge, which in females later becomes the ovary, these germ cells (now called oogonia) undergo mitosis and achieve their peak number of 6–7 million oocytes by 5–6 months of gestation. Through the process of apoptosis, the neonate eventually has 1–2 million oocytes at birth. At the time of puberty only 0.3–0.5 million oocytes remain [2, 32, 33]. Each ovary contains oocytes that are at different stages of development (Fig. 4.2). The menstrual cycle refers to the cyclic release of a single mature oocyte driven by alterations in hormonal levels and the feedback mechanism. On average the human menstrual cycle is approximately 28 days; however, a range between 21 and 37 days is considered normal [37].

In this section, we will describe the three main phases of the menstrual cycle.

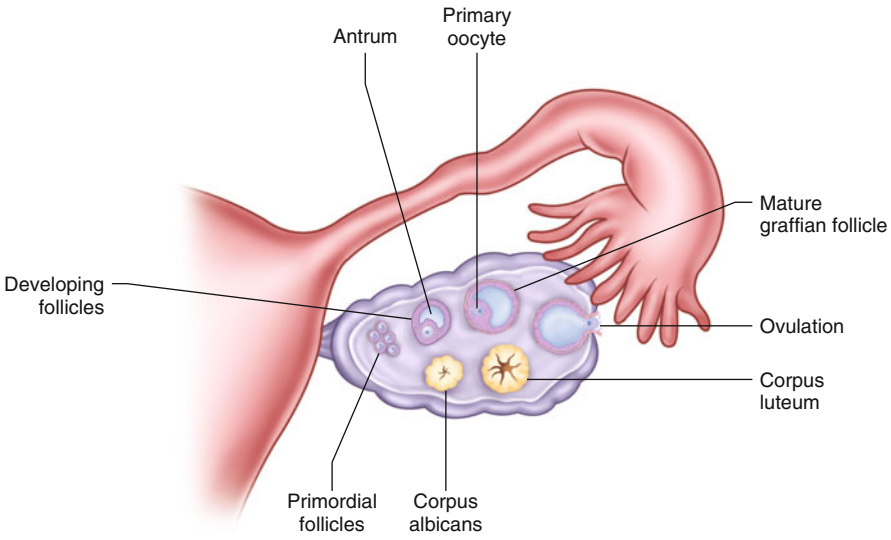

Fig. 4.2 Schematic representation of events occurring in the ovary during a complete follicular cycle

Phase 1: Follicular Phase

The follicular phase refers to the initial half of the cycle where recruitment and growth of the follicle take place; in a 28-day cycle, it corresponds to Day 0–13. Day 0 is assigned to the first day of menses when there is a low level of circulating estrogen and progesterone from the previous cycle, in response to the low levels of these hormones, the negative feedback of FSH (and to a lesser extent LH) to the anterior pituitary is removed. This stage also corresponds to the pulsatile mode of GnRH secretion where GnRH pulses can again cause an increase in LH and FSH levels. Initially, FSH release is preferentially higher due to the lower levels of estradiol which exerts a negative feedback effect on LH in the pituitary as mentioned above [11]. The increasing amount of FSH levels activates the FSH receptors on the granulosa cells and causes recruitment of follicles in the ovary which are propelled from primordial follicles to the preantral stage. At the preantral follicle stage, the follicle is a two cell (granulosa and theca cell) two gonadotropin (FSH and LH) system. Subsequently, the thriving granulosa cells cause estradiol levels to rise.

The dominant follicle also called the graffian follicle is selected between days 5–7 and this is the time that the dominant follicle develops receptors for LH. The physiologic mechanism by which the dominant follicle is selected has not been fully elucidated; however, this follicle has been shown to express a high concentration of FSH receptors [38]. As mentioned earlier, initially FSH release is greater

than LH, by mid- to late-follicular phase, an inhibitory signal develops for FSH and its level starts to decline. At this time, LH pulsatile release increases in frequency. Due to the declining level of FSH, non-selected follicles undergo atresia and the dominant follicle is spared as a result of its high density of FSH receptors and continues to secrete estradiol, and by this stage the dominant follicle also possesses LH receptors which respond to the increasing levels of LH [8–10].

Phase 2: Ovulation

As estradiol levels increases, a positive feedback loop is created for LH which leads to the ovulatory phase [11]. *Estrogen reaches a critical level at around 200 pg and is maintained for a sufficient duration of time which results in an LH surge*. The surge mode of GnRH secretion generates the preovulatory LH surge which triggers ovulation which occurs *about 36–44 h after the LH surge*, which is the process in which the oocyte is expulsed from the follicle. Though complex, the ovulatory phase is relatively short and corresponds to Days 13–14.

Phase 3: Luteal Phase

The luteal phase corresponds to Days 14–28; after ovulation, the evacuated graafian follicle becomes the corpus luteum, a temporary endocrine structure which secretes the hormone progesterone which is considered the "pregnancy hormone" as it is geared to support and maintain pregnancy. In the luteal phase, elevated circulating estradiol and progesterone suppress LH and FSH levels through negative feedback effect [39]. The lifespan of the corpus luteum is about 14 days. A sustained corpus luteum aids with implantation and retention of the pregnancy until B-HCG, produced from the fertilized egg, intervenes and contributes to maintaining the pregnancy. If the released egg is not fertilized, the corpus luteum regresses to become the corpus albicans. Progesterone is then no longer secreted and ongoing support of the endometrium is withdrawn, triggering a menstrual cycle. The levels of estradiol and progesterone plummet, and due to these low ovarian steriods, the feedback inhibition at the level of the hypothalamic-pituitary axis is removed. FSH levels start to rise and a new cycle is initiated (Fig. 4.3).

The ovaries produce other protein and hormones such as inhibin, activin, follastatin, and insulin growth factor (IGF) which play a critical role in the menstrual cycle and feedback mechanism [40]. Activin and inhibin are two closely related protein complexes that have opposite effects. Activin enhances FSH biosynthesis and secretion while inhibin downregulates FSH synthesis and inhibits FSH secretion [41]. There are two types of inhibin; A and B. Both possess a common alpha subunit but have different beta subunit. Inhibin *B* reaches a peak in the early- to mid-follicular phase, and a second peak at ovulation. Inhibin *A* reaches its peak in

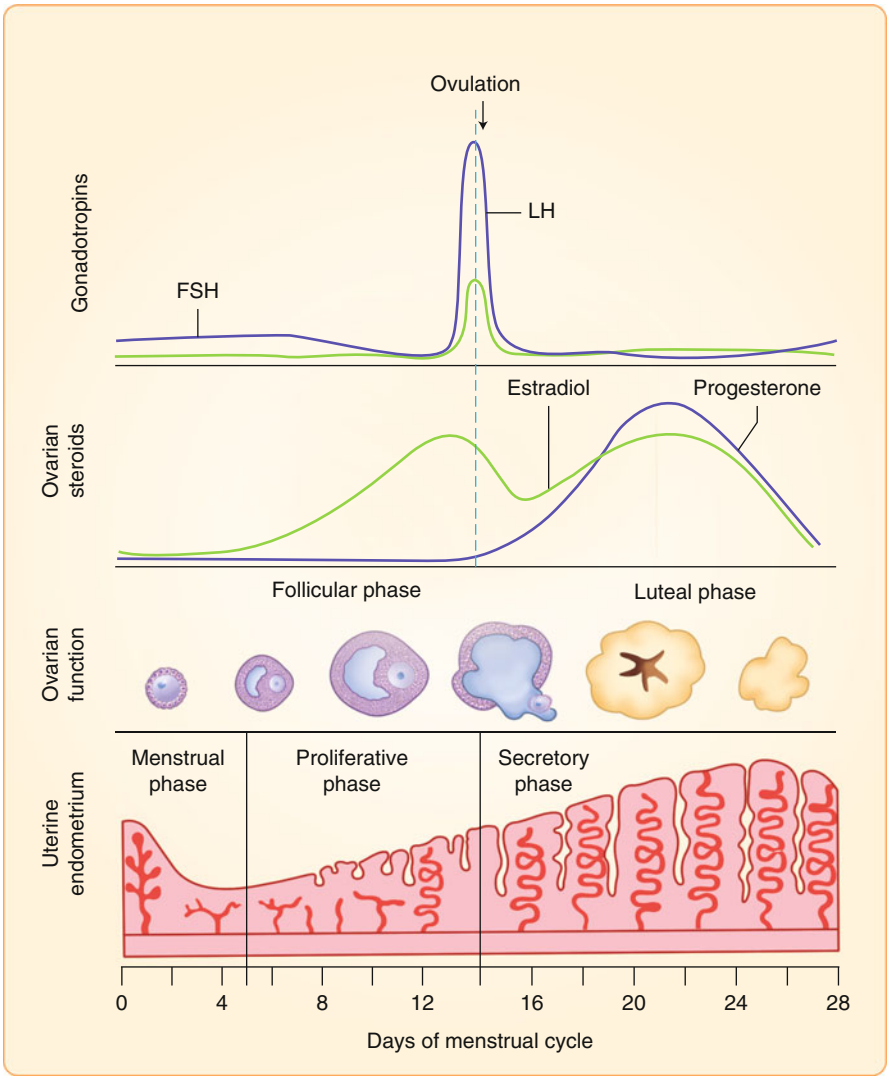

Fig. 4.3 Hormone levels during normal menstrual phase

the mid-luteal phase. Inhibin secretion is diminished by GnRH, and enhanced by insulin-like growth factor-1 (IGF-1). Follistatin is secreted by the ovaries and binds activin to decrease its activity thereby inhibiting FSH secretion [40]. IGF I and II promote steroidogenesis in theca and granulosa cells [34, 40, 42–44]. The insulin-like growth factors are peptides that are structurally similar to insulin and mediate growth hormone action. They induce the expression of cellular genes responsible for cellular proliferation and differentiation. IGF I has been demonstrated to stimulate DNA synthesis, steroidogenesis, aromatase activity, LH receptor synthesis, and

inhibin secretion. IGF II stimulates granulosa mitosis. All these hormones work synergistically to orchestrate the process of the menstrual cycle.

Endometrium During the Menstrual Cycle/Uterine Cycle [38]

The endometrium also responds to hormonal fluctuations during the menstrual cycle and has its own distinctive response. The epithelium lining the glands, stroma, and vasculature of the functional layer of the endometrium undergoes well-defined morphological changes. Similar to the ovarian cycle, there are also three main phases of the uterine cycle.

Menstruation Phase

When levels of hormonal steroid secretion decline as a result of corpus luteum regression, the menstrual cycle moves to the menstrual phase (menstruation), which signifies a failure to conceive. The spiral arteries of the endometrium constrict reduce the blood flow to the endometrium. Macrophages and leukocytes then invade the stroma and phagocytize the ischemic tissue. Eventually, the uterine lining sloughs off and is expelled through the vagina. This is the first day of menses, also described as a period. The normal duration of a period is less than 7 days and normal blood loss defined as less than 80 cc.

Proliferative Phase

This corresponds to the ovarian follicular phase, gradually rising estradiol levels lead to stimulation of the endometrium, allowing it to grow to a thick, blood vessel-rich, glandular tissue layer in preparation for pregnancy.

Secretory Phase

The last phase named the secretory phase (coincides with the ovarian luteal phase); once ovulation occurs, in addition to estrogen, the ovary also produces progesterone. This changes the proliferative pattern of the endometrium to a secretory pattern and is the time for continued increased vascularity in preparation for implantation.

Stages of Puberty

Puberty occurs as a result of hormonal influences and consists of a series of events that have been studied and described. While these events are mostly predictable, one must keep in mind that there is normal variance within ethnicities and environments.

Adrenarche is a process that typically occurs before the onset of puberty and refers to the activation of the adrenal cortex leading to the production of adrenal androgens [39]. Normal adrenarche may occur around the age of 6 years, when the zona reticularis of the adrenals respond to ACTH from the pituitary with the end product of DHEA-S and other androgens. The adrenals produce DHEA, DHEA-S, Androstenedione (all precursors of testosterone), testosterone, and androstenediol. Though it appears to be unrelated to the HPO axis, as mentioned earlier DHEA-S has been implicated in the upregulation of GnRH [27]. It has been hypothesized that adrenarche contributes to the triggering mechanisms of puberty and can perhaps be viewed as the initial stage of puberty. With the activation of the HPO axis, the ovaries also start to produce the androgens testosterone, androstenedione, and DHEA. DHEA-S is unique to the adrenals and can be used as a marker of adrenal androgen secretion.

Ultimately, androgens in the female (from the adrenals, ovaries, and peripheral conversion) contribute to the growth of sebaceous glands and promote hair growth in the axillae, pubis, and extremities. Abnormal production can lead to hirsutism and virilization. Estradiol, the main product of the follicle predominates during female development and promotes cellular differentiation and growth of primary sex organs: fat deposition, growth of breasts, oviducts, uterus, vagina, and external genitalia. Estradiol is also the principal hormone driving the pubertal growth spurt of females by increasing osteoblastic activity, epiphyseal maturation, and closure. Estrogen stimulation of the vagina mucosa also causes elongation of the vagina and a normal physiologic discharge which is a thin clear-white and non-foul smelling body fluid. All these increases in different hormonal levels manifest into the physical signs of puberty.

The earliest noticeable sign of puberty in the majority of females is breast development (therlache). Under the influence of estrogen and other steroids, the internal structure of the breasts starts to develop. Growth of underarm/pubic hair (Pubarche) follows, a process driven by androgens. Peak height velocity (growth spurt) occurs about 0.5 years prior to menarche and this process occurs earlier in females as compared to males. The first menstrual period (menarche) marks the end of puberty. Thus, the most common sequence of events during puberty is as follows: Thelarche > Pubarche > Growth spurt > Menarche.

Dr James M Tanner, a British pediatrician performed a study to describe the progression of puberty in males and females based on measurements and observation of secondary sexual characteristic development in males and females. In June of 1969, Drs. Marshall and Tanner published the Tanner Sexual Maturity Rating system (SMR) (also referred to as Tanner staging), a scale that ranges from prepubertal (stage I) to adult (stage V) and is wildly utilized in assessing human sexual

Table 4.1 Breast development

- Stage I (B1)—prepubertal; flat appearance with only the papilla (nipple) raised
- Stage II (B2)—the breast bud is present so that the areola protrudes
- Stage III (B3)—the breast tissue extends past the areola causing the elevation of the breast along with the areola. The contour of the areola is the same as the rest of the breast
- Stage IV (B4)—areola forms a separate contour from the rest of the breast creating what is referred to as the "mound on the mound" appearance
- Stage V (B5)—adult; the areola flattens down assuming the contour of the rest of the breast

Data from: American College of Obstetrics and Gynecology. Tool Kit for Teen Care: Tools for Adolescent Assessment. 2nd edition. 2010

Table 4.2 Pubic hair development

- Stage I (P1)—prepubertal, lanugo may be present in genital area but it is fine and downy
- Stage II (P2)—sparse growth of pubic hair in the midline, mainly at the base of the penis or along the labia majora
- Stage III (P3)—more hair grows so that it is visible from several feet, along with coarsening and increased pigmentation in some people
- Stage IV (P4)—hair now makes a triangle over the pubis
- Stage V (P5)—adult; hair is outside of triangle, extending up the abdomen and down the thighs

Data from: American College of Obstetrics and Gynecology. Tool Kit for Teen Care: Tools for Adolescent Assessment. 2nd edition. 2010

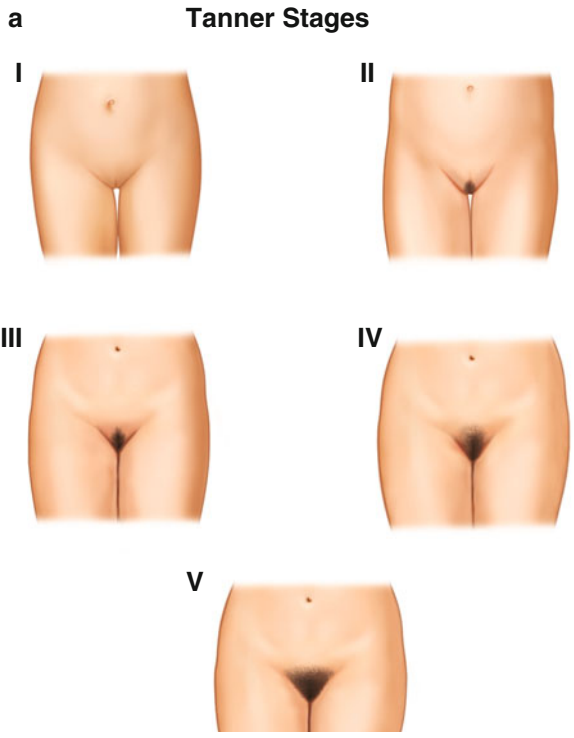

Fig. 4.4 Tanner stages of pubic hair (**a**) and human breast (**b**) development. (Created from data in Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969 Jun;44(235):291–303)

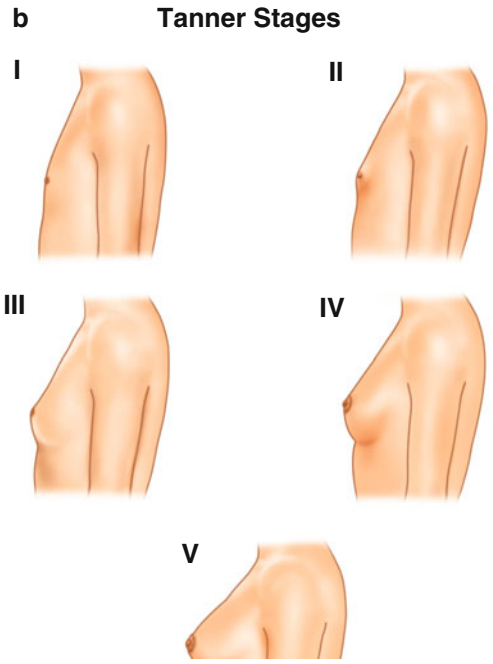

Fig. 4.4 (continued)

development. In the female, it describes the stages of puberty as based on breast size (B) and shape, and pubic hair (P) development and distribution (Tables 4.1 and 4.2, and Fig. 4.4a, b).

Nonetheless, despite achieving menstruation, the initial 3 years after menarche can be anovulatory. This is due to the delayed maturation of the positive feedback by estradiol [45]. A regular menstrual pattern is usually achieved by the third year post menarche. Furthermore, it is important to understand that ovulation is necessary for fertility, but may or may not accompany the earliest menses.

Age of pubertal onset and menarche is influenced by several factors and varies by geographical area and culture. In the United States, there is controversy regarding earlier sexual maturation as compared to data from the nineteenth century [46–52].

Dr. Henry P. Bowditch, an American physician, is often referred to as the pioneer of the study of menarche in the United States due to his publication in 1877 in which he reported the mean age of menarche as 14.75 [53]. Studies since then have indicated an earlier age of menarche. The first pubertal timing data on a representative US population was conducted by the CDC in a study called the National Health Examination Survey (NHES III) from the time period of 1966–1970. Results described the secondary sexual characteristics of American youth, ages 12–17 finding a mean age of menarche at 12.77 years. It was also noted in this study that African American girls were consistently more advanced than Caucasian girls for each chronologic age [54].

Table 4.3 Mean age of pubertal development summary of finding from various articles using data set from NHANES III

	African American	Mexican American	Caucasian
Thelarche (years)	9.5	9.8	10.3
Pubarche (years)	9.4	10.4	10.6
Menarche (years)	12.06	12.25	12.55

Data from: Sun et al. Is sexual maturity occurring earlier among U.S. children? Journal of Adolescent Health 2005 Nov 37 (5): 345–355; Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988–1994. Pediatrics. 2002 Oct;110(4):752–7; Sun SS, Schubert CM, Chumlea WC, Roche AF, Kulin HE, Lee PA, Himes JH, Ryan AS. National estimates of the timing of sexual maturation and racial differences among US children. Pediatrics. 2002 Nov;110(5):911–9

Table 4.4 Mean age of pubertal development summary of finding from PROS Study

	African American	Mexican American	Caucasian
Thelarche (years)	8.87 SD 1.93	ND[a]	9.96 SD 1.82
Pubarche (years)	8.78 SD 2.00	ND[a]	10.51 SD 1.67
Menarche (years)	12.16 SD 1.21	ND[a]	12.88 SD 1.20

Data from: Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997 Apr;99(4):505–12

[a]No data available

More recently, new data has been emerging studying development in different ethnic groups. Most recent National data comes from National Health and Nutrition Examination Survey (NHANES III), a survey carried out in the United States from the time period of 1988–1994. Mean age of menarche in this group was 12.43 years (Table 4.3) [48, 55, 56], with results revealing that African American girls and Hispanic girls tend to reach onset of puberty earlier as compared to their Caucasian peers [51, 52].

The Pediatric Research in Office Setting (PROS) network study [57] is the largest study to date and was a cross-sectional study of 17,077 girls ages 3–12 who presented to their pediatricians office from July 1992 to September 1993 and needed a complete physical exam. Tanner staging was utilized by the pediatricians in the collection of data. The data suggested that the girls were developing pubertal characteristics from an early age, even earlier than previously reported (Table 4.4).

Results from above-mentioned studies and others lead to the question as to whether American girls are reaching puberty at an earlier age. A review of sentinel articles performed by Slyper et al. looking at mean ages of secondary sexual characteristics using data available between 1948 and 2003 concluded that American girls are presenting to their physicians' offices with evidence of breast budding at a younger age. However, there has been little change in the timing of menarche with a mean age that is steady at approximately 12 years of age [46]. In an attempt to reach a consensus, an expert panel was asked to evaluate the weight of the evidence

available from all studies to date regarding puberty in American girls [49]. The entire panel did not reach the same conclusion; however, majority of the experts concluded that there was sufficient data to suggest a secular trend towards an earlier age of onset in breast development. In addition, the panel recommended the development of methods to discriminate fat versus breast tissue. Regarding menarche, majority of the experts based their conclusion mainly on results of the NHES III and NHANES III studies, and concluded that the data is sufficient to suggest a secular trend toward an earlier age of menarche given the decrease of approximately 2.5–4 months in the age of menarche between these two national studies. The minority did not believe that this was a significant difference to draw such a conclusion, thus it appears that the controversy regarding changes in menarche remains. Environmental factors such as obesity resulting in rapid body growth have also been implicated as a potential reason for reaching menarche earlier, but the evidence is inconclusive [46, 48, 56].

Psychosocial Development

Paralleling the biological process of puberty, the psychology of puberty is also quite complex. It is imperative that young women are provided with information regarding the changes their body is experiencing. There are additional implications as there can be a sense of confusion and a lack of understanding why the body is changing. In some cultures, it is considered taboo to discuss sexuality and yet the society in which our young women grow up in is becoming increasingly surrounded by sexuality. Furthermore, increase in sex hormones influences sexual behavior as neuropeptides involved in upregulation of GnRH are known to influence sexual behavior by acting mainly in the hypothalamic nuclei [58]. At the end of puberty, the young female becomes capable of participating in sexual reproduction, but not psychologically mature enough to be fully independent. The stage of adolescence which continues after puberty is divided into three periods: early (ages 11–13), middle (ages 14–16), and late (ages 17–20) [59]. The initial concerns among adolescents typically center around whether they are normal and fit in with their peers. Body image becomes the main focus following this, and certainly early or delayed puberty may result in distress or low self-esteem through alienation from peers [59, 60]. After this initial awareness, the stage of experimentation and authoritative defiance occurs as teens attempt to gain independence. This population is especially vulnerable for engaging in risky behaviors. Finally, towards the end of adolescence, the emerging young adult starts to think about the future and true independence. Some go through these stages smoothly while others do so with lots of turmoil. Throughout these stages friends, peers, school, and the family unit all play a critical role [61]. Healthcare providers who care for this population are also in a position to help with this transition. Imbalances can lead a young person down the wrong path. Therefore, it is important to be in a supportive environment where the adolescent develops a healthy identity and a sense of self.

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Chapter 5
Fetal and Neonatal Puberty

Nancy A. Sokkary

Abstract Pubertal development begins in utero with the formation of the fetal ovary, foundation of the hypothalamic-pituitary-ovarian axis, and production of sex hormones. Development of the fetal ovary and hormone production is incredibly complex. It has been studied extensively but the exact embryologic origin of the ovary remains uncertain. The gonadotropin and subsequent ovarian hormone production has been well documented, but the exact mechanism of the cycle is unknown. There are several physical findings that occur as a result of early hormonal exposure. Most of these findings are benign and self-limited, but it is important to be familiar with situations that are outside the realm of normal. There are circumstances where the hormonal milieu at birth is associated with developing medical complications later and these situations should be recognized.

Keywords Neonate • Fetus • Ovarian development • Hypothalamic-pituitary-ovarian axis development

The Fetal Ovary

Differentiation of Gonads

For the first 7 weeks of fetal life the gonads are identical in males and females [1]. The urogenital ridge is composed of the mesonephros and the gonadal ridge [2]. During week 5 the indifferent gonads develop from a protrusion in the urogenital ridge on the medial side of the mesonephros, forming the gonadal ridge (Fig. 5.1) [3].

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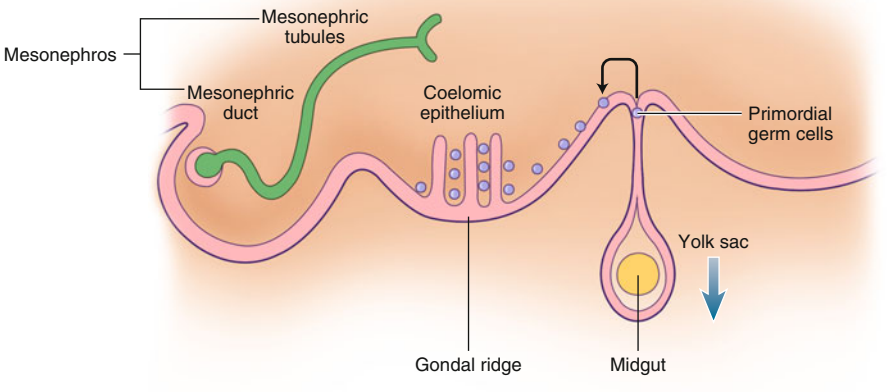

Fig. 5.1 The urogential ridge: The gondal ridge develops as a protrusion in the urogential ridge between the mesonephros and midgut. Gonadal formation will begin here as the primordial germ cells migrate and mature

The earliest form of the gonad contains germ cells and somatic cells. The somatic cells are likely derived from mesonephros, mesenchyme, and coelomic epithelium [2]. The coelomic epithelium is the fluid-filled cavity between intestines and the body wall. It is lined with mesonephros and develops into the peritoneal, pleural, and pericardial cavity [1]. The primordial germ cells are derived from the ectoderm. Germ cell migration to the gonadal ridge is signaled by adhesive and chemotactic peptides. This migration is necessary for the germ cells to survive and function properly, for both males and females [2].

The process leading to ovarian differentiation remains largely unknown. It is known that two factors are necessary for formation of a normal ovary: suppression of testicular development and functional ovarian germ cells. Extensive research has led to several plausible hypotheses of how these processes occur. Testicular development may be inhibited by reduced levels of *Sox-9* as a result of *WNT-4* and *RSPO1* suppression of fibroblast growth factor (FGF)-9 [2, 4]. A protein named Sprouty2 may also play a role in this suppression [2]. Ovarian development relies on the presence of viable germ cells [4]. Primordial germ cells then enter the outer cortical region of the ovary. If they fail to migrate to the genital ridge, the germ cells are abnormal, or if there is failure in the signaling cascade the gonads will regress and vestigial ovaries (streak ovaries) will persist [4].

Ovarian Development

The germ cells will become the oogonia once they migrate into the gonad. Mitotic proliferation will begin while the germ cells are migrating and continue until approximately the fourth month of gestation [2, 4]. Towards the end of the fourth

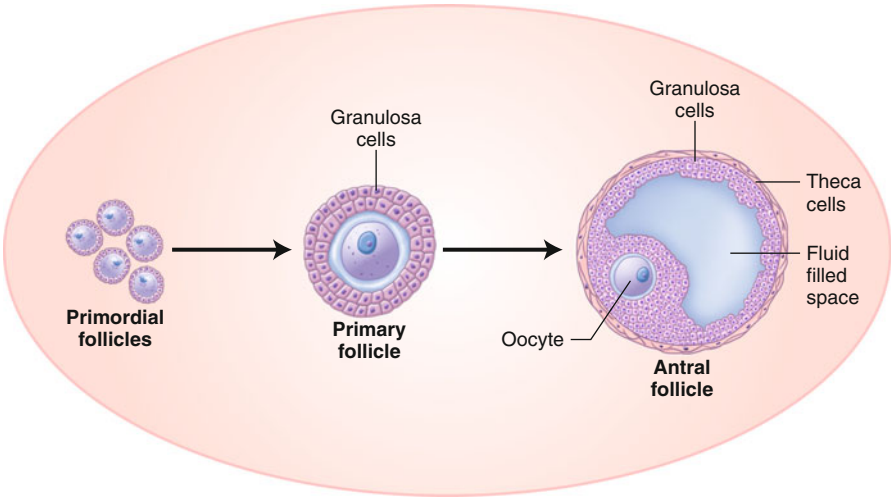

Fig. 5.2 Fetal ovarian development: Development of primordial follicle to the antral follicle. The antral follicle, formed by the third month of gestation, will contain thecal and granulosa cells surrounding oocyte

month the gonad will contain 6–7 million oogonia. Selected oogonia in the medullary region enter the first phase of meiosis I, prophase. The newly formed primary oocytes (gametes) will arrest in the dictyate phase, or diplotene phase of prophase I. They will remain in this resting phase until an oocyte is selected for ovulation in the postpubertal female. This arrest is likely maintained by inhibiting substances produced by the granulosa cells.

Follicle Formation

The origin of the follicle is not completely understood. Current evidence suggests these cells come from the primitive sex cords of the mesonephros, coelomic epithelium, or a combination of both [4]. The somatic cells surrounded by coelomic epithelium and mesenchyme likely go on to form follicular cells. These cells will go on to be the pregranulosa cells. The pregranulosa cells will surround individual oocytes to form the primordial follicle. The final stage in development is maturation of pregranulosa cells to granulosa cells. Approximately 105 granulosa cells will surround the oocyte to form a primary follicle (Fig. 5.2) [2]. Primary follicles are present in the fetal ovary from approximately 20 weeks [5]. The remainder of the mensynchemal tissue will become the primitive ovarian stroma that separates the primary follicles.

Finally, during the third month of gestation, antral follicles will develop. Preantral follicles are formed by the sixth month of gestation when the granulosa cells have completed their maturation process [6]. The antral follicle contains a large fluid-filled space; it is at this time that theca cells surround the follicles (Fig. 5.2) [2].

The production of estrogen is produced in low levels from as early as 9 weeks according to some sources, while other studies have been unable to identify estrogen production until later in pregnancy after follicular maturation occurs [2, 3]. At least some of the estrogen that the fetus is exposed to comes from maternal conversion. Estrogen is produced through a series of hormonal conversions starting in the fetal adrenal gland, then through the fetal liver and placenta, and finally conjugation by maternal liver [6]. There is no known effect of estrogen on female sexual differentiation in the fetus. Unlike males, the internal and external genitalia will develop without hormonal signaling.

Neonatal Ovary

At the time of birth the ovary is approximately 1 cm in diameter and weighs between 250 and 350 mg. The neonatal ovary will have all the structural components of the adult ovary including the medulla, inner cortex which contains the follicles, outer cortex, and hilum. It contains at most two million oocytes due to rapid atresia. Most of these oocytes will be in the form of primordial follicles with varying degrees of maturation [2].

Development of the Hypothalamic-Pituitary-Ovarian Axis

The hypothalamic-pituitary-ovarian (HPO) axis is an incredibly complex interplay of positive and negative feedback between the ovary, hypothalamus, and pituitary. This pathway in females is controlled primarily by gonadotropin releasing hormone, luteinizing hormone, and follicle stimulating hormone (FSH). Normal development relies on a delicate balance of these entities starting in utero.

Fetal Gonadotropins

The HPO axis also begins to function in the neonatal period. Luteinizing hormone (LH) and FSH are produced by the anterior pituitary in response to signaling from the hypothalamus [7]. Early literature suggests that the axis is developed and producing LH/FSH by 68 days of gestation [8]. As discussed previously, there is very low if any estrogen production in female fetuses. Unlike males, this lack of negative feedback results in higher levels of gonadotropins, specifically FSH.

In utero, the FSH peak is at midgestation and then steadily declines. The exact mechanism of decline is unknown but it may be related to inhibin secreted from both the ovary and possibly the placenta [9]. When the pituitary gland of fetuses was studied for concentration and content of FSH it was noted that the peak levels were between 25 and 29 weeks, the same time primary follicles are first able to be identified.

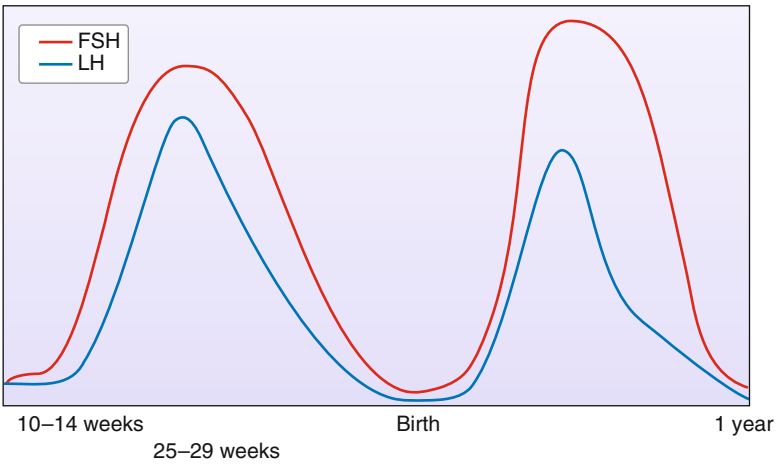

Fig. 5.3 Relative gonadotropin serum levels: Fluctuation in LH and FSH from birth to 1 year of life. Serum levels of both peak between 25 and 29 weeks gestation in utero and again shortly after birth. In the normal female fetus, the FSH levels are higher than LH during both peaks and most of development

After this time the concentration slowly declines (Fig. 5.3) [7]. This suggests that the production and release of FSH into circulation follow the same pattern.

When LH content of the pituitary of female fetuses was studied, there was a sharp rise noted between early second trimester (10–14 weeks) to late mid-trimester (25–29 weeks) (Fig. 5.3). The patterns of LH and FSH change as well as the concentration at any given gestational age are markedly different between male and female fetuses. Even in utero female fetuses have significantly higher FSH levels. Difference in LH levels among extreme premature infants suggests that LH is higher in male; however, this phenomenon is not as well documented [7, 9]. Interestingly, when the gonadotropin content of the pituitary was studied females had higher concentration of FSH and LH than their male counterpart [7].

Inhibin production also begins in utero as well. It appears to be elevated throughout the third trimester and is significantly higher in males at any gestational age. It is known that the fetal testis begins to synthesize inhibin before the fetal ovary which likely explains the higher concentration in the male fetus [9]. However, it has been noted that there are several non-gonadal origins of inhibin as well. The adrenal gland and placenta have both demonstrated synthesis and secretion of inhibin; this is likely the origin of inhibin production in females during early gestation [9].

Neonatal Gonadotropins

It has been noted that both LH and FSH surge after birth in females, but not males [10]. The exact timing of FSH peaks in the neonatal period remains unknown, but is likely between 2 and 4 weeks of life [10]. FSH levels rise significantly even during

the first 28 days of life. One study found an average of FSH of 2 mIU/mL at birth and 10 mIU/mL at day 28 among term, female infants [11]. FSH is produced at higher levels during the first year of life than in a postpubertal female at any point during the menstrual cycle (Fig. 5.3) [6]. This elevation is likely related to the lack of maternal estrogen after birth, hence less negative feedback to the HPO axis [10]. This elevation persists, although at a lower level, through the neonatal period and into infancy.

LH and inhibin are produced at levels similar to the follicular phase of the menstrual cycle in the neonatal period. These are generally low levels [9]. The differing levels of circulating gonadotropins have several fetal and neonatal affects that will be discussed at the end of the chapter.

There is good evidence that premature infants are born with significantly higher levels of FSH and LH and that female infants have a lower LH/FSH ratio. As the gestational age at birth increases (towards 40 weeks), the FSH and LH decline [7, 9]. It is unknown why premature female infants have such high levels of FSH but it is likely related to an immature HPO axis, or lack of negative feedback. The mechanism may also be gender-dependent as the levels of gonadotropins differ significantly, both in synthesis and secretion, between male and female infants [7, 8].

Hormone Exposure in the Neonate

The female fetus is exposed to some level of estrogen in utero. This exposure as well as changes in multiple other circulating hormones as the infant transitions from fetal to postpartum life have multiple effects. Distinguishing normal from abnormal can be difficult. Maternal hormones can result in several physiologic findings in the new born such as ovarian cyst, transient breast tissue growth, and vaginal maturation. Other aspects of neonatal development can actually have an impact on pubertal development later in life.

Ovarian Cysts

Neonatal cyst production begins in utero. Late in gestation, fluid-filled antral follicles are present. The exposure to LH results in a yellow coloring of the cyst and when examined microscopically vacuolization of follicular and thecal cells can be seen. Why one particular follicle is selected to grow into a large cyst is not known. It is known that certain maternal conditions are associated with development of fetal cysts such as diabetes, preeclampsia, and isoimmunization. After withdrawal of maternal estrogen and peak of LH and FSH shortly after birth these cyst usually resolve spontaneously [6, 12]. Up to 50 % of fetal cyst will resolve by 1 month and the majority by 3 months although some can take up to 6 months [13].

Fetal and neonatal ovarian cysts are usually detected incidentally on antenatal ultrasounds. When a fluid-filled non-midline pelvic mass is detected in the female neonate an ovarian cyst should be suspected. A single fluid collection is more consistent with a simple ovarian cyst; however they can be bilateral about 4 % of the time [14]. It is important that urinary, gastrointestinal, and reproductive tract anomalies are ruled out as they can have similar presentations.

These simple cysts can range in size which helps diagnosis and management. Fluid collections in the adnexa that are less than 2.5 cm are considered normal follicles. In utero serial ultrasounds can be done to assess for growth of the cyst but most remain the same from the time of diagnosis to delivery. Some authors have advocated for cesarean section if the cyst is greater than 4 cm, but this is not universally done [14]. Postpartum, those that are large enough to obstruct the bowel or urinary system should be managed promptly. Additionally, ultrasound findings that are suspicious for torsion (presence of debris, retracting clot, septations, or lack of flow) or malignancy should be treated sooner [14]. Asymptomatic simple cysts that are in between can be managed expectantly with ultrasound every 4–6 weeks until 6 months of age. Some advocated drainage of cysts that are greater than 5 cm due to risk of torsion [15]. It is agreed that cysts that have not regressed by 6 months, are getting larger on ultrasound, or are symptomatic should be treated. Laparoscopic cystectomy is reasonable; however if the cyst is simple, transabdominal drainage is a less invasive approach. Cysts that are complex or excessively large should be removed via laparoscopy or laparotomy [6, 15].

Premature Thelarche

Hormonal exposure in the neonate can also stimulate breast development. This benign form of premature thelarche is seen within the first few weeks of life. It is usually self-limiting and will resolve in the first several months of life without intervention. It can be associated with a white-thin nipple discharge, similar to breast milk. Expressing the nipple, or other stimulation, can prolong the time until regression and should be avoided [16]. True premature thelarche has a prevalence of 2 % and is most often seen between 1 and 3 years of age. Because true premature thelarche is most common at a young age it is important to assure resolution of neonatal breast development within the first 6 months of life [16].

Vulvovaginal Maturation

The clitoral size of a full term infant is 2–8 mm in length and 2–6 mm in width [17]. The clitoris is responsive to androgens at birth and definitely in utero because cliteromegaly is often present in infants with androgen exposure in utero such as

congenital adrenal hyperplasia and possibly neonate premature neonates. Some argue that the lack of vulvar fat pad in preterm neonates gives the appearance of an enlarged clitoris but the size is actually comparable to that of their full term counterparts [18].

The estrogen exposure from mom as well as the low levels of estrogen that can be produced from follicular cysts can result in labial edema in the neonate [6]. The hymen can also appear slightly enlarged and maybe confused with urethral prolapse or a vaginal lesion. Abundant hymenal tissue, although usually normal, can make it difficult to evaluate other structures such as the urethra and vaginal introitus. Normal levels of estrogen do not have a large impact on the clitoral structure [17].

Pubertal Development in the Low Birth Weight Infant

Several studies have now documented a link between low birth weight and early pubertal development. Small-for-gestational-age infants typically have a period of rapid weight gain to "catch up" to their peers. Increasing evidence suggests that this may be detrimental. By the age of 8 years, girls that had low birth weights tended to have higher body mass index' (BMI) than 8-year-olds with a normal birth weight. Likewise, rapid weight gain during the ninth and tenth month of life have been associated with higher BMIs by the age of 10 and a younger age of menarche [19]. Premature pubarche has also been well documented in females with low birth weight [20].

Additionally, low birth weight and accelerated weight gain postpartum has been associated with other health risks including glucose intolerance, hypertension, and elevated triglycerides. The exact mechanism is unknown but it is likely related to insulin, as this is known to be an important mediator of fetal growth. It has been postulated that insulin resistance begins in utero to spare nutrients in fetus' that are underweight [19]. Conversely, it is possible that abnormal phosphorylation of the insulin receptor associated with premature pubarche, ovarian androgen excess, and hyperinsulinemia is also responsible for abnormal fetal growth [20].

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Chapter 6
Central Precocious Puberty

Jennifer E. Dietrich

Abstract *Background:* Central precocious puberty occurs in 0.2 % of young girls and is officially defined as the presence of pubertal signs or characteristics in girls under the age of 7 years. This condition occurs as a result of early activation of the hypothalamic pituitary axis. The most common type is idiopathic, although this is diagnosis of exclusion. *Purpose:* To alert providers about the warning signs and when to intervene as if left untreated, central precocious puberty will result in progressive sexual characteristic development, early menstrual onset and rapid skeletal maturation, resulting in early epiphyseal stimulation. *Conclusions:* Central precocious puberty is an important condition to recognize. It is important to screen when advanced pubertal characteristics are seen under age 7 years. Once idiopathic precocious puberty has been confirmed there are many options for treatment with good long-term outcomes, which allow for attainment of predicted genetic height.

Keywords Central precocious puberty • Short stature • Diagnosis • Treatment • Idiopathic

Background

In girls, central precocious puberty is defined as the sign of secondary sexual characteristics occurring before the age of 7 years in Caucasian girls and 6 years in Black girls. It should be stressed however, that for any pubertal characteristics presenting before the age of 8 years in girls, a high index of suspicion should still remain [1–3]. This type of pubertal precocity is due to early activation of the

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hypothalamic pituitary axis. The overall prevalence is estimated to be 0.2 %. Fortunately, in 90 % of cases early puberty is idiopathic. This is the case even among patients with precocious thelarche who progress to central precocious puberty [4]. Nonetheless, 20 % of cases of central precocious puberty may be due to organic pathology within the brain [1–3]. There does appear to be a familial tendency as rarely central precocious puberty may be associated with autosomal dominant or X-linked mutations. Affected children with no familial tendency and no evidence of underlying organic central nervous system pathology in the setting of early development may ultimately be considered to have the idopathic type. Therefore, an MRI of the brain is helpful in determining the presence or absence of pathology. Common brain pathology resulting in organic causes of central precocious puberty includes hamartomas, granulomatous conditions, infections, trauma, and prior radiation. Any of these entities tend to result in early oversecretion of GnRH [1–3].

In the past the age limits for diagnosis were classically defined by two standard deviations (less than third percentile) below the mean age for pubertal onset. This was based on the work of Marshall and Tanner in the late 1960s [2, 5]. However, with a parallel decline in the mean age of menarche for girls over the last several decades, what is defined as the third percentile for meeting criteria of "too early" is now much lower than it was previously. Because of the changes in thinking with regard to the ages of normal and abnormal pubertal development, many pediatric endocrinologists are keenly aware that the change in thinking with regard to what is normal may miss 5–10 % of girls with pubertal signs who have underlying pathology. As a result, experts have recommended that the cutoff values for specific ages at which diagnostic evaluation is needed should not change at present to avoid a failure to identify children with rapidly progressive precocious puberty as well as failed detection of underlying pathology. The criteria for evaluation of central precocious puberty should rely on history, physical exam, evidence of pubertal progression, skeletal maturation, and growth tempo [2, 5].

If left untreated, central precocious puberty will result in progressive sexual characteristic development, early menstrual onset, and rapid skeletal maturation which result in early epiphyseal stimulation. Early epiphyseal stimulation results in tall stature initially; however, the epiphyses tend to fuse early with stimulation patterns that occur too early; therefore, a shorter predicted adult height occurs due to early epiphyseal closure [1–3, 5].

Presentation and Evaluation

The most common presentation is that of early pubertal development before age 7 years. The timing of symptoms as rapid and progressive versus slowly evolving is important since the development of signs and symptoms over several weeks time as opposed to several months time can be indicative of the type of underlying process [5]. For instance, with signs of central precocious puberty occurring quickly, a central nervous system lesion should be suspected. With signs occurring slowly, one

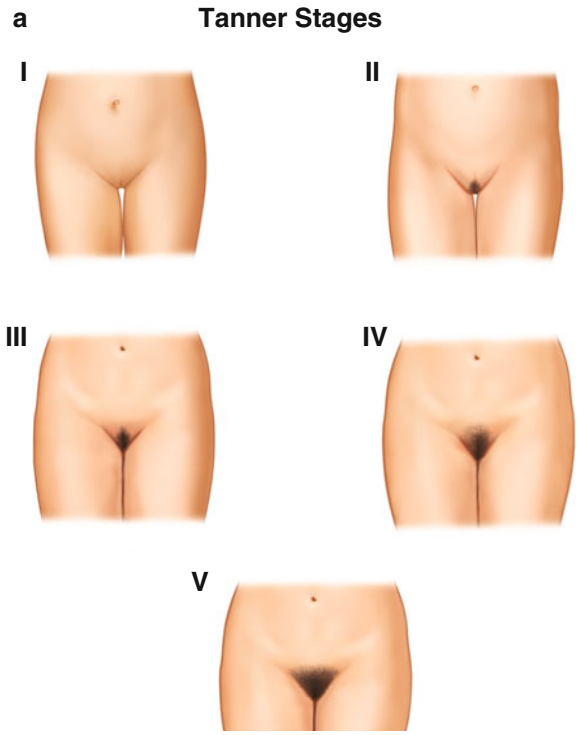

Fig. 6.1 Tanner stages I–V for pubic hair (**a**) and for breasts (**b**). (Created from data in Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969 Jun;44(235):291–303)

might consider underlying risk factors such as a history of precocious thelarche, precocious adrenarche, adrenal insufficiency, thyroid disease, brain trauma or infection, and irradiation to the brain. In the absence of these risk factors, idiopathic central precocious puberty is the likely diagnosis [5]. Nonetheless, at the time of initial presentation, it is important to review the history, perform a physical exam to check for Tanner stage of the breasts and genitalia (Fig. 6.1a, b), review growth charts and whether there have been major changes in percentiles from one curve to the next and to order additional studies, such as imaging and labs. Imaging studies include a bone age of the hand and wrist and a pelvic ultrasound to check the size of the ovaries and uterus and to exclude the presence of hormonal secreting cysts or masses. A bone age revealing advancement of greater than two standard deviations from the mean for chronological age is indicative of early hormone exposure resulting in bone maturation [5, 6]. Laboratory evaluation is also important to consider (Table 6.1). Because many causes for both central and peripheral precocious puberty can overlap, it is important to send tests that will help elucidate whether the early pubertal signs are caused by a central or peripheral process [2, 5]. A basal FSH and LH are very useful along with an estradiol level. Interestingly, high FSH in the

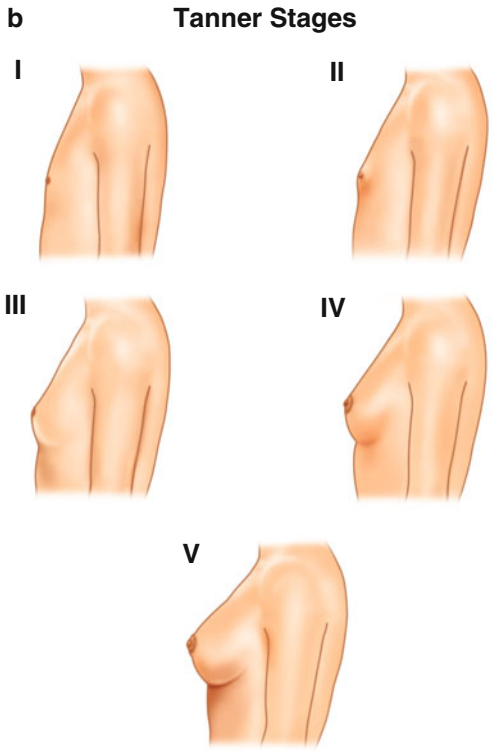

Fig. 6.1 (continued)

pubertal range or low estradiol in the prepubertal are not as sensitive as a basal LH or stimulated LH level of >5 IU/L. If the basal LH is not elevated, one remains clinically suspicious that a GnRH stimulation test may help elucidate further. If the stimulated LH level is >5 IU/L, a central process should be suspected and an MRI brain ordered to rule out pathology [7].

It is also important to send thyroid stimulating hormone, since an elevation in this hormone results in elevation of ovarian hormones [2, 5]. The same type of secondary trigger in ovarian hormones may occur in the setting of human chorionic gonadotropin secretion. Androgen levels, such as testosterone, DHEA-S, and 17-OH progesterone should also be sent as these hormones may be secreted by the ovaries or adrenal glands [8]. Whenever ovarian hormones such as estradiol or testosterone are significantly elevated, tumors should be suspected. Therefore, an MRI brain and pelvic ultrasound should be included in this initial workup (Fig. 6.2) [9]. Ovarian volumes and uterine size are helpful in some cases to predict early puberty, although it is important to recognize that some small ovarian cysts can also be normal in prepubertal girls [9].

Table 6.1 Laboratory work up for central precocious puberty

Serum human chorionic gonadotropin
Testosterone
DHEA-S
17OH progesterone
Estradiol
FSH
LH
TSH
Prolactin

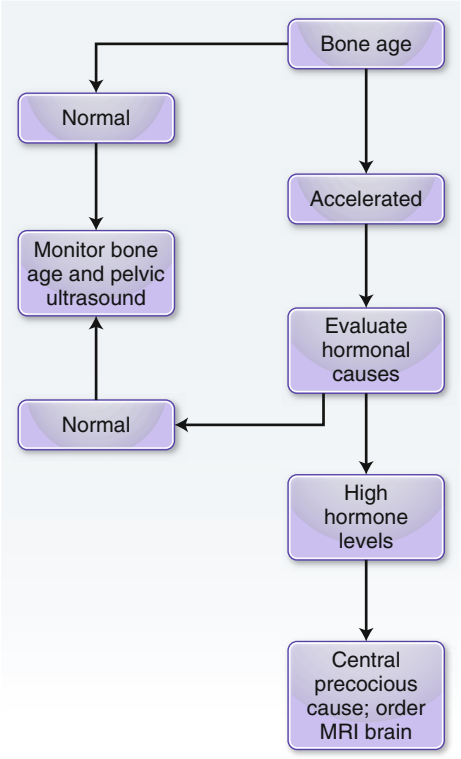

Fig. 6.2 Decision tree for additional evaluation of central precocious puberty based on bone age results

GnRH Stimulation Tests

There is one main confirmatory test utilized to confirm the diagnosis of central precocious puberty. This test is the gonadotropin releasing hormone (GnRH) stimulation test [10–13]. Typically, a dose of 20 μg/kg is given (max of 500 μg) and FSH, LH, and estradiol may be checked pre injection, and then again post injection at various intervals [10–14]. If the stimulated LH level is >5 IU/L, a central process

Table 6.2 GnRH stimulation test responses in types of precocious puberty

Type of precocious puberty	Gonadal size	FSH and LH	Estradiol and testosterone	DHEA-S	Stimulation test response
Idiopathic	Increased	Elevated	Elevated	Normal to elevated	Pubertal
CNS tumor	Increased	Elevated	Elevated	Normal to elevated	Pubertal
Peripheral	Increased	Suppressed	Elevated	Normal to elevated	Flat
Adrenal	Normal prepubertal	Normal	Normal to elevated	Elevated	Flat

should be suspected, but some authors have suggested that LH >9.2 IU/L increases the specificity for diagnosing central precocious puberty when truly present. Some studies suggest checking LH and FSH after GnRH is given at 30 and 60 min intervals, while others suggest repeating these at 1 and 3 h intervals to confirm if LH is elevated in the pubertal range by 3 h [14]. At least one study has confirmed that LH values at 30 min versus 3 h intervals were similar in their peak and that either values was sufficient for ruling in the diagnosis of central precocious puberty, thereby potentially reducing the amount of time patients spend undergoing diagnostic testing [15]. Nonetheless, the response to this hormone is important in order to distinguish between precocious puberty types (Table 6.2) [10–13].

Management

Treatment is indicated when a child in comparison to her age-matched peers has evidence of advanced pubertal development and skeletal age who is at risk for foreshortened height. The treatment of choice is GnRH analogues with the main goal of allowing for attainment of expected adult height [1–3, 6]. GnRH analogues work to fully saturate GnRH receptors at the level of the hypothalamus that when otherwise stimulated, will result in release of FSH and LH from the pituitary gland. Once these receptors are saturated, FSH and LH secretion is obliterated; therefore the hormonal stimuli causing early pubertal development are removed [1–3]. Several forms of GnRh are available: Leuprolide acetate pediatric at doses of 7.5–15 mg IM monthly, Histrelin acetate subcutaneous implant yearly or nafarelin acetate 16–1.8 mg intranasally daily [1–3, 5]. The goal of this hormonal treatment is to fully suppress the independent gonadotropin production, which results in early pubertal development [1–3]. Nonetheless, experts have cited risks as the potential for growth deceleration or unknown consequences of an extreme hypogonadotropic state. Studies do not universally support that this growth deceleration occurs, nor have available data suggested any long-term gonadal problem post treatment. During the course of therapy regression of pubertal characteristics,

height, hormonal suppression, and skeletal maturity are monitored. Therapy is continued until such time that the expected adult height (based on mid parental height) on treatment is achieved [16]. It is important to counsel families on expectations as well since children beginning therapy early as opposed to later when a child is perhaps further along in her pubertal advancement may not make up as much ground with regard to final height despite GnRH initiation. Literature definitely supports that GnRH therapy initiated before 5–6 years of age improves adult height [16–18]. Although hormonal suppression is the goal during the therapy, concerns about bone mineral density for children on GnRH analogues has been evaluated [17]. Although this hormone has more pronounced effects in adult women, these same effects are different in children as the GnRH in this instance merely restores them to the prepubertal state in which they would have had precocious puberty not ensued. It is thought that normal bone accretion occurs with no long lasting effects post therapy regardless of the length of time the therapy is required. Once therapy is complete, normal pulsatile secretion of the body's normal GnRH typically begins within weeks to months time, but has been reported to take up to 4.5 years [5, 17, 18]. Generally, pubertal tempo resumes and menstrual cycles are expected to occur normally. There is little long-term data on future effects with regard to fertility and offspring, but limited data do suggest normal fertility rates and normal offspring [5].

Counseling

Counseling patients and families is very important to help facilitate understanding of reversible and irreversible cause for precocious puberty and to educate about the potential for social stigma with short stature. In addition, early developmental processes in girls can cause them to feel self-conscious about being different than their peers because of such early pubertal changes [19].

Conclusions

Central precocious puberty is an important condition to recognize. It is important to screen when advanced pubertal characteristics are seen under age 7 years. If screening tests indicate a central pubertal process, ruling our central pathology is important as although idiopathic precocious puberty is most common, it is a diagnosis of exclusion. If central types are confirmed, treating the underlying pathology if present resolves the continued precocious development. In the case of idiopathic central precocious puberty, there are several options for treatment, allowing these affected children to better reach their genetic height potential.

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Chapter 7
Peripheral Precocious Puberty

Jennifer Bercaw-Pratt

Abstract Peripheral precocious puberty (also known as gonadotropin independent puberty) is the result of autonomous peripheral secretion of excess sex hormones independent of the hypothalamic-pituitary-ovarian axis. If left untreated peripheral precocious puberty can lead to central precocious puberty. The differential diagnosis includes sex hormone secreting tumors of the adrenal gland and ovary, McCune–Albright syndrome, Van Wyk–Grumbach syndrome, adrenal gland enzyme deficiencies, and exogenous exposure to sex hormones. The treatment of peripheral precocious puberty depends on the underlying cause.

Keywords Peripheral precocious puberty • Gonadotropin independent puberty • McCune–Albright syndrome • Van Wyk–Grumbach syndrome • Sex cord tumors of the ovary

Abbreviations

ACTH	Adrenocorticotropic hormone
FSH	Follicle stimulating hormone
GNAS	α-Subunit of the stimulatory G protein
GnRH	Gonadotropin releasing hormone
LH	Leutinizing hormone
SCTAT	Sex cord tumor with annular tubules
TSH	Thyroid stimulating hormone

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Introduction

A normally timed puberty results when pulsatile secretion of gonadotropin releasing hormone (GnRH) activates the hypothalamic-pituitary-ovarian axis in females [1]. Peripheral precocious puberty (also known as gonadotropin independent puberty) is the result of autonomous peripheral secretion of excess sex hormones independent of the hypothalamic-pituitary-ovarian axis [1]. If left untreated, peripheral precocious puberty can lead to central precocious puberty [1]. Depending on the type of excess sex hormone produced, the peripheral precocious puberty can be subdivided into isosexual where the secondary sexual characteristics are consistent with the patient's gender versus contrasexual where the secondary sexual characteristics are not consistent with the patient's gender.

Peripheral precocious puberty can occur from many different causes. The differential diagnosis includes sex hormone secreting tumors of the adrenal gland and ovary, McCune–Albright syndrome, Van Wyk–Grumbach syndrome, adrenal gland enzyme deficiencies, and exogenous exposure to sex hormones (Table 7.1).

The sequence and pace of pubertal development in children with central precocious puberty mimics normal pubertal development but is at an earlier age. If the sequence or pace of the puberty is disrupted, it is a suggestion of a peripheral source of gonadal hormones. Virilization in females with precocious puberty is typically only seen in peripheral precocious puberty.

When a female is diagnosed with precocious puberty an evaluation must be performed to determine if the puberty is centrally versus peripherally mediated. It is critical that a detailed history must be taken. The history of present illness must include information about the timing and progression of the secondary sexual characteristics. Exposure to any exogenous hormones should be discussed. The clinician should also question the caretakers about the use of any over-the-counter medications and/or homeopathic therapies.

Table 7.1 Differential diagnosis of peripheral precocious puberty

Adrenal causes	Ovarian causes	Other
Adrenal rest tumors	Sex cord stromal tumors such as Sertoli-Leydig, gynandroblastoma (arrhenoblastoma), sex cord tumor with annular tubules, thecomas	Van Wyk–Grumbach syndrome
Adrenal carcinomas and adenomas	McCune–Albright syndrome	Exogenous exposure to sex hormones such as oral contraceptive pills, topical hormone creams, and anabolic steroids
Adrenal gland enzyme deficiencies such as 21-hydroxylase deficiency	Germ cell tumors	

The stage of pubertal development can be assessed easily with physical exam. An assessment for signs of virilization and/or other phenotypic findings consistent with a specific cause of precocious puberty such as café-au-lait lesions should be noted when performing the physical exam.

During the evaluation of precocious puberty a GnRH stimulation test is often undertaken. The typical findings of peripheral precocious puberty during a GnRH stimulation test are a low baseline luteinizing hormone (LH) level and a suppressed level when stimulated with GnRH [2]. When peripheral precocious puberty is suspected, biochemical testing of testosterone, estradiol, cortisol, dihydroepiandrosterone, and 17-hydroxyprogesterone should be performed. Imaging of the adrenal gland and ovaries is indicated if extremely elevated estradiol and/or androgen levels are detected. A pelvic ultrasound is usually a good initial imaging technique for evaluating the ovaries. An ultrasound, CT scan, or MRI can be used to evaluate the adrenal glands.

Therapy for peripheral precocious puberty ultimately depends on the underlying cause. Females with tumors of the adrenal gland and ovary may be treated with surgery. Malignant tumors may require chemotherapy and/or radiation depending on the site and histologic type. Patients with defects in adrenal steroidogenesis should be treated with glucocorticoid therapy and mineralcorticoid therapy, if indicated. Van Wyk–Grumbach syndrome is treated specifically with thyroid hormone replacement. McCune–Albright syndrome is also different in that it is typically treated with therapies that inhibit estradiol action. While patients are treated for the cause of the peripheral precocious puberty, they must also be monitored for signs of continued development which may signify the onset of central precocious puberty [1]. The mechanism of the secondary development of central precocious puberty in patients with peripheral precocious puberty is not well understood [1].

McCune–Albright Syndrome

McCune–Albright syndrome is a rare cause of peripheral precocious puberty that typically affects girls. The estimated prevalence is between 1/100,000 and 1/1,000,000 [3]. The syndrome is a sporadic disease first described in 1936 by McCune and again by Albright. The syndrome is classically characterized by a triad of physical signs: café-au-lait pigmented skin lesions, polyostotic fibrous dysplasia of the bone, and peripheral precocious puberty. Other hyperfunctional endocrinopathies have also been reported such as pituitary adenomas secreting growth hormone and/or prolactin, hyperthyroidism, adrenal hyperplasia, and hypophosphatemic osteomalacia. Although traditionally described with the classic triad, there have been many reports of patients with suspected McCune–Albright syndrome presenting with only one or two of the classic symptoms [4].

The peripheral precocious puberty associated with McCune–Albright syndrome results from autonomous activation of gonadotropin receptors in the ovarian cells with subsequent estradiol production. This results in ovarian growth and cyst formation.

The typical phenotypic manifestations are rapidly progressive estrogen effects due to excessive estradiol secretion with vaginal bleeding often preceding any other visible signs of puberty. In this condition it is also possible for significant acceleration of growth velocity to occur which will compromise final adult height.

The typical café-au-lait spots of McCune–Albright Syndrome are hyperpigmented with irregular borders (often described as "the coast of Maine") that distinguish them from the smooth bordered lesions seen in neurofibromatosis. The spots are usually unilaterally distributed and observed on the same side as bone lesions, if present. The size and number are variable, but may increase with age [5].

Fibrous dysplasia is a developmental abnormality of bone that is characterized by a highly disorganized mixture of immature fibrous tissue and fragments of immature trabecular bone [6]. The typical radiographic appearance of these lesions is a hazy, radiolucent, or ground glass pattern resulting from defective mineralization of immature dysplastic bone [6]. The fibrous dysplasia lesions of the bone may remain silent for many years only to be revealed by spontaneous fracture or on the occasion of slight injury [5].

It has been determined that the syndrome is caused by post-zygotic activating missense mutations in the gene for the α-subunit of the stimulatory G protein (GNAS) that regulates cell function by coupling hormone and other receptors to adenylyl cyclase, with either cysteine or histidine substituting for arginine at position 201 [7]. The post-zygotic nature of the mutation results in somatic mosaicism with varied distribution of the defect in tissues and explains the broad spectrum of presentations. Successful diagnosis using GNAS mutation analysis in the blood has been reported to be associated with disease severity yet less than 50 % yield positive results in patients with the classic triad [8]. Genetic analysis of serum leukocytes for the GNAS mutation exhibits positive results in only 8–46 % of cases [9]. Mutation analysis may be performed on café-au-lait spots, however, only 27 % of cases may exhibit a mutation abnormality [9]. Analysis of affected tissues (with the exception of skin) yields the best results with >90 % of patients yielding a positive result; however, the invasive means necessary to obtain the affected tissue makes it difficult to take this diagnostic approach [9]. Thus, the diagnosis of McCune–Albright Syndrome remains challenging and primarily based on clinical suspicion.

Treatment of sexual precocity in McCune–Albright Syndrome is aimed at blocking sex steroid synthesis and counteracting the peripheral effects of these hormones such as pubertal development, menses, and bone advancement. As with other types of peripheral precocious puberty gonadotropin levels are often low or in the prepubertal range; thus, GnRH agonists have no utility as treatment unless there is evidence of concurrent central puberty. Surgical cystectomy and oophorectomy are ineffective since new follicular cysts may develop in the remaining ovarian tissue [10].

Several medications have been evaluated for the treatment of the peripheral precocious puberty seen with McCune–Albright syndrome; however, traditionally only two types of treatments have shown any real signs of promise: selective estrogen receptor modulators and aromatase inhibitors. Tamoxifen is a well-studied selective estrogen receptor modulator that has been used in the treatment of

breast cancer and has shown some efficacy in treating McCune–Albright related precocious puberty. A study showed that tamoxifen was effective in reducing vaginal bleeding episodes and growth acceleration in patients with McCune–Albright Syndrome, but the enlarged uterine and ovarian size in affected patients persisted [11]. Aromatase inhibitors have also been effectively used since the mid 1980s to treat the precocious puberty in McCune–Albright syndrome. These medications inhibit aromatase activity, thereby, decreasing estrogen biosynthesis. Testolactone, a first generation aromatase inhibitor, was shown to be partially effective, but the high doses required and dosing frequency made it an undesirable option [12]. Newer third generation aromatase inhibitors have also been studied due to their advantages of increased potency and once daily dosing. Letrozole has been shown to be effective in a small pilot study with reported decrease in growth rate and bone maturation without changes in ovarian volume [13]. Recently, a pure estrogen receptor blocker, fulvestrant, showed promising potential in a multicenter international study for the treatment of McCune–Albright syndrome [14]. Participants showed decreased vaginal bleeding and decreased rate of skeletal bone maturation without changes in ovarian volume [14]. As no completely effective treatment method for the precocious puberty of McCune–Albright syndrome has been found, it is still an extremely challenging disease to treat.

Van Wyk–Grumbach Syndrome

Van Wyk and Grumbach first described a syndrome of breast development, uterine bleeding, and multicystic ovaries in the presence of long-standing primary hypothyroidism in 1960 [15]. The typical presenting phenotype is precocious thelarche and uterine bleeding in the absence of pubic or axillary hair. Galactorrhea may or may not be detected in conjunction with these previously mentioned findings. Unlike other causes of peripheral precocious puberty, patients paradoxically have a delayed bone age. During the biochemical evaluation of precocious puberty, the thyroid stimulating hormone (TSH) levels will be extremely raised with a low to undetectable free thyroixine level. Typically a suppressed luteinizing hormone (LH) level with a normal to high follicle stimulating hormone (FSH) level is detected, and estradiol levels are elevated. With GnRH stimulation, a peripheral precocious puberty pattern is detected. Prolactin levels may also be elevated. The pelvic ultrasound will show a pubertal uterus with enlarged ovaries with multiple follicular cysts. Most cases of Van Wyk–Grumbach syndrome are secondary to autoimmune thyroid disease but rarely can be due to unrecognized congenital hypothyroidism [16]. With treatment of the hypothyroidism, symptoms regress and no other interventions are needed. The unique feature of this syndrome which helped lead to its diagnosis is peripheral precocious puberty combined with a delayed bone age in the presence of hypothyroidism.

The pathophysiology of the syndrome is poorly understood and is complex, but is at least in part caused by stimulation of the gonadal FSH receptor by TSH [16].

This syndrome highlights the importance of screening for hypothyroidism when evaluating for precocious puberty. Early recognition and initiation of thyroid hormone replacement can avoid further diagnostic procedures, avoid unnecessary surgery, resolve the syndrome, and improve the patient's final height [16].

Sex Cord Tumors of the Ovary

Sex cord stromal tumors of the ovary are uncommon. These tumors account for 7 % of all ovarian malignancies [17]. Sex cord stromal tumors arise from the cells surrounding the oocytes. There are many different benign and malignant sex cord stromal tumors of the ovary including granulosa cell tumors, thecomas, Sertoli-Leydig cell tumors, gynandroblastomas (arrhenoblastoma), and sex cord tumor with annular tubules (SCTAT). These tumors can secrete sex hormones such as estradiol and androgens, which can trigger precocious puberty and/or virilization.

Granulosa cell tumors are the most common sex cord stromal tumors of the ovary in females which have a malignant potential [18]. Histologically, the tumors are divided into adult and juvenile subtypes [18]. These masses are typically large, unilateral, and multicystic or solid [18]. Granulosa cell tumors typically secrete estrogen, but can secrete androgens [18]. As it is difficult to distinguish the cause of elevated estradiol levels from other causes of peripheral precocious puberty versus secretion by a tumor, other tumor markers have been used for diagnosis in granulosa cell tumors. Inhibin A and B are the typical peptides that are used as tumor markers for this type of tumor [19]. Granulosa cell tumors should be managed by an experienced surgeon who has experience treating young children with a conservative unilateral oophorectom, uterine preservation, and staging. Systemic chemotherapy is generally reserved for more advanced disease [18].

Thecomas are rare ovarian tumors [20]. Thecomas are generally unilateral, solid tumors which can secrete estrogen. They are rare in children but have been reported to be a cause of peripheral precocious puberty [21]. Since these tumors have low malignant potential, it is reasonable to treat this tumor with a unilateral oophorectomy [18].

Sertoli-Leydig cell tumors account for less than 0.5 % of all ovarian tumors [18]. They are typically unilateral and may have cystic and solid components. Virilization is found in one third of females with this type of tumor [22]. Elevated levels of androgens such as 17-hydroxyprogesterone, testosterone, and androstenedione are often produced and can be used as tumor markers. Similar to granulosa cell tumors, an experienced surgeon can often perform excision via a unilateral oophorectomy with uterine preservation and staging. Systemic chemotherapy is generally reserved for more advanced disease in this tumor type as well [18].

Gynandroblastomas are very rare. These are usually benign tumors with both Sertoli-Leydig and granulosa cell differentiation [23]. They can produce either androgens and/or estrogen which can cause virilization and/or precocious puberty.

SCTAT is another rare type of tumor described in patients with precocious puberty [24]. The cells found in SCTAT are thought to be an intermediate between

Sertoli-Leydig cells and granulosa cells [25]. These types of tumors can secrete estrogen, progesterone, and/or androgens. An association between SCTAT and Peutz–Jeghers syndrome has been well described [26]. Peutz–Jeghers syndrome is an autosomal dominant disorder characterized by mucocutaneous melanin deposits, hamartomatous polyps of the gastrointestinal tract, and increased risk for cancer of both gastrointestinal and non-gastrointestinal sites [27]. When associated with Peutz–Jeghers syndrome, SCTAT tumors tend to be bilateral and small in size ranging from microscopic to 3 cm [26, 28]. In contrast, patients with SCTAT in the absence of Peutz–Jeghers syndrome, typically have large, unilateral tumors [26, 28]. SCTAT associated with Peutz–Jeghers syndrome is not typically metastatic and can be treated conservatively with unilateral oophorectomy. Non Peutz–Jeghers syndrome associated SCTAT is more likely to be metastatic and require further staging at the time of surgery [25, 28].

Germ Cell Tumors

There are a few case reports of germ cell tumors of the ovary causing precocious puberty [29, 30]. If an ovarian mass is seen in the ovary, these types of tumors should be considered.

Adrenal Tumors

Adrenocortical tumors (adrenal adenomas and adrenal carcinomas) are very rare tumors. In childhood, the median age of diagnosis is 3 years old in a review of 520 patients by Ribeiro [31]. The tumors are diagnosed in females more often than in males [32]. Unlike adult adrenocortical tumors, the childhood adrenocortical tumors are usually functional [33]. Precocious puberty with virilization with or without evidence of Cushing's syndrome is the typical presentation of these tumors [34]. Imaging of the adrenal glands by either ultrasound or CT scan is usually completed to detect the tumor. The mainstay of treatment for these tumors is surgical resection.

Adrenal Gland Enzyme Deficiencies

Undiagnosed or incompletely treated adrenal gland enzyme deficiencies can result in precocious puberty. The most common adrenal gland enzyme deficiency is 21-hydroxylase deficiency, otherwise known as congenital adrenal hyperplasia [35]. This enzyme deficiency causes cortisol precursors to accumulate, which may then be diverted to sex hormone biosynthesis. About 75 % of patients with classic congenital adrenal hyperplasia have aldosterone deficiency with resulting salt wasting [35].

Treatment is achieved with replacement therapy with glucocorticoids and mineralcorticoids, if needed. Children with non-classical congenital adrenal hyperplasia (a milder version of congenital adrenal hyperplasia) should be treated if the child has rapidly progressing precocious pubarche or the bone age is accelerated with projected final height compromise [35]. If treated, the therapy can be discontinued once the symptoms resolve.

Adrenal Rest Tumors

Adrenal rest tumors are tumors of adrenal tissue located outside of the adrenal gland in ectopic locations. In females, these tumors can be found in the ovary and are known as ovarian steroid cell tumors, not otherwise specified. These tumor cells are believed to develop from the adrenal rests which become entrapped in the gonads during embryogenesis [36]. In syndromes with elevated levels of adrenocorticotropic hormone (ACTH), such as in Addison's disease and congenital adrenal hyperplasia, ACTH stimulation of these ectopic tissue causes the tumors [30]. The tumors are rare and typically benign [36].

Summary

Peripheral precocious puberty is the result of autonomous peripheral secretion of excess sex hormones independent of the hypothalamic-pituitary-ovarian axis. If left untreated peripheral precocious puberty can lead to central precocious puberty. The differential diagnosis includes sex hormone secreting tumors of the adrenal gland and ovary, McCune–Albright syndrome, Van Wyk–Grumbach syndrome, adrenal gland enzyme deficiencies, and exogenous exposure to sex hormones. The treatment of peripheral precocious puberty depends on the underlying cause.

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Chapter 8
Isolated Precocious Puberty

Leslie A. Appiah

Abstract Incomplete or isolated precocious puberty is defined as partial sexual development that is transient and occurring in the absence of other stigmata of puberty. It encompasses isolated breast development (premature thelarche), isolated pubic hair appearance (premature adrenarche or pubarche), and isolated uterine bleeding (premature menarche). Isolated pubertal signs may be seen in prepubertal girls 1–4 % of the time. The major underlying theme in the setting of isolated pubertal signs includes an absence of increased linear growth or advanced skeletal maturation. In addition, baseline hormonal values are typically within the normal range for age and sexual development. There may be slow progression, stabilization, or waning over the course of time following the diagnosis of isolated precocious puberty. It is important to recognize the condition and follow up at appropriate intervals as approximately 20–30 % of cases may progress to central precocity. Nonetheless, 2/3 of patients will not progress and eventually experience puberty and growth at the normal expected time without sequelae.

Keywords Isolated premature thelarche • Isolated premature pubarche • Isolated premature menarche

Introduction

Incomplete or isolated precocious puberty is defined as partial sexual development that is transient and occurring in the absence of other stigmata of puberty. It encompasses isolated breast development (premature thelarche), isolated pubic hair

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appearance (premature adrenarche or pubarche), and isolated uterine bleeding (premature menarche). Isolated pubertal signs may be seen in prepubertal girls 1–4 % of the time. The major underlying theme in the setting of isolated pubertal signs includes an absence of increased linear growth or advanced skeletal maturation. In addition, baseline hormonal values are typically within the normal range for age and sexual development. There may be slow progression, stabilization, or waning over the course of time following the diagnosis of isolated precocious puberty. It is important to recognize the condition and follow up at appropriate intervals as approximately 20–30 % of cases may progress to central precocity. Nonetheless, 2/3 of patients will not progress and eventually experience puberty and growth at the normal expected time without sequelae.

Isolated Premature Thelarche

Premature thelarche (PT), defined as isolated breast development before the age of 8 years, occurs in 1–2 % of girls. Proposed mechanisms for isolated breast development include intermittent and/or transient activation of the hypothalamic–pituitary–ovarian (HPO) axis, transient secretion of Estradiol (E_2) from ovarian cysts, exogenous estrogen intake, and increased sensitivity of breast tissue to E_2 [1]. A history of the presence of breast tissue at birth or from early infancy may be elicited. PT may be unilateral or bilateral with or without areolar development. The tissue may regress after a few months, wax and wane, or persist until puberty. There are two forms of PT: classical and nonclassical. The classical form usually occurs in the first 2–3 years of life during a period of relative but decreasing activity of the HPO axis. It is usually transient, or self-limited, requiring no intervention. The nonclassical or "atypical" form usually affects older girls, with occasional menstrual withdrawal bleeding and tends to be more associated with progression to precocious puberty [2]. Studies have shown that thelarche before the age of 2 usually regresses completely. After age 2, it persists more frequently, but usually represents the first stage of an early, normal puberty [3]. Earlier literature quoted the risk of progression to central precocious puberty (CPP) to be as low as 0–6 % [4–6]. However, recent studies suggest risk of progression may be as high as 23–29 % [7].

Diagnosis

The diagnosis is frequently a clinical one, in which a child presents with isolated breast development without other pubertal signs. Development occurs outside the 6–9 month newborn period in which maternal hormonal effects, may be seen. A careful history should be undertaken to rule out iatrogenic causes, such as hormone ingestion or exposure. A bone age may be ordered, but does not show bone age advancement. Nonetheless, if concern remains, a laboratory evaluation may be

undertaken, but is not required [8]. In the classic evaluation, serum Luteinizing Hormone (LH) levels fall in the prepubertal range, whereas immunoactive and bioactive follicle stimulating hormone (FSH) levels may be normal or elevated for age. The gonadotropin releasing hormone (GnRH) stimulation test will ultimately differentiate CPP from isolated thelarche as LH and FSH will be elevated in the situation of CPP whereas only FSH will be elevated in the setting of isolated thelarche [5, 6, 8]. A pelvic ultrasound can also be helpful to rule out any peripheral hormonal causes. On ultrasound, the uterus and ovary demonstrate prepubertal size and morphology [9].

Management

Once the initial diagnosis has been made, follow up evaluation should occur every 6 months to 1 year to rule out the possibility of pubertal progression [10]. Longitudinal follow-up distinguishes premature thelarche from CPP, demonstrating a lack of characteristic pubertal progression, which can occur in ½ of cases. Evaluation includes breast exam, bone age or growth velocity, and assessment of pubic hair development. Pubertal breast tissue regression usually follows during subsequent visits and occurs over a 2–4 year period. Bone age is recommended in the follow-up of girls after 2 years of age [8]. For girls less than 2 years of age, growth velocity (GV) is more helpful given its use as a sensitive index of systemic estrogen effect [2, 11]. An annualized GV > 1 SD has been proposed as a reliable indicator of risk of progression or recurrence of breast development after regression [8]. There are currently no standard predictive laboratory values to determine which patients might develop CPP. However, basal LH Levels greater than 0.3 IU/L have been found to be a reliable predictor of progression to CPP [8, 12, 13]. Once resolved completely, it is reassuring to note that normal puberty in affected girls typically occurs at an appropriate age and final adult height is uncompromised.

Isolated Premature Pubarche (Adrenarche)

Premature pubarche (PP) or adrenarche (PA) is the presence of pubic and/or axillary hair before 8 years of age in girls and 9 years of age in boys in the absence of other signs of sexual maturation. In African–American girls, pubarche may occur several months earlier and usually, just before or synchronous with thelarche. The incidence is approximately 1 % among girls and is found to be ten times more common in girls than boys. It typically occurs between the ages of 3–8 years. PP; It has traditionally been considered a benign and normal variant of puberty in that it does not typically progress to puberty or affect final adult height. However, more recent literature indicates that PP is associated with a past medical history of lower birth

weight with rapid weight gain in early childhood, childhood obesity, insulin resistance, and alterations in insulin-like growth factor 1 (IGF-1) [14]. Girls with a prior diagnosis of premature adrenarche are also at higher risk for the development of adrenal and ovarian hyperandrogenism, polycystic ovarian syndrome (PCOS) [15], and CPP (30–40 %). The pathophysiology of this condition results from an early and modest increase in adrenal androgens, such as androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate.

Diagnosis

Premature pubarche adrenarche is a diagnosis of exclusion. The differential diagnosis includes benign pubic hair of infancy, CPP, virilizing tumor, nonclassical congenital adrenal hyperplasia (NCAH), Cushing disease, and iatrogenic causes. Bone age may be advanced with tall stature for age [16]. Conversely, bone age and height may be normal [17]. The history should include age at onset of symptoms as for well as the rate of change in order to rule out rapid signs of progression concerning virilization. In the presence of isolated early pubic hair growth, testing for enzymatic adrenal defects is rarely indicated unless a bone age is significantly elevated. In the setting of advanced bone age, serum androgens and imaging studies are warranted. If baseline early morning androgens are elevated, an adrenal corticotropic hormone (ACTH) stimulation test may be pursued. An ACTH stimulation test is not necessarily warranted, however, if a normal early morning 17-hydroxyprogesterone level is demonstrated.

Management

Treatment is not typically indicated because the transient acceleration in linear growth and bone maturation has no major effect on puberty or final adult height. However, surveillance should continue as these patients have an increased incidence of anovulation, hirsutism, hyperinsulinemia, PCOS, and risk of progression to CPP [18]. The link between hyperinsulinemia, premature adrenarche, and PCOS has long since been established [19] with the degree of hyperandrogenemia directly linked to the hyperinsulinemia. Specifically, insulin is known to directly stimulate the theca cells of the ovary in a synergistic fashion with LH, with resultant ovarian hyperandrogenism and anovulation. Similarly, insulin enhances ACTH-mediated adrenal steroid precursors in hyperandrogenic women through 17, 20-lyase deficiency [20].

Some authors recommend a surveillance period of 3 months in order to monitor clinical features and assess height velocity [21]. An ACTH stimulation test should be performed in the presence of an advanced bone age and circulating androgens out of the normal range for early puberty. ACTH testing may identify patients with mild errors of steroidogenesis. The mild enzyme changes, if present, do not require treatment.

Treatment is indicated for unequivocal cases of 21-hydroxylase deficiency wherein baseline elevated 17-hydroxyprogesterone levels are diagnostic. Early treatment with metformin has been shown to decrease the prevalence of PCOS and androgen excess in patients with premature adrenarche and LBW [22, 23]. The proposed mechanism is through early reduction of intraabdominal fat with resultant improvement in insulin levels. Early treatment with metformin has also been shown to delay the onset of menarche by approximately 1 year and to augment adult stature toward normal [24].

Isolated Premature Menarche

Premature menarche may occur and is expected within the first 6–9 months after birth due to withdrawal of maternal estrogens. Otherwise, the presence of uterine bleeding in the absence of pubertal maturation is rare and occurs in <4 % of girls. More commonly, non-endocrine causes such as vulvovaginitis, exogenous administration of estrogen, the presence of a foreign body, abuse, and trauma are higher on the differential. McCune–Albright syndrome and genital tumors such as clear cell adenocarcinoma, endodermal carcinoma, and rhabdomyosarcoma can manifest as vaginal bleeding and should also be ruled out. Precocious menarche is therefore a diagnosis of exclusion. Premature menarche is typically associated with normal growth and development with onset of puberty at the average expected time and no adverse effects on future fertility [24]. However, premature menstrual bleeding is more often the heralding event of CPP. The proposed mechanism of action is activation of the HPO axis with a resultant increase in FSH and increased endometrial sensitivity to estradiol, the levels of which are too low to stimulate breast development [25, 26]. The cause of the early HPO activation is unknown. FSH stimulation may result in ovarian cysts which may be diagnosed with pelvic ultrasound.

Diagnosis

At the time of presentation, the evaluation should rule out serious causes of bleeding. For instance, physical exam should note the presence or absence of lesions or trauma. A vaginal culture can also be obtained if concerned for infectious causes. If discharge is noted, vaginal irrigation may be performed to flush the vagina. History can also help elucidate whether concerns exist for a foreign body. If a more thorough exam is required, this may be performed in the office or during an outpatient surgical procedure for ease of evaluation. Imaging studies should be obtained to evaluate uterine and ovarian size and rule out pelvic pathology. For example, an ovarian cyst that spontaneously resolves may present with isolated uterine bleeding. A bone age will help determine if further evaluation needs to be undertaken, and is helpful whether advanced, normal, or delayed. For example, hypothyroidism is a condition that may stimulate ovarian cyst formation and secondarily cause uterine bleeding. In this specific situation, however, excess thyroid stimulating hormone

does not result in any other pubertal signs and skeletal maturation is typically delayed in these patients. McCune–Albright syndrome, in contrast, results in the development and regression of estrogen-producing ovarian cysts that may cause uterine bleeding. In this circumstance, the ovaries are enlarged with or without enlargement of the uterus and skeletal maturation may not be advanced. Gonadotropin levels are within the prepubertal range, whereas estrogen levels may vary. In the setting of classic isolated menarche, gonadotropins and estradiol levels are prepubertal at baseline and following GnRH stimulation, to differentiate isolated menarche from CPP and peripheral precocious puberty.

Management

Once serious causes of vaginal bleeding have been ruled out, reassurance may be provided. In the majority of patients, puberty continues to progress at the expected age with no future adverse effects. However, follow up is still warranted since a small percentage may progress to central precocity. Furthermore, recent literature finds early menarche before age 12 to be an established risk factor for adult morbidity including breast cancer, cardiovascular disease, and type-2 diabetes [27–30]. Close follow-up and early intervention with weight management may minimize the prevalence of the latter.

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Chapter 9
Constitutional Delay of Puberty

Xiomara M. Santos

Abstract Constitutional delay of puberty is the single most common cause of delayed puberty in females, occurring in 30 % of cases. Patients will eventually progress spontaneously through puberty, however, constitutional delay is a diagnosis of exclusion. In many cases it is difficult to make a distinction between constitutional delay and GnRH deficiency. Only observation with eventual spontaneous progression of puberty can make the diagnosis of constitutional delay. Final height is usually appropriate for their genetic potential, but is commonly in the low normal range. Treatment options include observation or short-term estrogen therapy if psychosocial concerns are significant.

Keywords Delayed puberty • Constitutional delay of puberty • Hypogonadism • Hypogonadotropic hypogonadism

Introduction

Delayed puberty in females is defined as the lack or incomplete development of secondary sexual characteristics by the age of 13 years [1]. This age is considered to be 2–2.5 standard deviations later than the population mean [1]. Breast development (thelarche) is the first pubertal sign [2, 3]. While the majority of females will experience menarche on average 2 years after thelarche, some girls may present with delayed pubertal development. Constitutional delay of puberty, the single most common cause of delayed puberty, occurs in 30 % of these cases [2, 3].

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Patients generally have short stature initially, reflective of delayed skeletal maturation [1]. Females with constitutional delay of puberty will eventually progress spontaneously through puberty [1, 4]. Additionally, final height is usually appropriate for their genetic potential, but is commonly in the low normal range [4].

Diagnosis of Constitutional Delay of Puberty

Many of the different disorders that would result in delay of puberty have in common a defect in gonadotropin-releasing hormone (GnRH) secretion and/or its action [5–7]. There is no single test that can distinguish between constitutional delay of puberty and other causes of delayed puberty. Only observation with eventual spontaneous progression of puberty can make the diagnosis of constitutional delay [1, 4]. However, history, physical exam, and laboratory findings may help identify other causes (Table 9.1). Constitutional delay of puberty is a diagnosis of exclusion [1].

History

It is important to determine if pubertal development is completely delayed or if it started and then stalled [1]. Patients with constitutional delay have delayed growth without evidence for pubertal halt. In this situation both thelarche and pubic hair development (adrenarche) are delayed [3]. In contrast, patients with GnRH deficiency usually undergo adrenarche at a normal age [3, 8]. Other important

Table 9.1 Differential diagnosis of delayed puberty

Hypogonadotropic hypogonadism (low LH, FSH, and estradiol)	Hypergonadotropic hypogonadism (high LH and FSH, low estradiol)
Constitutional delay of puberty	Gonadal dysgenesis
Systemic illness	Turner's syndrome
Inflammatory bowel disease	Gonadal failure due to chemotherapy or radiation therapy
Celiac disease	
Eating disorder	
Hypothyroidism	
Excessive exercise	
Tumors or infiltrative diseases of the central nervous system	
GnRH deficiency	
Isolated hypogonadotropic hypogonadism	
Kallman's syndrome	
Combine pituitary hormone deficiency	
Chemotherapy or radiation therapy	

aspects of the history include nutritional habits, exercise, past medical history, and medication use [2, 4, 9]. Prior treatments, such as chemotherapy or radiation, may cause gonadal failure [1, 4]. Disorders such as inflammatory bowel disease, hypothyroidism, or psychosocial deprivation can also present with delays in sexual maturation [4].

Associated congenital abnormalities, such as midline defects, skeletal abnormalities like cleft lip, or scoliosis, suggest congenital GnRH deficiency [10]. A central nervous system disorder is suggested by neurologic symptoms such as headache, visual disturbances, anosmia, seizures, and intellectual disability [2]. Absent or abnormal sense of smell suggests Kallman syndrome, which is characterized by GnRH deficiency [10]. An underlying genetic syndrome is suggested by delayed cognitive development associated with obesity or dysmorphic features [1].

It is important to also inquire about family history of delayed puberty [1]. An autosomal dominant mode of inheritance (with or without incomplete penetrance) if often seen in cases of delayed puberty and higher rates of constitutional delay of puberty have been observed in families with congenital GnRH deficiency [11].

Physical Examination

The most important aspects of the physical examination include height, weight, and secondary sexual characteristics [1, 2, 4]. Previous height and weight should be obtained in order to assess longitudinal growth [1]. Height and growth rate are usually within the prepubertal normal range in cases of constitutional delay of puberty [1]. Patients who are underweight for height are more likely to have an underlying condition, such as a chronic disease, delaying hypothalamic-pituitary-gonadal axis [1]. The Tanner criteria should be used in order to stage secondary sexual characteristics [12]. Patients with constitutional delay of puberty will typically have delays in thelarche and adrenarche [3].

Imaging Studies

A bone age (X-ray of the left hand and wrist) should be ordered to assess skeletal maturation [1, 13]. A bone age will also help determine the potential for future skeletal growth and allows for adult height prediction [13]. A delay in bone age is usually seen in constitutional delay, other causes of hypogonadotropic hypogonadism and gonadal failure [1]. The bone age of patients with constitutional delay of puberty is usually appropriate to their reduced stature and to their pubertal development stage [13].

A pelvic ultrasound is important to determine the presence or absence of a uterus [2]. An MRI of the brain is indicated if signs or symptoms suggest a lesion in

the central nervous system or if hypothalamic or pituitary disease is suggested by laboratory results [1, 2, 4]. When suspecting constitutional delay of puberty or congenital GnRH deficiency, some authors suggest delaying brain MRI. This is simply because many patients with constitutional delay begin puberty spontaneously at this time, and once puberty ensues, no further testing is needed [1].

Laboratory Evaluation

Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol should be obtained to distinguish between hypogonadotropic hypogonadism and hypergonadotropic hypogonadism (Table 9.1) [1, 4]. Patients with constitutional delay and patients with congenital GnRH deficiency usually have low LH and FSH [1, 2, 4]. GnRH stimulation testing may not distinguish between constitutional delay and congenital GnRH deficiency, since there is a significant overlap of gonadotropin response between the two conditions. Some experts have suggested that specific testing is not recommended [14–16]. Alternatively, patients with hypergonadotropic hypogonadism require a karyotype [2].

Testing to rule out chronic diseases includes a complete blood count, erythrocyte sedimentation rate, electrolytes, blood urea nitrogen, creatinine, and liver function tests [1]. Thyroid disease should be ruled out with thyroid-stimulating hormone and free thyroxine [1]. A prolactin level should also be obtained since hyperprolactinemia can present as stalled puberty [2]. Screening for celiac disease and inflammatory bowel disease might be indicated based on family history and in the setting of related symptoms and signs [2, 4].

Treatment of Constitutional Delay of Puberty

Females with constitutional delay of puberty will eventually spontaneously progress through puberty [1, 4]. Until then, the distinction between congenital GnRH deficiency and constitutional delay is not clear in most patients and the initial therapeutic approach is similar for both conditions [17, 18]. The two major treatment options are observation with reassurance and psychological support for the patient and family and administration of estrogen therapy [1]. In some circumstances, reassurance and education is not sufficient to address the patient's psychological concerns about the delay. Pubertal delay can have a negative impact on the patient's interactions with her peers and can contribute to a decreased self-esteem [1, 2]. In those circumstances, short-term estrogen therapy should be considered [1].

The short-term goals of estrogen therapy are to achieve age-appropriate secondary sex characteristics and induction of a growth spurt without inducing premature epiphyseal closure [1–3]. Options for estrogen therapy include a transdermal patch of 17β-estradiol 3.1–6.2 μg/24 h with an increase of 3.1–6.2 μg/24 h every 6 months

or oral conjugated equine estrogens at an initial low dose of 0.3 mg daily, followed by gradual increases in the dose over time [1, 4]. If estrogen treatment continues for longer than 1 year or if breakthrough bleeding occurs, it is recommended to add an oral progestin cyclically [1, 4]. To avoid premature epiphyseal closure, a bone age every 6 months during therapy is recommended [2]. It is also recommended to coordinate therapy with an endocrinologist to optimize growth. However, growth hormone is not recommended for patients with constitutional delay of puberty [1].

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Chapter 10
Hormonal Causes of Delayed Puberty

Nirupama K. De Silva

Abstract Puberty marks the transition of a female from childhood to adulthood. Any variations in development can be a cause of delay in puberty. Delayed puberty is technically defined as being two standard deviations above the mean age of onset of any area of development.

This chapter will focus on the evaluation of delayed puberty, discuss the most common hormonal causes for pubertal delay, and address treatment options.

Keywords Puberty • Delayed • Abnormal development • Hypomastia • Amenorrhea • Hypogonadism

Definitions and Incidence

Puberty marks the transition of a female from childhood to adulthood. It is a continuum of events with wide variations among individuals, thus making it hard to define. In females, most people identify the formation of breast buds as the first visible sign of puberty. This usually occurs between 8 and 12 years of age, with menses occurring 2–2.5 years later (median 12, range 9–16). Less notable changes include enlargement of the uterus and ovaries, labia and clitoris [1]. On a hormonal level, changes include an initiation of pulsatile releases of gonadotropins and gonadal secretion of sex steroids.

Any variations in development can be a cause of delay in puberty. Delayed puberty is technically defined as being two standard deviations above the mean age of onset of any area of development. Thus, lack of breast development or signs of pubertal development by age 13.7 years (two standard deviations above the mean)

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is considered abnormal and warrants a workup for delayed puberty. Other delays that warrant evaluation include a lack of maturation from breast development to menarche in 4 years and/or the absence of menses by age 15 [2].

While this chapter will focus on the most common hormonal causes for pubertal delay, it is important not to confuse delayed puberty with primary amenorrhea. While they can go hand in hand, amenorrhea in the face of normal phenotypical development warrants an additional workup for hormonal and anatomic abnormalities.

Evaluation

History and Physical

A thorough history and physical is imperative for a proper evaluation of an adolescent with possible alteration in pubertal development. Things to consider include review of family history, neonatal history, previous surgery, radiation exposure, history of chemotherapy, neurologic symptoms, history of chronic disease or illness, presence of stressors, current medications, substance abuse, and/or abnormal eating patterns. A review of the timing when pubertal changes occurred is also important.

Physical examination should focus on review of growth charts, assessing current height and weight, as well as body mass index (Fig. 10.1). Additional focus should be given to vital signs, such as blood pressure. Sexual maturity rating and skin features, such as the presence of acne or hirsutism should be noted (Fig. 10.2). Next an external genital exam is important to rule out obvious congenital anomalies. A simple neurologic exam may reveal an abnormal sense of smell or restricted visual fields. Finally, in patients who tolerate a vaginal exam, the degree of estrogenization and status of the pelvic organs can be assessed. If an internal exam is needed, but not tolerated, imaging may be warranted.

Laboratory and Imaging

If an ultrasound is obtained to evaluate pelvic pathology, consider performing it at a center that is familiar with the pediatric population as the pelvic structures may appear quite small in a prepubertal female. Laboratory testing that may be helpful includes a complete blood count, thyroid-stimulating hormone, prolactin and follicle-stimulating hormone (FSH). Measurement of androgens, especially serum DHEA-S, can assess for congenital adrenal abnormalities. In females with chronic illness, an erythrocyte sedimentation rate, chemistry panel, liver function tests, calcium and a celiac screen may also be helpful.

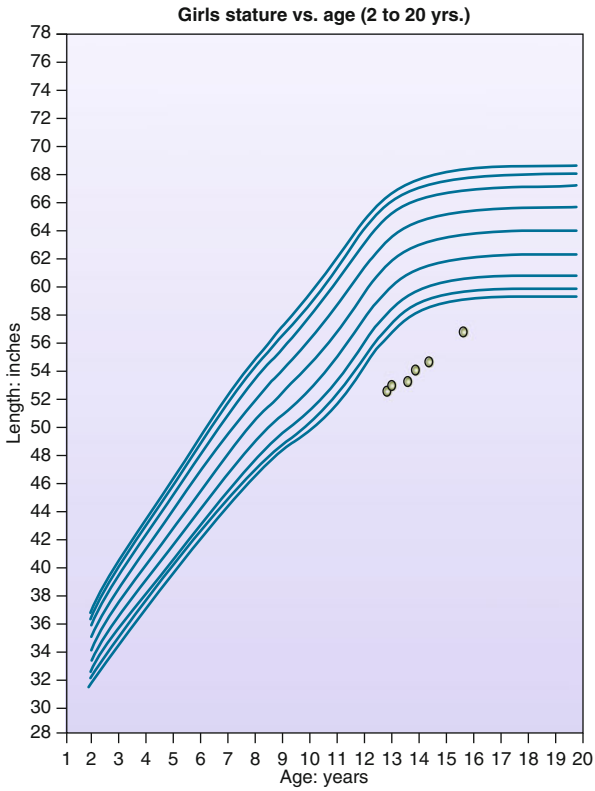

Fig. 10.1 Height chart of an adolescent female with delayed puberty. Delayed puberty and poor linear growth warrants an evaluation for an underlying disorder

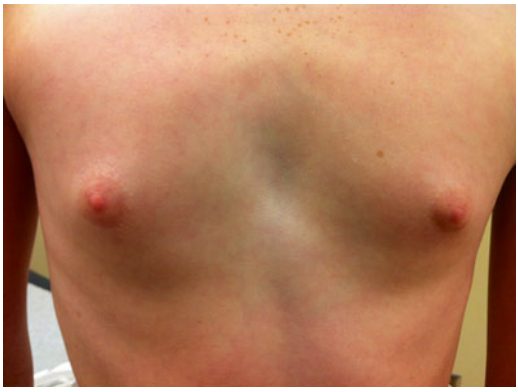

Fig. 10.2 Breast with sexual maturity rating 3. Absence of breast development by age 13 is considered abnormal

For delayed puberty, the differential can often be directed based on the FSH value. A high FSH should be repeated to ensure the diagnosis of premature ovarian insufficiency (POI) is accurate. Ultrasound can help evaluate pelvic structures if needed. Finally, a bone age of the left hand and wrist is helpful to determine the degree of delay and to help predict final adult height (Fig. 10.3) [3].

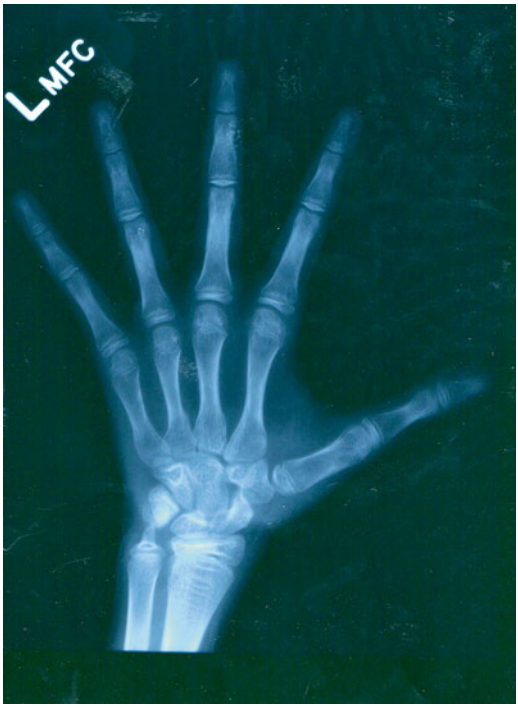

Fig. 10.3 Bone age of the left wrist is useful to correlate skeletal height with chronological height

Possible Etiologies

History, exam, and labs together will hone down the possible etiologies (Table 10.1). For instance, the absence of pubic hair with a uterus and ovaries in the face of primary amenorrhea is concerning for hypopituitarism and adrenal insufficiency. A lack of smell must warrant consideration for Kallman's Syndrome. Alternatively, excessive exercise may be a cause for delay. While there are multiple causes of delayed puberty, the most common ones are delineated here.

Constitutional Delay

Constitutional delay accounts for approximately 10–30 % of cases and is one of the most common causes of delayed puberty [4]. However, this is a diagnosis of exclusion and thus a full workup is warranted to look for other causes of delay before this diagnosis can be entertained.

Table 10.1 Common causes of delayed puberty

1. Constitutional delay
2. Chronic disease
3. Hypogonadotropic hypogonadism
   (a) Thyroid abnormalities
   (b) Kallman's syndrome/GnRh defects
   (c) Craniopharyngioma/CNS tumor
   (d) Pituitary tumors or mutations/panhypopituitary
   (e) Excessive exercise
   (f) Eating disorders
   (g) Malnutrition
   (h) Drugs
   (i) Depression
   (j) Stress
4. Hypergonadotropic hypogonadism
   (a) Idiopathic premature ovarian insufficiency
   (b) Fragile X carrier
   (c) Turner syndrome
   (d) Pure gonadal dysgenesis
   (e) 17 Hydroxylase deficiency/aromatase deficiency
   (f) Galactosemia
   (g) Sickle cell disease
   (h) Chemotherapy/radiation
   (i) Oophorectomy

Chronic Disease

Any child with chronic illness can present with delayed puberty due to a variety of factors, including recurrent illnesses/infections, immunodeficiency or due to a disturbance in any major organ that the underlying illness may affect. A chronic illness can cause growth delay as well as pubertal delay, with the degree of the delay being based on individual factors, such as the severity of the illness and the age of onset. Common causes of delay include eating disorders and other causes of malabsorbtion such as inflammatory bowel disease, celiac disease, or regional ileitis. Chronic renal disease, cystic fibrosis, and hemoblobinopathies can also cause a delay in pubertal development. Finally, any poorly controlled illness, such as diabetes, hypothyroidism, or Cushing's, can result in pubertal abnormalities.

Recurrent treatments for chronic disease may affect the timing of puberty, as can the emotional stress associated with the illness. Further, most theorize that malnutrition and the associated inflammatory response are some of the most important mechanisms responsible for the delayed puberty, as a result of poor nutrition [5]. While the pathophysiology of poor nutrition and pubertal delay is not clearly understood, in children with inflammatory bowel disease, it has been shown that poor nutrition affects growth hormone and insulin-like growth factor-1, which may also affect the

growth plates of the long bones [6]. Further, leptin has been suggested to be a trigger of puberty onset. Inflammation-induced malnutrition results in decreased fat mass and reduced leptin levels, another possible mechanism for delayed puberty [6].

Hypogonadotropic Hypogonadism

Separate from patients with chronic disease or poor nutrition, a CNS disorder or an endocrinopathy, such as a thyroid abnormality, can result in delayed puberty with low levels of gonadotropins. Lastly, tumors, exposure to certain drugs, or extreme exercise in an athlete can be potential causes.

Tumors of the Brain/CNS Disorders

When evaluating a patient for CNS disorders, labs would look for an elevated prolactin, while imaging should look for pituitary tumors/abnormalities, other brain tumors, and/or a lack of olfactory bulbs. Craniopharyngiomas are the most common neoplasm associated with delayed puberty. The peak incidence is between 6 and 14 years of age and the tumor resides in Rathke's pouch, with pituitary origin and suprasellar extension. It is discoverable by imaging and treatment is surgical with an additional need for radiation in some cases [7]. Patients with Kallman's Syndrome will have delayed puberty and anosmia. The illness is caused by a deficiency in GnRH production. A lack of smell, the hallmark of the disease, is due to a lack of full development of the olfactory bulbs in these patients.

Extreme Exercise

Chronic exercise leads to hypogonadotropic hypogonadism through effects on the hypothalamic–pituitary–ovarian axis. The exact etiology of pubertal delay is unknown, but centers around the combination of high energy output in the face of low caloric intake and low body fat. As noted previously, lack of fat stores leads to a lack of leptin, which is postulated to effect puberty [8]. Further, excessive physical training has also been shown to affect menarche [9]. The effects vary based on the age of training and the intensity of the training. The highest risk groups are those for whom a lean physique is important and when there is a history of beginning extreme training at a younger age (gymnastics, ballet, figure skaters, and long-distance runners) [8].

Other Causes

One should not forget to evaluate for isolated failure of gonadotropin secretion, which is diagnosed with low gonadotropins levels and absence or poor response to GnRH administration in a female patient with a bone age greater than 11 years [10].

Additionally, ingestion of certain medications can suppress sex steroid levels. Medications that may result in pubertal delay include glucocorticoids, opiates, and psychotropic agents, such as phenothiazines [11]. Lastly, stress should not be forgotten as a cause of reversible hypogonadotropic hypogonadism due to its effects on the release of insulin-like growth factor, involved in the progression of puberty.

Hypergonadotropic Hypogonadism

Elevated FSH is indicative of POI. Thirty percent of patients with POI have autoimmune dysfunction and so a workup for potential causes of POI must ensue. POI may be related to multiple endocrinopathies, including hypoparathyroidism or hypoadrenalism [12]. Rare causes that should not be overlooked include galactosemia (as 70–80 % of patients with galactosemia have POI [13]) and sickle cell disease (as 20 % of these patients have delayed puberty [7]). A history of post-ablative treatments, such as radiation or chemotherapy, and/or ooporhorectomy will also result in gonadotropin elevation. Finally, genetic abnormalities, such as Fragile X mutation or premutation may result in this clinical picture.

Chromosomal Abnormalities

When adolescents present with primary amenorrhea and no associated comorbidities, 50 % of these women are found to have abnormal karyotypes. Thirteen percent of patients with secondary amenorrhea have also been noted to have an abnormal karyotype [14]. Such affected females may have associated anomalies and failure to develop secondary sexual characteristics or may appear with some degree of puberty.

Turner Syndrome

Once a diagnosis of POI is made, a chromosome analysis is warranted. A karyotype of 45XO will diagnose Turner syndrome (refer to chapter on delayed puberty), estimated to occur in 1 in 2,500 live births [3] and appropriate treatment and evaluations for comorbidities of this condition should ensue. If any elements of Y chromosome are seen within the genetic material (estimated to occur between 3 and 12 %), gonadal excision is required due to the 20–30 % risk of malignant transformation [3].

Pure Gonadal Dysgenesis

Pure gonadal dysgenesis refers to patients with normal stature, elevated FSH, and streak gonads. The term is “pure” as there are no dysmorphic features. Karyotype is either 46 XX or XY. When 46XY, this diagnosis is Swyer’s syndrome.

With this syndrome, the streak ovaries do not produce androgens or anti-mullerian hormone, and so the mullerian system develops in utero without complication. These patients require removal of the gonads because of the risk of malignancy [3].

Fragile X Syndrome

Fragile X syndrome is the most common form of hereditable mental retardation. Six percent of females with POI and a normal karyotype have a premutation in the FMR1 gene [14]. Although the onset of menstruation may be normal among premutation carriers in adolescence, approximately 1 % of premutation carriers will experience their final menses prior to age 18 years [15]. Fragile X testing is recommended for young women with a normal karyotype and an elevated FSH levels, especially if there is a family history of POI, fragile X syndrome, or undiagnosed mental retardation.

Loss After Chemotherapy/Radiation

Chemotherapy and/or radiation can be detrimental to a patient's normal pubertal development. The immediate loss of ovarian function after chemotherapy or radiation is termed acute ovarian failure (AOF) and may be transient. With chemotherapy, the age of the patient at time of delivery, type of medication(s), as well as the number of doses, has an impact on the possibility of gonadotoxicity. While the highest incidence of AOF occurs after the use of alkylating agents or procarbazine, the younger the patient at the time of receiving the chemotherapy, the more likely it is that some follicles will survive [16–18].

Whole body, whole brain, pelvic and spinal radiation also increase the risk of AOF [19]. Pelvic radiation doses are directly proportional to AOF, with individuals receiving over 10 Gy acquiring acute failure [18]. Chemotherapy in addition to radiation compounds the insult and increases the chance of AOF. It should be noted that even females who menstruate after treatment have an increased lifetime risk of POI [19].

Other Hormonal Causes of Delayed Puberty

17 OH Hydroxylase/Aromatase Deficiency

These are enzyme deficiencies that result in delayed puberty. For 17 OH hydroxylase deficiency, patients have hypertension, adrenal insufficiency, and lack of secondary sex characteristics. Patients with 46XX have a female phenotype with no secondary sex characteristics. Those patients with 46XY have a female phenotype

and a lack of breast development, a vagina or mullerian structures. Aromatase deficiency results in the inability to convert testosterone to estradiol. This is a rare disorder that presents with mild virilization, absent breast development, multicystic ovaries, insulin resistance, and delayed bone age [3].

Treatment

Treatment is based on the cause. For instance, in a patient with nutritional delay or malnutrition, the treatment is optimizing nutrition. For celiac disease, a gluten-free diet will often optimize nutrition and initiate the onset of puberty without hormonal intervention. Eating disorders should be treated with particular attention to optimal nutrition. A thyroid abnormality should be treated by replacing the appropriate hormone.

For patients with hormonal estrogen deficiency, the treatment is estrogen add back. Estrogen treatment should be initiated when age appropriate. Treatment is usually between 12 and 14 years of age to optimize height (as estrogen ingestion will promote closure of the epiphyseal plates). Goals include inducing normal breast development and menses, while optimizing height and bone mass. For those with Turner syndrome, ensure growth hormone is given prior to hormonal estrogen initiation to ensure optimal linear growth [3].

There are a number of estrogen options available to initiate pubertal development. Oral contraception is not recommended as the initial treatment as this level of synthetic hormone is not at physiologic levels. Oral estradiol is used by many, but the transdermal route appears to provide more physiologic levels of estradiol and IGF-1 [3]. A study of transdermal estrogen versus oral conjugated estrogen found faster uterine growth and more optimal bone density in 1 year with the transdermal approach [20]. Estrogen doses should be increased slowly to promote breast development. Ideally, the first menses should be induced with progesterone and after full breast development is achieved. The timing of increasing doses must be individualized based on the bone age, the predicted height, and the desire for rapidity of breast development [3], but some guidelines are noted below:

1. Initiate 0.3 mg conjugated estrogen or 0.5 mg micronized estradiol daily. After 6 months to a year, move to a sequential program with 0.625 mg conjugated estrogen or 1.0 mg estradiol and 5 mg medroxyprogesterone acetate for the first 14 days of each month [7].
2. Transdermal estrogen 6.5–12 μg initially (patches can be cut into ½ or ¼ segments to start) and increase the dose increased gradually over 12–24 months. Once breast development has been initiated and transdermal estrogen has increased to a 50 microgram patch (3), or menses spontaneously occurs, begin progesterone addback. Usually a short course of medroxyprogesterone or micronized progesterone given at the same time monthly is optimal for patients so that they can have predictable cycles.

After puberty has been established, long-term maintenance involves an estrogen and a progesterone. Either estrogen and cyclic progesterone or an oral contraceptive pill are reasonable options. Patients with POI require prolonged treatment, while those with constitutional delay can stop when pubertal development has progressed.

Psychological Considerations

It is important not to forget the psychological component of delayed puberty. Puberty is a time of change and any abnormality raised during this time can be a source of great stress to a patient or her family. Physicians should approach the patient with honesty and candor and the normal aspects of her condition should be focused on. Resources should be given as needed. Patient pamphlets and appropriate Internet sources will promote accurate information should the patient do her own research. Finally, regular follow-up in the initial stages of evaluation and treatment will help ensure optimal care for the patient's physical and psychological needs.

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Chapter 11
Anatomic Causes for Delayed Puberty

Jennifer E. Dietrich

Abstract *Background*: Anatomic abnormalities resulting in absent menses and delayed puberty occur with an incidence of 23.7 %. An understanding of the embryology, diagnosis, and treatment is critical in order to offer appropriate treatment. In many cases, menses can be restored, however, some anatomic abnormalities will not allow for menstrual restoration; therefore, careful counseling about the condition, future expectations, and options for fertility is important. *Purpose*: To systematically review the anatomic causes for delayed puberty in females. *Conclusion*: There are many anatomic causes which can explain delayed puberty. Some of these anatomic causes may be addressed with surgery. For those anatomic causes which cannot restore menses or the connections of the outflow tract due to congenital absence of the uterine or vaginal structures, there are medical and surgical options available to minimize pain, reduce the risk of endometriosis, and to create a functional vaginal space for intercourse.

Keywords Mullerian anomalies • Outflow tract • Delayed puberty • Vaginal agenesis • Lower vaginal atresia • Vaginal septum • Imperforate hymen • Cervicovaginal atresia

Background

Approximately 23.7 % of girls will experience normal pubertal milestones with the absence of menses. Within this group, approximately 25 % of these will have an underlying anatomic abnormality, which explains menstrual absence [1]. Such anatomic problems resulting in outflow tract obstruction with pain or outflow

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tract obstruction without pain, present within a spectrum, ranging from an abnormality of the hymen to an abnormality of the uterus [2]. Typically these differences occur due to multifactorial reasons, and despite extensive genetic research in this area, no causal association has been made in humans to explain the spectrum in presentation [3–5]. Some studies hypothesize that environmental factors may play a role, but this has not been well established thus far. In contrast, many mice studies suggest a variety of genes are involved in the development of the reproductive tract and that mutations of these genes result in infertility and maldevelopment of uterine and vaginal structures [6]. Genes of interest based on these studies include genes within the WNT, DACH, and HOX families as well as SOX9. A few such studies have been conducted in humans as well however information thus far does not suggest a single gene alone may be involved [6–14]. Furthermore, no current literature supports risk of offspring transmission from affected females, except in the situation of syndromes, which may have a very separate and distinct underlying genetic cause [6].

Ultimately, in order for correct development to occur both fusion and absorption events must occur. Reproductive tract development begins at 6–7 weeks gestational age and is really guided by the presence of absence of SRY, the sex determining gene. In the absence of the SRY gene, female anatomy ensues. The Mullerian ducts will begin to fuse around this time and through 14 weeks gestational age [2, 6, 8]. Once these ducts fuse, canalization occurs to form the uterine cavity. At around 12 weeks gestational age, the most caudal portions of the Mullerian ducts begin to fuse with the sinovaginal bulb, forming the vagina, with the top third originating from Mullerian ducts and the lower 2/3 originating from the urogenital sinus. Subsequently the vaginal canal must also go through a process of fusion and canalization to result in a normal vaginal cavity [2].

In general, menstrual absence within the structural category may be subcategorized into those occurring with pain or without pain. The first group to be discussed includes those occurring with pain. Hymenal abnormalities are most common within this group, with imperforate hymen occurring in 1/2,000 girls (Fig. 11.1) [2]. Typically, because this defect is lower and the hymenal tissue is very thin, menstrual blood backed up behind this thin membrane not only results in pain over several months time, but causes hematometrocolpos. With a large amount of menstrual fluid collected, the thin membrane may appear purplish in hue and with a bulging appearance (Fig. 11.2) [15]. A much more rare type of obstruction is that involving a complete transverse vaginal septum (as rare as 1/72,000), which may present in the lower, middle, or upper thirds of the vagina (Fig. 11.3) [15]. The septum may be thin or thick, but without an outflow tract for menstrual blood to flow outside the body, this menstrual fluid also backs up and results in hematometrocolpos. Lower vaginal atresia is another rare entity which results in a similar presentation to the aforementioned structural abnormalities, but no bulge is present on the perineum. Rather in this situation, the hymen appears normal and the vagina appears nonpatent. Nonetheless the vagina is present, but simply at a distance much higher from the perineum (Fig. 11.4a, b) [15]. An even more rare form of outflow tract obstruction is that of cervicovaginal agenesis. This occurs when the cervix does not form properly as the Mullerian ducts fuse and additionally, the vagina does not cannulate during the process of development (Fig. 11.5) [15].

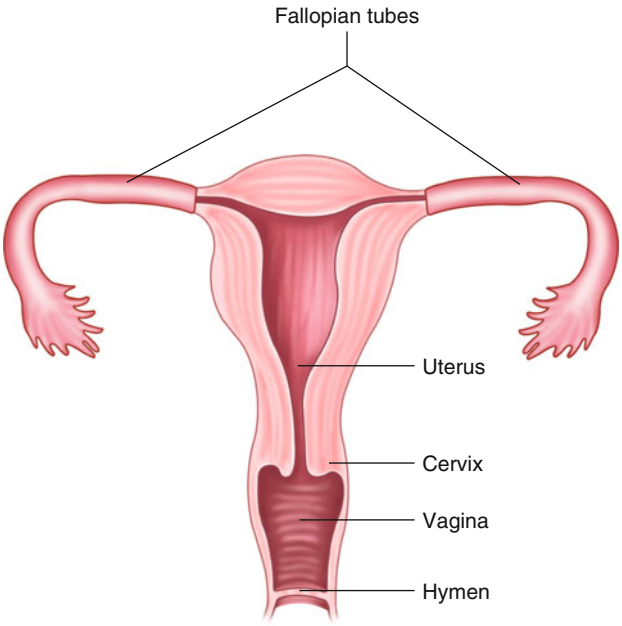

Fig. 11.1 Reproductive tract anatomy, sagittal view, picturing the hymen most distally

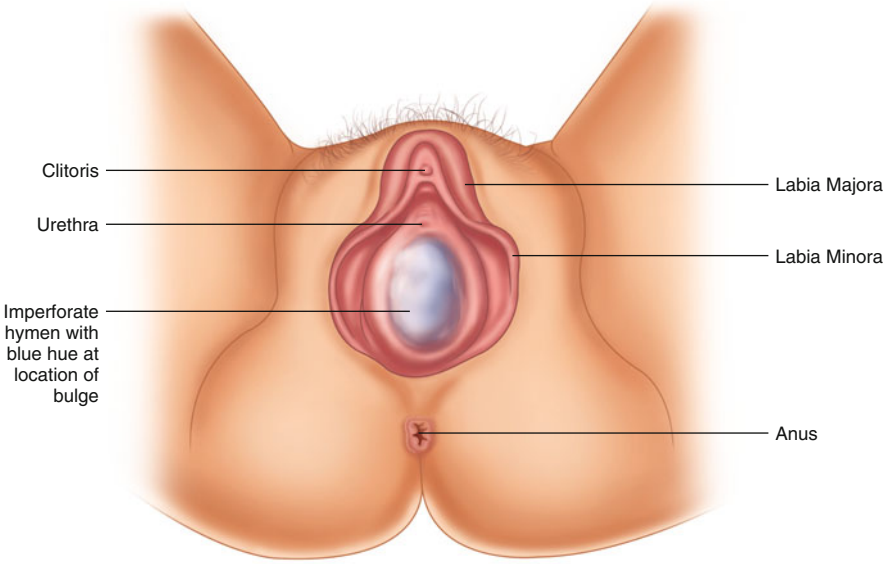

Fig. 11.2 Imperfortate hymen with blue bulge indicating the presence of hematocolpos

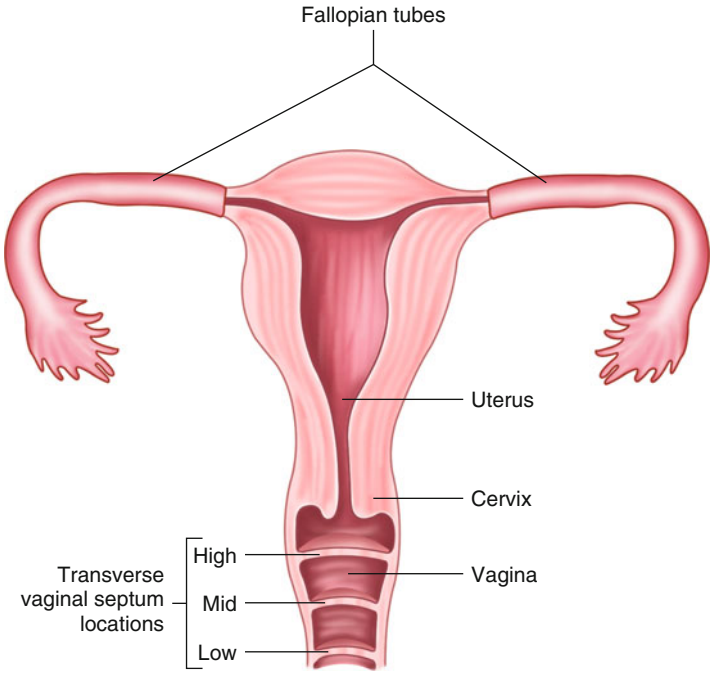

Fig. 11.3 Locations of vaginal septum, sagittal view

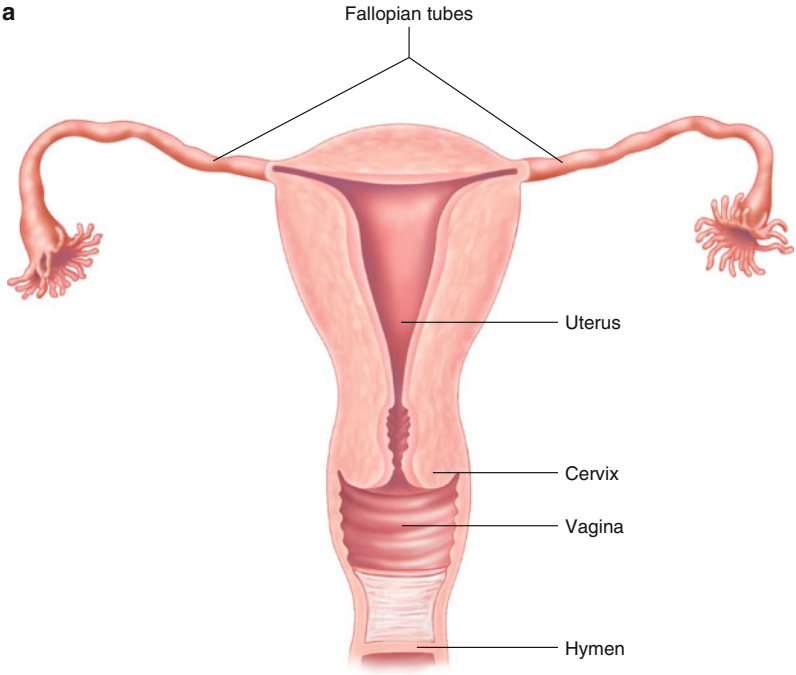

Fig. 11.4 (**a**, **b**) Lower vaginal atresia prepubertal (**a**) and lower vaginal atresia pubertal with hematometrocolpos (**b**)

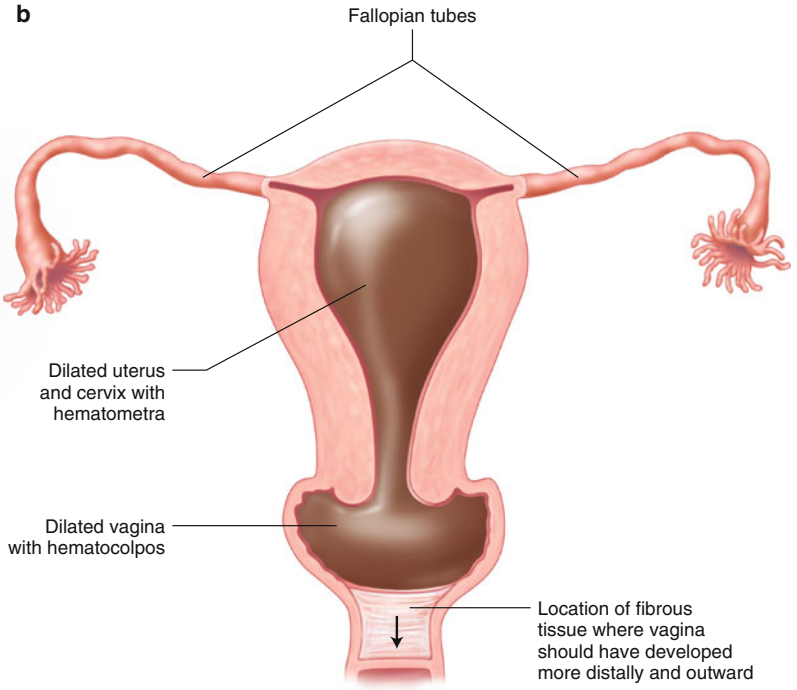

Fig. 11.4 (continued)

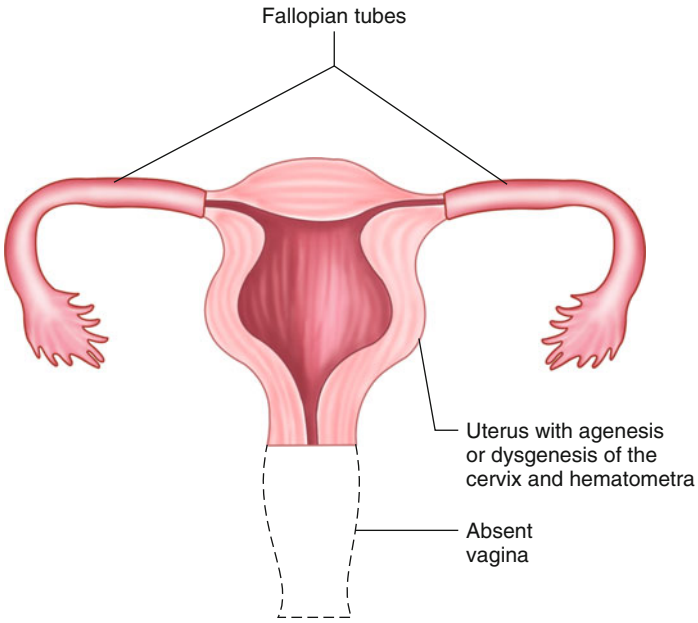

Fig. 11.5 Cervicovaginal agenesis

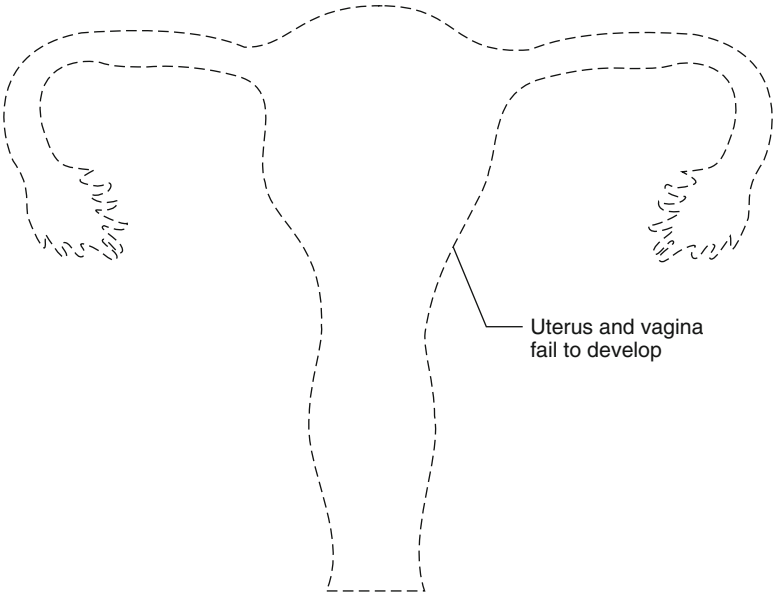

Fig. 11.6 Absent uterine structures consistent with uterovaginal agenesis. Seen in MRKH and MURCS

The next group of anatomic variants involving the reproductive tract includes those occurring without pain during the pubertal years. Such conditions include Mullerian aplasia syndromes affecting 46XX females, such as Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome or MUllerian–Renal–Cervical Syndrome (MURCS) [16]. This occurs with varying frequency but is frequently reported to have an incidence of 1/4,000–1/5,000 [16]. In this situation, the Mullerian structures have not developed at all or possibly may be minimally developed, and these conditions occur in conjunction with absent vaginal development (Fig. 11.6) [17]. Vaginal agenesis may also occur in conjunction with certain disorders of sexual differentiation [2], such as mixed gonadal dysgenesis (MGD) or complete androgen insensitivity syndrome (CAIS). In these instances, it is important to establish a timeline for pubertal characteristic progression as well as clinical exam features. In addition, hormonal and genetic evaluation will help elucidate the underlying diagnosis [17].

Presentation

The typical time of presentation for an outflow tract obstruction is at the time of puberty, although occasionally such conditions may be diagnosed in infancy. The most common diagnosis appreciated in infancy is that of imperforate hymen when an infant presents with mucocolpos (mucus-filled vagina) [15]. This is a result of

maternal estrogen stimulation during gestation. This estrogen effect resolves spontaneously and mucocolpos subsequently requires no intervention until the time of puberty. Rarely, mucocolpos may be significant and result in bladder dysfunction or ureteral obstruction. In these rare cases, occasionally a large mucocolpos must be addressed early in life. Adolescents may have experienced a normal pubertal progression, but with cyclic abdominal pain developing approximately 2–3 years following thelarche. Depending on the degree of pain the adolescent may be experiencing or other associated symptoms involving the urinary tract or GI tract, patients may present in the emergency or outpatient setting. As with any outflow tract abnormality, the pain is from menstrual fluid collection, which distends over time to result in hematometrocolpos (blood-filled vagina and uterus, Fig. 11.4), hematocolpos (blood-filled vagina, Fig. 11.4) or hematometra (blood-filled uterus, Figs. 11.4 and 11.5). A physical exam is important to aid in the differential diagnosis. The imperforate hymen will present with a large hematocolpos due to the elastic nature of the vaginal tissue and minimal resistance of the thin hymen. Imperforate hymen usually is associated with minimal uterine distension as a result of most fluid accumulation occurring within the vagina. At the perineum, a classic bulging hymen with blue hue is seen [15].

A transverse vaginal septum results in hematometrocolpos as well, but tends to have more fluid accumulated within the uterus as compared to imperforate hymen. This septum may be thin, in which case fluid behind this membrane may result in a bulging effect [15, 18]. Alternatively, the septum may be thick, in which case the provider may only appreciate a blind-ending vaginal pouch with a flat top. For the adolescent tolerant of exam, this may be appreciated by simple bimanual exam or with use of a small Pedersen speculum. Alternatively, a q-tip may be utilized to gain an appreciation of the vaginal depth distal from the obstruction. As mentioned previously, the location of the septum may be low, mid, or high. The most common presentation is low in the vagina. In the adolescent presenting with pain and a non-patent appearing vagina, it is important to consider performing a rectal examination. This will help elucidate if a bulge effect is present much higher than the level of the perineum or if a bulge effect is absent. Pairing this exam with q-tip placement at the vaginal dimple is also helpful to determine vaginal pliability and distal vaginal depth if any [15, 18].

A lower vaginal atresia will present with a bulge effect at a variable distance from the perineum and therefore, while a hematometrocolpos can be appreciated from ultrasound or MRI, the distance away from the perineum is not always clear [15, 18]. Conversely, among patients presenting with cervicovaginal atresia/agenesis, only a hematometra is appreciated on imaging studies and no bulge effect is present deep within the pelvis on rectal examination. Among adolescents presenting in the early teen years, pelvic ultrasounds are performed transabdominally. This may provide useful initial information; however, an MRI of the pelvis is the gold standard imaging study to assess Mullerian anomalies [2, 15, 18].

Patients with absent vaginal development frequently present at the time of puberty, when menses do not occur [2, 6, 15, 19, 20]. Among patients with absent uterine development and absent vaginal development, thelarche and adrenarche

have occurred as expected, but greater than 2–3 years following pubertal onset, the menarche fails to occur. It is recommended that any female with absent pubertal signs by age 13 years of absent menses by 15 years be evaluated by a gynecologist [2, 15]. It is typically in the office setting that the diagnosis is made and it is determined the vagina is not patent. Assessing Tanner stage characteristics can aid clinical suspicion for the diagnosis of MRKH, MURCS, MGD, or CAIS [2, 17]. Hormonal and karyotype assessment can be helpful in the setting of this clinical presentation. Among those with MRKH and MURCS, a 46XX karyotype, normal hypothalamic gonadal axis, and normal ovaries are present in the setting of absent menstruation [2, 17]. Among patients with MGD, a mixed/mosaic karyotype may be seen or a karyotype that is not concordant with the phenotype seen. In the setting of a Y component, the risk of gonadal cancer is present. Finally, typically these patients present with hypergonadotropic hypogonadism and absent menses. Among patients with CAIS, breast development may be normal, however, the hallmark sign indicative of this disorder is that of absent body hair, including pubic and auxiliary hair. Patients with this presentation have a 46XY karyotype, have normal gonadotropin levels, but have testosterone levels consistent with normal male range. This condition results from a mutation involving the androgen receptor, which prevents androgen from binding and having normal hormonal effects, even as early as 6–7 weeks gestational age [20]. Because of this lack of androgen-binding affinity, the external genitalia develop phenotypically female. The gonads in these patients are testes; therefore, antimullerian hormone is present is normal quantity. As such, the Mullerian structures do not develop internally. Nonetheless, the testes may be located within the pelvis, inguinal canals, or within the labia majora. Due to a risk for malignant transformation around the time of puberty, it is recommended that gonads be removed following breast development. Occasionally, females may present at an earlier age with an inguinal hernia. If at the time of hernia repair the gonad appears abnormal or cannot be relocated to the pelvis, it may be necessary to remove earlier in life. Approximately 1–2 % of females presenting with inguinal hernia may have an underlying diagnosis of CAIS; therefore, experienced surgeons have recommended a karyotype be checked at the time of hernia diagnosis [2, 17].

Management

Depending on the underlying reason for outflow tract obstruction or absent menarche, management strategies are different. Once a pubertal progression timeline has been established, important information gained from history includes the presence of pain (constant or cyclic) and/or palpable abdominal or pelvic mass [19]. For any reproductive tract anomaly, it is beneficial to obtain an ultrasound. Because it is desired to avoid the transvaginal approach in this population, a transabdominal ultrasound is an appropriate initial imaging modality. When the diagnosis is uncertain, a pelvic MRI may be beneficial to better elucidate the specific reproductive tract problem [2, 21, 22]. In any cases of reproductive tract abnormalities involving

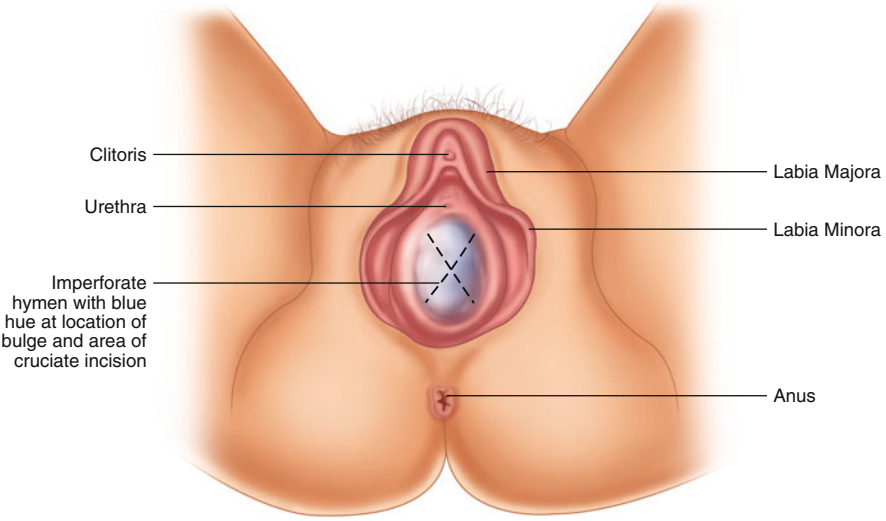

Fig. 11.7 Cruciate incision lines for surgical management of imperforate hymen

Mullerian structures, there is a high incidence of renal (40 %) and spinal (10–20 %) abnormalities [6]. It is important to screen for these problems depending on the underlying diagnosis [6].

Once a diagnosis has been established, the reproductive tract concern may be addressed medically or surgically. In the situation of imperforate hymen presenting with progressive worsening pain, a Foley catheter can be placed and surgically, the excess hymenal tissue can be excised in a cruciate fashion to create a patent vaginal space (Fig. 11.7) [15, 18]. Once the hymenal membrane is removed and all menstrual contents are suctioned, the obstruction and pain sensation are relieved immediately. MRI becomes important for cases of vaginal septae presenting with hematometrocolpos. First, one must establish if the septum is low, mid, or high in its presentation within the vagina. Second, the thickness of the septum must also be considered. In cases of thin septal walls, these may be excised directly with complete removal of the septal tissue. Subsequently, the normal vaginal mucosa is sewn together to anastomose the upper and lower part of the vagina. When the septal tissue is thick, a variety of techniques have been described to repair this condition. First the septum may be divided into two parts: a distal section and a proximal section (Fig. 11.8) [15]. Each section is then marked to create triangular leaflets. It is helpful to make one section in an "X" fashion and the other section in a "+" fashion. The eight leaflets that are subsequently created can then be interdigitated to bridge a larger distance while maintaining normal vaginal calibur (Fig. 11.9) [15]. Finally, MRI is critical when attempting to establish the diagnosis of cervico vaginal agenesis. With this diagnosis, the vagina is congenitally absent, however, a small uterus with atretic or absent cervix is seen in conjunction with hematometra [15, 18, 19, 23].

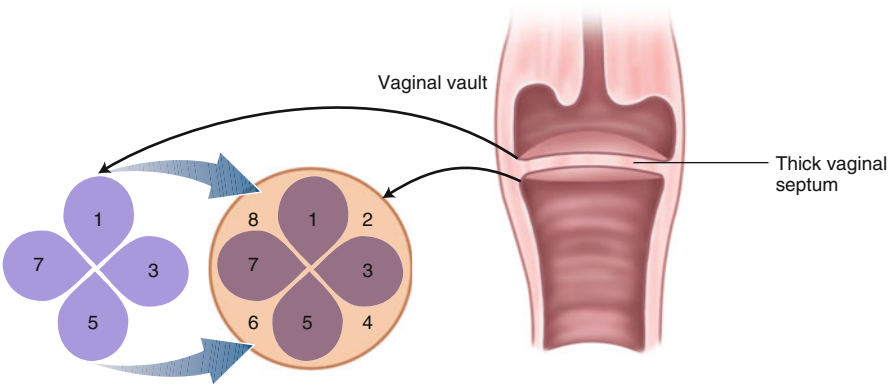

Fig. 11.8 Surgical planning for interdigitation of flaps for repair of a thick vaginal septum

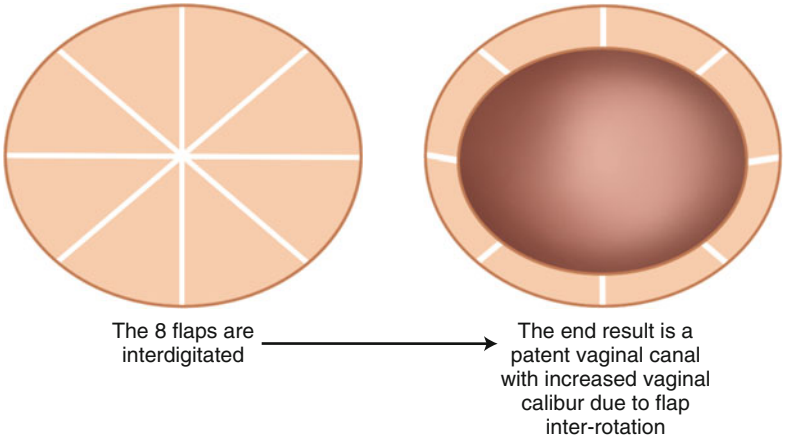

Fig. 11.9 End result post-resection and repair of a thick vaginal septum using the interdigitation technique

A hematosalpinx may also be present since blood may flow retrograde since it is unable to travel outward distally [15]. In the period of immediate diagnosis, it is possible to offer menstrual suppression with combined hormonal contraception, such as pills or patches. Alternatively, GnRH injections may be utilized short term or DMPA injections may be utilized longer term. In cases, where medical management has failed, it is important to present options to the family. While recent research has looked into ways to reconstruct the cervix, outcomes associated with reconstructive cases to date have largely resulted in postoperative complications such as sepsis or death. In addition, the field of transplant medicine continues to expand, although, no studies address uterine transplant in humans thus far. The implications and risks following a transplant would also need to be weighed with the potential benefits [2, 15, 18].

Because these options are still very much in the research realm, patients who remain symptomatic on hormonal suppressive therapy may choose to have the uterine remnant structure removed entirely, which will ultimately prevent cyclic pain episodes. Nonetheless, should pain necessitate removal of the uterine remnant, the ovaries should be preserved, since pregnancy can be achieved with IVF and a surrogate carrier [2, 15, 18, 24]. For patients presenting without pain, an MRI is critical to confirm the absence of reproductive structures. In addition, an MRI may help confirm the presence and location of the gonads. For instance, in cases of MRKH or MURCS, the gonads (ovaries) may be located within the pelvis as expected, but approximately 20 % will be undescended and be located above the pelvic brim. In the case of MGD or CAIS, the gonads (ovotestis, ovaries, or testes) may be located in the abdomen, the inguinal canal, or in the labia majora [2, 6]. While the management for creation of a vagina is very similar in all cases of vaginal agenesis, the management strategy for the gonads is different and is dependent on the underlying diagnosis. The majority of patients will respond to vaginal dilation using either the Frank or Ingram methods. Approximately 90 % of individuals are successful with this approach [2, 17, 25]. For individuals failing vaginal dilation, a variety of surgical approaches are available; however, the choice of surgical operation should be individualized [25]. Studies performed on cost-effectiveness of dilation, followed by surgery for failed cases, versus surgery as the initial step, have been studied. It was determined that dilation was most cost-effective, with the option for surgery only in cases of failed dilation compared to surgical management for all patients [26].

Counseling

Patient counseling is very important for any of the aforementioned presentations in terms of what to expect for the future [24]. Typical questions that parents ask include things such as “Will this affect my daughter’s fertility?” or “Will this affect my daughter’s ability to have sex?” or “Can she pass it on to one of her children someday?” The good news is that with many of these conditions, relieving the obstruction results in full resolution of the problem [24]. This is the case for imperforate hymen, lower vaginal atresia, and transverse vaginal septae. However, for cases of vaginal septum in which a thick septum is present or the septum is high in the vaginal vault or when vaginal atresia is noted to be well away from the perineum, patients and families should be counseled that there is a higher risk for stricture formation, which may result in a narrowed vaginal vault [15]. For the patient who is sexually active, this may result in dyspareunia. In many cases this narrowing is easily overcome with self-dilation using graduated cylinders to dilate the vagina slowly [15]. There does not appear to be any increased risk of transmission to offspring, except in the case of MURCS so this is also reassuring to most families [2]. Although endometriosis is found in many cases of vaginal or Mullerian anomaly, endometriosis associated with obstructive types tends to be of a less aggressive nature and typically resolves with simple relief of the obstruction [2, 26, 27].

Among patients with uterovaginal agenesis, patients can be reassured that there are many options for vaginal creation. Fortunately 90 % of cases respond to self-dilation alone. For the 10 % of women who fail dilation or are unable to dilate, there are many options for vaginal reconstruction. Many of these women report normal sexual function after self-dilation or surgical neovagina creation [25]. For women with uterovaginal agenesis, while a vagina can be created, there is no current way in which to reconstruct the uterus. Since these women have normal ovaries, it is possible for the ovaries to be stimulated with gonadotropin fertility agents and for eggs to be retrieved via in vitro technology. These women will require a surrogate carrier nonetheless. Additionally, there are no known cases of transmission to offspring among those with pure MRKH [24]. Endometriosis is still a factor for consideration in these women since uterine remnants may be present up to 85 % of the time and may have active endometrium resulting in bleeding within a closed space. Among women with cyclic pain or progressive pelvic pain symptoms unrelated to other causes, functional remnant horns should be suspected and a diagnostic laparoscopy may be required to make a diagnosis. Both surgical and medical treatment may be needed to fully treat functional remnants. Supporting women through the time of their diagnosis is important as the diagnosis can be difficult to handle. Occasionally psychological support is necessary in the initial months following diagnosis and may be needed from time to time throughout adulthood [24].

In the situation of CAIS, women will need to understand that the gonads will not be functional long term and will need to be removed due to risk of malignant transformation. Following removal, women will require hormone replacement. Due to the presence of Mullerian inhibiting substance, the uterine structures are absent; therefore, counseling these women about the possibility for use of a donor egg with a surrogate carrier and adoption is important. Once again, supporting women through the time of their diagnosis is important and occasionally psychological support is necessary in the initial months following diagnosis and/or throughout adulthood [17, 25].

Conclusions

In summary, there are many anatomic causes which can explain delayed puberty. Some of these anatomic causes may be easily addressed with surgery without concern for infertility in the future. For those causes which cannot restore menses or the connections of the outflow tract due to congenital absence of the uterine or vaginal structures, there are medical and surgical options available to minimize pain, reduce the risk of endometriosis and create a functional vaginal space for intercourse. It is imperative to counsel patients with an inability to have menses or an inability to recreate the outflow tract, that counseling be offered to help them better understand their options in the future with regard to fertility.

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Chapter 12
Genetic Causes of Delayed Puberty

Xiomara M. Santos

Abstract Genetic conditions account for about 20 % of cases of delayed puberty in females. A number of congenital or genetic syndromes are associated with delayed puberty. Patients present with either hypogonadotropic hypogonadism or hypergonadotropic hypogonadism. A full evaluation is indicated in all patients with delayed puberty to correctly identify the cause. The main causes of delayed puberty due to a genetic etiology include isolated gonadotropin deficiency and gonadal dysgenesis. Due to the lack of estrogen production, patients require hormone replacement in order to achieve breast development and eventually start menstruation. In addition, growth hormone is indicated for some cases and it is the standard of care for females with Turner syndrome. Finally, a multidisciplinary approach is recommended for all patients with delayed puberty to optimize growth and development.

Keywords Delayed puberty • Hypogonadism • Hypogonadotropic hypogonadism • Hypergonadotropic hypogonadism • Turner syndrome • Gonadotropin deficiency

Introduction

Delayed puberty in females is defined as the lack or incomplete development of secondary sexual characteristics by the age of 13 years [1]. This age is considered to be 2–2.5 SD later than the population mean [1]. Breast development, or thelarche, is the first pubertal sign [2]. Genetic causes account for about 20 % of cases of delayed puberty in females [1, 3]. Patients present with either hypogonadotropic

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hypogonadism (low gondotropins resulting in low production of estrogen) or hypergonadotropic hypogonadism (gonadal failure resulting in elevated gonadotropins due to lack of negative feedback from estrogen) [2].

Differential Diagnosis

A number of congenital or genetic syndromes are associated with delayed puberty (Table 12.1) [2, 4]. As part of the initial evaluation of a female with delayed puberty, it is important to determine if pubertal development is completely delayed or if it started and then stalled [1]. Females with gonadotropic-releasing hormone (GnRH) deficiency usually undergo adrenarche at a normal age, however, the progression of thelarche is delayed [3, 5]. Other important aspects of the history include nutritional habits, exercise, past medical history, and medication use [2, 6, 7]. Prior treatments, such as chemotherapy or radiation, may cause gonadal failure [1, 6]. Nonetheless, patients with hypergonadotropic hypogonadism require a karyotype to rule out gonadal dysgenesis [2].

Associated congenital abnormalities, such as midline defects, skeletal abnormalities like cleft lip, or scoliosis, suggest a congenital type of GnRH deficiency [4]. A central nervous system disorder resulting in pubertal delay may be suggested by neurologic symptoms such as headache, visual disturbances, anosmia, seizures, and intellectual disability [2]. Absent or abnormal sense of smell suggests Kallman's syndrome, which is characterized by GnRH deficiency [4]. An underlying genetic syndrome may be suspected when delayed cognitive development is associated with obesity or dysmorphic features [1].

It is important to also inquire about a family history of delayed puberty [1]. An autosomal dominant mode of inheritance (with or without incomplete penetrance) if often seen in cases of delayed puberty and higher rates of constitutional delay of puberty have been observed in families with congenital GnRH deficiency [8].

Table 12.1 Congenital and genetic conditions associated with delayed puberty

Hypogonadotropic hypogonadism	Hypergonadotropic hypogonadism
GnRH deficiency	Gonadal dysgenesis
Idiopathic hypogonadotropic hypogonadism	Turner syndrome
Kallman's syndrome	Swyer syndrome
Genetic syndromes	Congenital galactosemia
Prader-Willi syndrome	Fragile X permutation carrier
Laurence-Moon-Biedl syndrome	17α-hydroxylase deficiency
CHARGE syndrome	

Genetic Causes of Hypogonadotropic Hypogonadism

Isolated Gonadotropin Deficiency

Hypogonadotropic hypogonadism is present when there is low or normal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in conjunction with low estrogen levels [2]. If there is no evidence of extreme weight loss, an eating disorder, stress, over-exercise, brain MRI is normal and thyroid disease and hyperprolactinemia have been ruled out, then the diagnosis is either constitutional delay of puberty or isolated hypogonadotropic hypogonadism [4]. If hypogonadotropic hypogonadism persists beyond the age of 17 years, then the diagnosis is idiopathic or isolated hypogonadotropic hypogonadism [4]. When this is present in association with anosmia or hyposmia, the diagnosis is Kallman's syndrome [4].

Kallman's syndrome is a genetic disorder where fetal GnRH-secreting neurons fail to migrate from the olfactory placode to the medial basal hypothalamus, which results in agenesis or hypoplasia of the olfactory bulbs and tracts [6]. The incidence is estimated to be 1 in 50,000 females [6]. Mutations in *KAL1* (X-linked recessive, identified only in males) and *FGFR1* (autosomal dominant) genes are associated with the disorder [4].

In addition to a reduced sense of smell, which is usually unrecognized by the patient, other typical clinical features of Kallman's syndrome include delayed puberty and eunuchoid body habitus [6]. The lack of sex hormones causes failure of growth plates in the bone to fuse, resulting in eunuchoid habitus (arm span exceeds height by ≥5 cm). Milder presentations in females, with spontaneous menses have been recognized as well [6]. Other clinical features can include unilateral renal agenesis, midline facial anomalies, short metacarpals, cerebellar ataxia, sensorineural deafness, and synkinesia [4].

Idiopathic hypogonadotropic hypogonadism without the features of Kallman's syndrome has also been reported [9]. The inheritance pattern is autosomal-recessive and the most common cause is related to specific mutations in the gonadotropin releasing hormone receptor (*GNRHR*) gene [4]. Nonetheless, in many cases of idiopathic hypogonadotropic hypogonadism, the cause is unknown [4].

Genetic Syndromes

Different genetic syndromes present with nonisolated congenital hypogonadotropic hypogonadism. Patients with Prader-Willi syndrome present with massive obesity, infantile hypotonia, mental retardation, short stature, and characteristic facies [2]. Delayed puberty is hypothalamic in origin and in some patients, related to a deletion of the long arm of chromosome 15 is found [2]. Laurence-Moon-Biedl

syndrome is an autosomal-recessive disorder associated with obesity, polydactyly, mental retardation, and retinitis pigmentosa, in addition to delayed puberty [10]. The CHARGE syndrome (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness) is linked to a heterozygous mutation of the CHD7 gene and is associated with multiple malformations, developmental delay, and idiopathic hypogonadotropic hypogonadism [11].

Genetic Causes of Hypergonadotropic Hypogonadism

Gonadal Dysgenesis

Turner syndrome is a chromosomal disorder with an incidence of 1 in 2,500 live-born females [12]. Patients have a 45,X karyotype with or without mosaicism [13]. Other karyotypes that may be mosaic with 45,X most commonly include 46,X,i(Xq), 46,XX, 46,X,del(Xp), and 46,XY [13]. The classic presentation includes short stature and delayed puberty [13, 14]. While most patients with 45,X genotype will have delayed puberty due to ovarian failure, about 10 % of them progress through puberty and menstruate spontaneously [13]. Patients with mosaicism are more likely to have normal puberty [13]. For patients with 45,X/46XY the phenotype can be variable and unpredictable, with some patients presenting with normal female phenotype and others with ambiguous genitalia [13]. In patients with 45,X karyotype it is recommended to exclude the presence of a Y cell line with the use of fluorescent in situ hybridization (FISH) [13]. While most patients with Turner syndrome have normal intelligence, about 10 % have substantial developmental delays [14]. In addition, many patients have difficulties with visual-motor skills, visual attention, executive functioning, planning, and problem solving [14].

Other features of Turner syndrome are variable and include edema of the hands or feet, webbed neck, low posterior hairline, nail dysplasia, small mandible, characteristic facies, cubitus valgus, short fourth metacarpal, and high arched palate [15, 16]. Cardiac anomalies occur in approximately 50 % of patients and include bicuspid aortic valve, coarctation of the aorta, and dilated aortic root [17]. All patients should undergo comprehensive cardiovascular evaluation [14]. One major concern is the occurrence of aortic dissection during or after pregnancy and Turner syndrome should be viewed as a relative contraindication to pregnancy [14, 18]. Congenital malformations of the urinary system are present in about 30–40 % of patients [14]. In addition, there is an increased incidence of autoimmune disorders in patients with Turner syndrome, including autoimmune thyroid disease, celiac disease, inflammatory bowel disease, alopecia areata, and diabetes mellitus [19].

Swyer syndrome is characterized by a 46,XY karyotype with gonadal dysgenesis, resulting in female phenotype with normal external female genitalia [2]. Patients have streak gonads and do not produce antimullerian hormone, therefore allowing

the Mullerian system to develop [2]. In only 20 % of cases, a mutation of the SRY gene is found [20]. Patients present with normal or tall stature and delayed puberty. Due to androgen production from adrenal glands, some patients may have sparse pubic hair development [6, 21].

Other Genetic Causes of Hypergonadotropic Hypogonadism

Premature ovarian failure occurs in about 80 % of patients with congenital galactosemia and is usually present at an early age [22]. Fragile X permutation carriers can also present with premature ovarian failure [23]. 17α-hydroxylase deficiency is a rare disorder resulting in adrenal insufficiency, hypertension, and lack of sex hormones, including androgens and estrogen [24]. Patients with 46XY karyotype present with female phenotype, delayed puberty, and lack of mullerian structures [24]. A female phenotype, in the setting of normal breast development, but lack of adrenarche and menarche is seen in 46XY patients with complete androgen insensitivity syndrome. This syndrome is caused by a mutation of the gene coding for the androgen receptor [2]. Patients have elevated LH levels with adult male testosterone levels and normal FSH [2].

Treatment of Genetic Causes of Delayed Puberty

Treatment for delayed puberty should be aimed at the specific cause for the delay. Females with a genetic cause resulting in delayed puberty universally lack estrogen production, whether it is due to gonadal failure or low gonadotropin production. The main goals of treatment with estrogen include allowing for the development of secondary sex characteristics, inducing a peripubertal growth spurt and improving the constitution of bone mass to prevent accelerated bone loss [2].

In general, estrogen therapy should be initiated around the time that coincides with normal pubertal development [1]. The goal is for the patient to have breast development and eventually menstruation around the same time as peers [14]. One important consideration about the timing of therapy initiation is the patient's current height and bone age [2, 14]. Estrogen therapy is usually initiated when the bone age is between 12 and 13 years [2]. For patients with Turner syndrome, the timing of initiation of estrogen therapy is usually more complex than in other conditions, due to their short stature and use of growth hormone [14]. Management of patients with Turner syndrome requires a multidisciplinary team, involving pediatric endocrinologists, gynecologists, cardiologists, geneticists, behavioral health experts, and social workers [14].

Estrogen therapy is initiated at a low dose, followed by progressive dose increases over time [2, 6, 14]. Progesterone is usually added after 1 or 2 years of estrogen monotherapy or at the time of breakthrough bleeding [2, 14]. The initial focus of

treatment is achieving breast development and after 1 or 2 years, menstruation. Estrogen can be given orally or transdermal [1, 14]. Oral options include conjugated equine estrogen, starting at a low dose of 0.3 mg daily [1, 6]. For Turner syndrome patients, the transdermal route is preferred at the initial stages of development [14]. The transdermal patch contains 17β-estradiol and beginning doses can be as low as 6–7 μg of estradiol daily and then may be gradually increased over several years [14]. After 1 or 2 years of initiating estrogen or upon breakthrough bleeding, progesterone should be added. Options for progesterones include oral micronized and non-micronized progesterone for 10 days monthly. Another option is switching to oral contraceptives pills [6, 14].

While patients with Kallman's syndrome and other causes of delayed puberty usually have normal stature, short stature is a common feature of Turner syndrome [14]. Growth hormone therapy has become the standard of care for height augmentation in this condition and should be considered as soon as decreased linear growth velocity is noted [14, 25]. Final height is maximized if therapy is started at a young age and dosing should be individualized and adjusted according to the patient's growth velocity [14]. As mentioned above, consultation with a pediatric endocrinologist is recommended for optimal treatment of height in a patient with Turner syndrome.

Another important aspect in the management of females with delayed puberty is the need for gonadectomy specifically among those with a 46,XY cell line [13]. Turner syndrome patients with mosaicism containing Y material, Swyer syndrome patients and 46,XY patients with 17α-hydroxylase deficiency, all require removal of the gonads due to the risk of gonadoblastomas and subsequent germ cell tumors [6, 13, 24].

A multidisciplinary approach is recommended for all patients with delayed puberty to optimize growth and development. Hormone replacement therapy should be timed appropriately and need for growth hormone should be assessed. The presence of a Y cell line should be investigated since its presence is an indication for gonadectomy due to the risk for development of gonadoblastoma.

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Chapter 13
Consideration of Pubertal Events Among Patients with Disorders of Sexual Differentiation

Roshanak Mansouri

Abstract Disorders of sexual differentiation (DSD) are a diverse group of disorders defined as congenital conditions with atypical development of chromosomal, gonadal, or anatomic sex. These disorders are frequently identified in the neonatal period, although some can be identified in utero or later in life. They can result from exogenous hormonal exposures, aberrant gonadal hormonal production, or defects of anatomic development. Patients can require complex hormonal and genetic testing and consideration of anticipated gender identity. The diagnosis and treatment of these disorders is best approached by a specialized multidisciplinary team that includes endocrinologists, urologists, gynecologists, geneticists, psychiatrists, psychologists, and social workers. Treatment should encompass medical, surgical, and psychosexual needs. When considering pubertal development in relation to disorders of sexual differentiation, the clinician must consider the presence or absence of gonads at the time of puberty, functionality of the gonads, adult height potential, sex assignment, presence of reproductive organs, and potential for fertility. Because disorders of sexual development can affect the hypothalamic–pituitary–gonadal axis, either secondary to absence of sufficient hormone or overproduction of undesired hormone, clinicians often have to manage the peri-pubertal period with medication to achieve desired pubertal results.

Keywords Sexual differentiation • Gonadal dysgenesis • Androgen insensitivity syndrome • 5α Reductase deficiency • CAH • Gonadectomy • Hormonal therapies • Sex assignment • Pubertal progression

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Introduction

Disorders of sexual differentiation (DSD) are a diverse group of disorders defined as "congenital conditions with atypical development of chromosomal, gonadal, or anatomic sex." [1]. These disorders are frequently identified in the neonatal period, although some can be identified in utero or later in life. They may result from exogenous hormonal exposures, aberrant gonadal hormonal production, or defects of anatomic development. Patients require complex hormonal and genetic testing in order to assign gender. The diagnosis and treatment of these disorders is best approached by a specialized multidisciplinary team that includes endocrinologists, urologists, gynecologists, geneticists, psychiatrists, psychologists, and social workers. Treatment should encompass medical, surgical, and psychosexual needs [2].

When considering pubertal development in relation to disorders of sex differentiation, the clinician must consider the presence or absence of gonads at the time of puberty, functionality of the gonads, adult height potential, sex assignment, presence of reproductive organs, and potential for fertility. Because disorders of sexual development can affect the hypothalamic–pituitary–gonadal axis, either secondary to absence of sufficient hormone or overproduction of undesired hormone, clinicians often have to manage the peri-pubertal period with medication to achieve desired pubertal results.

Diagnosing Disorders of Sexual Differentiation

One difficulty in considering puberty in the setting of DSD is the realization that DSDs can be diagnosed over a wide range of time periods in the patient's life. The clinician will need to treat each case differently based on the age of the patient and the stage of development at the time of diagnosis. The earliest time at diagnosis can be prenatal. The circumstances of diagnosis can range from targeted diagnosis secondary to a family history of DSD, discovery of abnormal genitalia by prenatal ultrasound, or a discrepancy between phenotypic sex observed by ultrasound and that observed by prenatal karyotype, either by amniocentesis or chorionic villus sampling [3].

Many who are not diagnosed prenatally are diagnosed in the neonatal period. In the case of ambiguous genitalia, often an extensive workup including hormonal and genetic testing, imaging, and occasionally surgical management may be undertaken. Diagnosis and sex assignment are only achieved after considering numerous factors, including anatomic structure, hormonal exposures in utero, potential for fertility and reproduction, and potential gender identity. Given the complexity of these decisions, often management occurs with a specialized multidisciplinary team [4].

Others are born with apparent male or female genitalia, but in the process of undergoing puberty are found to have precocious, delayed, or heterosexual (rather than isosexual) pubertal development, ultimately leading to clinical investigation.

Pubertal Progression in Common DSDs

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is the most common DSD. It results most commonly from 21-hydroxylase deficiency, but can also be secondary to other mutations in the steroidogenesis pathway. In its classical form, where loss of functional enzyme is in the range of 95–100 %, the adrenal gland is unable to convert 17-hydroxyprogesterone to 11-deoxycortisol, and the excess 17-hydroxyprogesterone is shunted toward the androgen pathway. Variable penetrance of loss of function of the enzyme results in both mild and severe forms, with either presence or absence of salt-wasting. The treatment for this condition is glucocorticoid therapy starting from birth, with or without mineralocorticoid therapy. Untreated or poorly controlled CAH leads to chronically elevated androgen levels. In both males and females, chronically elevated androgens can lead to precocious adrenarche and subsequently central precocious puberty [5].

In women, chronically elevated androgens around the time of puberty can contribute to continued relative hyperandrogenism, resulting in anovulation or even a phenotype similar to that of polycystic ovarian syndrome (PCOS) [6]. This environment of androgen excess, whether attributed to PCOS or CAH, has also been associated with insulin resistance, obesity, and decreased fertility secondary to anovulation.

Females with CAH who have been appropriately treated may progress through pubertal development normally. The mean age at menarche for this population who receives treatment falls within the range of normal, although mean adult heights are reported to be slightly lower than that of the general population [7]. Because precocious puberty can contribute to accelerated epiphyseal closure and reduction of final adult height, children who present with precocious puberty need suppression of early central precocious puberty, usually with a GnRH agonist. Frequently, women with CAH will require treatment for irregular menses and androgen excess, which can be achieved with a combined hormonal contraceptive after puberty.

Gonadal Dysgenesis

Gonadal dysgenesis results from a failure of the gonads to develop during embryogenesis. Proper gonadal development requires the presence of germ cells, gonadal ridge somatic cells, and sex chromosomes. In gonadal dysgenesis, these cells fail to appropriately develop and instead functional gonadal tissue is replaced by non-functional fibrous tissue, hence the name streak gonads [8].

Gonadal dysgenesis can occur with both 46,XX and 46,XY genotypes, potentially secondary to an autosomal mutation. In both conditions, at variable points in development, there is acceleration of germ cell loss and premature degeneration of the gonads. In complete gonadal dysgenesis, internal and external genitalia are

developmentally female. Many of these patients are diagnosed at puberty, when pubertal delay prompts checking of a karyotype. There may be a small amount of adrenarche secondary to adrenal androgen production. Once detected, intra-abdominal gonads in the presence of a Y chromosome should be removed. There is a risk of tumor development, most commonly gonadoblastoma, but also dysgerminoma, mixed germ cell types or embryonal carcinoma [8].

Complete gonadal dysgenesis patients will have non-function of the gonads, with or without gonadectomy whereas those with mixed gonadal dysgenesis will have some function of varying degress. Puberty is induced with exogenous estrogen or testosterone, based on the assigned sex. Timing the initiation of pubertal development depends on height potential, bone age, and evidence of central hypothalamic and pituitary activation (elevated LH, FSH).

A variant of 46,XX gonadal dysgenesis is Perrault syndrome, which is the association between gonadal dysgenesis and deafness. Multiple mutations that may contribute to gonadal dysgenesis have been identified [9].

The absence of two functional X chromosomes, as in Turner syndrome (TS), the most common sex chromosome DSD, also results in gonadal dysgenesis. Patients with Turner syndrome can be suspected and diagnosed prenatally or at birth if there are other stigmata of Turner syndrome present, such as cystic hygroma, cardiac defects, or renal anomalies on prenatal ultrasound, or if there is webbed neck, shield chest, widely spaced nipples, low hairline, or high arched palate found during the newborn exam. Because of the lack of functional gonadal tissue, another 35 % of patients are diagnosed with short stature in childhood or with pubertal delay [10].

An important component of pubertal development for all children is achievement of an appropriate adult height within the realm of their inherent genetic potential. In Turner syndrome, approximately 95 % of patients have short stature. Girls with TS who do not receive growth hormone have an average adult stature approximately 20 cm below normal. Growth hormone should be considered in TS as soon as decreased growth velocity is noted. Monitoring for side effects and dose adjustments based on growth velocity are best achieved by a pediatric endocrinologist [10].

Hormonal management for pubertal development is approached similarly for patients who are hypogonadal secondary to 46,XX gonadal dysgenesis, Perrault syndrome, and Turner syndrome. While patients with Turner syndrome can have some spontaneous pubertal development, especially in those with mosaic karyotypes, most patients will require hormone therapy for breast development, uterine growth, and bone health. Hormone therapy is begun around the age of normal pubertal development. LH/FSH are checked prior, and increasing levels to the failure range can indicate both that the central pubertal activation has begun and that spontaneous puberty from gonadal hormone production is unlikely to occur. In patients with TS, anti-mullerian hormone and inhibin B values also have been shown to be predictive of ovarian failure. Approximately 20–30 % of TS will have some spontaneous pubertal development, and if this does occur, it can be monitored clinically for appropriate progression [10, 11]. Hormone therapy can then be started at the time indicated for ovarian failure or if irregular menses occur. It is currently difficult to predict the timeframe of normal ovarian function in patients who undergo spontaneous pubertal development in TS [12].

Exact timing of estrogen supplementation in the peri-pubertal period has also been controversial. There has been a concern that early addition of estrogen or doses that are too high in early puberty can accelerate closure of the epiphyseal growth plate, in the same way in which precocious puberty can cause short stature [13]. However, studies have shown that earlier addition of low-dose estrogen can increase the growth velocity just before final closure of the epiphyses, mimicking the growth spurt that occurs with natural puberty [14]. Development of secondary sex characteristics at this time also helps with psychosocial development and maturation [15, 16].

When the patient is ready to begin hormonal therapy, the optimal dosage and timing must be considered. The general principal is to begin with estrogen monotherapy at the lowest available dose and to increase dosing slowly. Breast exams must be monitored for shape and size of breast growth. Estrogen alone is usually continued until menstrual bleeding occurs or until 1–2 years have passed, especially if the uterus has achieved an adult size in this timeframe.

Pubertal development can be achieved with any delivery method of estrogen (oral, transdermal, injectable). One study has shown that transdermal estradiol more closely replicates circulating estrone, estradiol, and bioestrogen concentrations to normal adolescent girls than oral formulations such as micronized estradiol, which undergoes first-pass metabolism through the liver and results in higher circulating estrone concentrations [17]. However, some patients might find taking a daily pill easier or more acceptable and may prefer pubertal induction with that method.

Once pubertal development has been achieved with estrogen monotherapy, and after the passage of 1–2 years' time or when breakthrough bleeding occurs, cyclic progesterone is added to the regimen. At this time, some patients prefer to switch to cyclic oral contraceptive pills, both for acceptability and ease of use. The combined hormonal patch or combined hormonal vaginal ring formulations can be acceptable for this use as well. Some patients will prefer to continue with the original transdermal or oral estradiol and add progesterone in a cyclic fashion.

In patients with TS, there has been some concern that a theoretically elevated baseline thrombotic risk may be exacerbated by estrogen supplementation. However, the elevated risk with estrogen use has been extrapolated from other populations, such as post-menopausal women. Currently no studies address this adequately in TS patients and therefore this concern requires further study in this population [18].

Aside from the pure forms of gonadal dysgenesis, there is mixed gonadal dysgenesis, in which there is usually one testis of variable functionality and one streak gonad. There are variable levels of virilization of the external genitalia. Internal genitalia can also be variably developed, with the side of the testis usually developing Wolffian structures and the side of the streak gonad developing Mullerian structures. Frequent genotypes are 45X/46,XY mosaic, or 46,XY. For some of these patients, because of the presence of Y chromosome and intra-abdominal dysgenetic gonads, unilateral or bilateral gonadectomy may be required. Pubertal development will occur via a combination of natural pubertal progression and hormone replacement in concordance with the sex assignment at the time of natural puberty [19, 20].

Androgen Insensitivity Syndrome

Androgen insensitivity syndrome encompasses a set of conditions that are due to mutations or deletions of the androgen receptor causing either reduced or completely absent functionality. In complete androgen insensitivity syndrome (CAIS), there are no responses from the target tissues to androgens, but a functional gonad that produces normal levels of these androgens. Thus, affected patients have an externally female phenotype but 46,XY karyotype and hormonally active testes. Due to the presence of anti-Müllerian hormone from the testes, patients have regression of the Müllerian structures, leading to an absent uterus and fallopian tubes, and a blind ending vaginal pouch [21].

Because of a small increase in cancer risk, many patients with CAIS undergo gonadectomy at an early age, while others elect to defer this removal until after puberty occurs [2]. If gonadectomy occurs prior to puberty, hormonal replacement therapy is required, both to advance through puberty with the correct secondary sexual characteristics and to achieve greatest adult height potential, but also to achieve protection of bone density and progression of normal psychosocial and psychosexual development. As with other hypogonadal states, treatments attempt to replicate the normal hormonal increase and timing of natural puberty, either with oral, transdermal, or injectable estrogen monotherapy. Few studies looking at estrogen delivery are specific to CAIS. Information can be extrapolated from other populations that patients generally have a low thrombotic risk, and treatment should continue from the onset of puberty to the average age at menopause to prevent other comorbidities associated with premature ovarian insufficiency. At present, specific information is not available for the best delivery method in CAIS, though transdermal approaches have been studied in patients with Turner syndrome and in adult perimenopausal women [22]. Because patients with CAIS do not have a uterus, there is currently no good evidence necessitating the use of cyclic progesterone in these patients. However, like other hypogonadal patients, they are often transitioned to a combination method such as an oral contraceptive pill after the development of secondary sexual characteristics is complete to simplify hormonal delivery.

Some data are available regarding spontaneous progression through puberty if gonads are not removed in CAIS. Increasing gonadal production of testosterone can lead to female pubertal development through peripheral conversion of androgens to estrogens. Timing of the onset of puberty is at around the same age as normal girls, and the pubertal growth spurt resembles that of a normal female, but final height is between what is expected for women and for men [23]. Studies looking at bone density and body proportions have indicated that body proportions, bone maturation, and adult height in those with intact gonads more closely resembles that of normal male development. One proposed theory suggests that estrogen supplementation, even in this subset of patients with intact gonads, may skew pubertal development more toward female parameters [22].

Partial androgen insensitivity syndrome (PAIS) encompasses the spectrum of patients who have reduced functionality of the androgen receptor. Like CAIS, all of these patients have functional testes, but these patients can present at birth with

external phenotypes on a spectrum from minimally virilized female to minimally undervirilized male. Especially when genitalia are ambiguous, a specialized multidisciplinary team needs to evaluate the patient to confirm the diagnosis, determine the reconstructive surgical possibilities, anticipated gender assignment, and ultimate gender identity, as well as the potential for future sexual function and fertility. Cryptorchid testes in this population carry a risk of malignancy; therefore, removal is generally recommended [24].

Once a sex assignment is made, hormonal replacement may then be used for pubertal development according to the sex assignment. Many patients with PAIS receive a male sex assignment. If there is a descended testis that is left in situ for pubertal development, then development may progress on its own or require augmentation. If a bilateral gonadectomy has occurred, then testosterone is begun at the time of expected pubertal development and increased slowly to replicate the usual tempo of puberty. Some retrospective evidence suggests that patients with PAIS may benefit from supraphysiologic testosterone doses for the benefit of their secondary sexual characteristics, but this has not been studied prospectively, nor have there been studies looking at other factors or risks, such as body composition, as a result of this supraphysiologic dosing [25].

In the case of female sex assignment, gonadectomy would generally be performed prior to puberty, and estrogen monotherapy begun around the age of normal female puberty. Rarely, AIS patients have been reported to have Mullerian remnants [26]. Some of these remnants may be removed at the time of gonadectomy. However, if there is a possibility of functional endometrium with Mullerian remnants in place, the patient should be monitored for vaginal bleeding or abdominal pain, which may result from activation of functional endometrium when the outflow tract is obstructed and distends the remnant cavity.

5α Reductase Deficiency

5α Reductase deficiency is an autosomal recessive condition that results in the inability of the body to convert testosterone to dihydrotestosterone (DHT), the hormone which is responsible for the virilization of the external genitalia in genetic males. Thus, affected patients would have 46,XY karyotype and either ambiguous or female external phenotype at birth. Testes are normal and secrete Müllerian inhibiting factor, so the uterus and fallopian tubes are absent. There can be difficulty in diagnosis, especially because a wide spectrum of phenotypes has been reported [27]. If the patient appears more virilized, the condition can be confused with the androgen insensitivity syndromes. If the external genitalia are largely feminized (for example, isolated mild clitoromegaly), the condition may be missed in the neonatal period. If no diagnosis is made until the time of puberty, the patient will begin to virilize at puberty, which can be difficult if the sex assignment at birth was female. These patients have also been noted to have a predominantly male gender identity, and recommendations are currently to strongly consider male sex assignment [1].

Like the other 46,XY DSDs, sometimes gonads can be intra-abdominal, though the data is sparse about the risk of malignancy in this condition. In this case, patients must be counseled about the risks and unknowns. Many patients currently do receive gonadectomy, and in hypogonadal patients, hormonal supplementation at the time of puberty in accordance with the sex assignment can be carried out, as previously described. For undervirilized patients raised as males, DHT gel has been used successfully in prepubertal children to increase penile length [28], but its use in pubertal children has not been well studied [29].

Ovotesticular DSD

Ovotesticular DSD refers to a set of conditions where both ovarian tissue and testicular tissue are present in the gonads of the same patient. The tissue can be present in the form of an ovotestis, with both ovarian and testicular tissue present in the same gonad, or in the form of one ovarian gonad and one testicular gonad. Several techniques for identification of the ovotestis have been described, including hMG, ultrasound, or stimulation with FSH to evaluate for follicular tissue in a patient with suspected ovotestis. Because the risk of malignancy requires removal of the intra-abdominal testicular tissue, and because sex assignment may also necessitate gonadectomy, pubertal development may require hormonal replacement and will need to be tailored to the individual patient in consultation with a multidisciplinary team [30].

Gonadectomy and Pubertal Hormonal Replacement

In general, DSD is associated with gonadectomy both for the prevention of malignancy and for the prevention of future virilization [2]. Patients with DSD may have an increased risk of gonadal malignancy, and assessing parameters, risk factors, and mutations that may predispose to these malignancies has been a large area of study. Those with dysgenetic intra-abdominal gonads and a Y chromosome are at the highest risk, with the risk of malignancy reported with an incidence between 15 and 50 %. Others are divided into intermediate (Turner + SRY, 17β-HSD, those with gonadal dysgenesis or PAIS with a scrotal gonad) and low-risk (CAIS, ovotesticular DSD, Turner syndrome–SRY) categories. There is a paucity of information regarding tumor risk with 5α reductase deficiency and Leydig cell hypoplasia [31].

The optimal timing for gonadectomy is in childhood (or at diagnosis) among those with dysgenetic intra-abdominal gonads with the presence of a Y chromosome [2, 20, 32]. However, in the low-risk category, some patients may defer gonadectomy. Tumor risk increases with age, but in CAIS the incidence is around 3.6 % at age 25. In situ gonads can confer the benefit of some natural pubertal development and allow the patient to take part in the decision making process. Thus, patients with CAIS may elect to leave gonads in place until after pubertal development occurs [2].

Effect of Pubertal Progression on Genitalia

For patients with DSD who are born with genital ambiguities, many of them undergo genitoplasty to feminize or masculinize the genitalia in infancy or early childhood. These surgeries must be undertaken with the recognition that there may be hormonally-mediated changes in the appearance of the genitalia over time, and that they may need revision for surgical scarring or stricture.

For patients with virilizing disorders such as congenital adrenal hyperplasia, many are born with virilized genitalia and undergo clitoroplasty and vaginoplasty at birth. At puberty, these patients must be assessed for patency of the vaginal outflow tract for menstruation and later on vaginal caliber for sexual function. Also, if the underlying disease is poorly controlled and they have persistently elevated androgens, the clitoris can enlarge and require further revision.

For other patients with DSD who receive a male sex assignment, sometimes a uterus or uterine remnant is present internally. Removal of this structure must be carefully considered; while malignancy risk is low, the possibility of hormonal stimulation with estrogen or testosterone, can introduce a risk of menstruation into an obstructed passage, which can ultimately cause pain. This risk, and the future plan for therapy for the patient, can be weighed against the prospective surgical risks of hysterectomy [33].

As mentioned previously, patients who have had gonadectomy will require hormonal replacement to undergo a physiologic puberty. One measure of the progression and effectiveness of this puberty can be the effects on the genital tissues. Clinicians will need to assess the genitalia, degree of virilization, and desired final sex assignment to determine an optimal treatment plan.

Conclusions

Disorders of sexual development are a complex set of disorders arising from abnormalities in the development of the external genitalia and gonads. As such, when diagnosing, treating, and assigning sex to these individuals, consideration of future pubertal development is integral to the decision making process. Though there are some unifying principles, in this heterogeneous group of disorders, often pubertal management must be individually tailored within patient groups.

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Chapter 14
Puberty in Developmentally Delayed or Physically Challenged Patients

Jennifer Bercaw-Pratt

Abstract Puberty is a time of both physical and psychological changes where patients have increasing special needs regarding sexual education, prevention of sexual abuse, and prevention of pregnancy and sexually transmitted infections. Patients with both cognitive and physical disabilities need the same reproductive health care as women without disabilities but may also need specialized care depending on the underlying disability.

Keywords Puberty • Developmental delay • Cognitive disability • Physically disabled

Introduction

The Americans with Disabilities Act of 1990 described a disability as a physical or mental impairment that substantially limits one or more major life activities. Approximately 18.7 % of Americans were found to have a disability in 2010 [1]. Approximately 8.4 % of children under the age of 15 years were found to have a disability in 2010 [1]. Females with disabilities need the same reproductive health care as women without disabilities but may also need specialized care depending on the underlying disability.

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Puberty in Females with Cognitive Difficulty

For all females, puberty is a time of both physical and psychological changes. There is growth in stature, development of secondary sexual characteristics, changes in the neuroendocrine system, onset of menses, and changes in bone size and composition. These changes are challenging for all females but may cause difficulties in females with cognitive difficulty particularly. Nonetheless, parents and providers must begin the transition of caring for a child to caring for a young woman.

In general, females with cognitive difficulty should undergo puberty at the same time and with the same tempo as females without cognitive difficulties. However, depending on the cause for cognitive difficulty, there may be an increased risk for either precocious or delayed puberty. There are many common conditions causing abnormalities of puberty in developmentally delayed females (Table 14.1). When one of these conditions is identified, providers should have a high level of suspicion for pubertal abnormalities and should monitor the patient's height, weight, and pubertal development closely. As with the female without cognitive difficulties, delayed puberty is diagnosed when there is no pubertal development by age 13 or no menarche with other pubertal developments at age 15.

Educating Parents of Females with Cognitive Difficulty Concerning Puberty

The parents of females with cognitive difficulties must educate their daughters about body changes that are occurring as puberty progresses. The level of the discussion should be appropriate to the patient's cognitive level of understanding, if possible.

The first step in counseling is ensuring that parents are aware of the normal timing and tempo of puberty. Once menstrual cycles begin, parents need to understand

Table 14.1 Causes of puberty abnormalities in females with cognitive difficulties

Causes of precocious puberty	Causes of delayed puberty
Structural brain anomalies	Malnutrition
Brain tumors	Structural brain anomalies
CNS infections (i.e., encephalitis)	Genetic syndromes (for example: Trisomy 21, fragile X syndrome, Prader-Willi syndrome)
History of brain radiation	Brain tumors
History of brain trauma	Polypharmacy (for example: antiepileptic and antipsychotic medications)
	Galactosemia
	History of brain radiation
	History of brain trauma

Table 14.2 The NO, GO, TELL model

NO	The child should be taught to say "No" to an unwanted touch. The child should practice saying "No" loudly and clearly.
GO	The child should look for an avenue of escape and/or call for help to draw attention to the situation.
TELL	The child should have multiple trusted individuals to tell if there is unwanted touching. The child should keep telling others until someone listens and takes action.

Data from Schwier K, Hingsburger D. Sexuality: your sons and daughters with intellectual disabilities. Maryland: Brookes Publishing Co; 2000

what constitutes a normal menstrual cycle in the first few years after menarche. Parents are often concerned about hygiene following menarche and can be reassured that females who are able to self toilet are also often able to manage menstrual hygiene [2]. Occupational therapists have experience in teaching about body cleansing and can assist in teaching females menstrual hygiene although no studies specifically address this.

As the patient develops secondary sexual characteristics, it is important for the parents and providers to provide sexual education to these females. The education should be given proactively and at a level appropriate for the level of understanding if possible. The sexual education discussion may include reviewing the names of various body parts, teaching modesty and privacy, understanding the difference between appropriate and inappropriate touching, discussing how babies are conceived, and knowledge of contraception as well as sexually transmitted infections [2].

Sexual abuse is often a concern for parents of females with cognitive disability when the child reaches puberty. Unfortunately, children with cognitive disabilities are at increased risk of sexual assault with prevalence statistics ranging from 25 to nearly 83 % [2]. The unfortunate reality is that the victims often know the perpetrators [2]. A popular tool for young children with cognitive difficulties to use to protect themselves is the "No-Go-Tell" tool which is described in Table 14.2 [3]. Sexual abuse can result in unintended pregnancy and exposure to sexually transmitted infections including the human papilloma virus. Parents and providers can minimize these risks by having a high awareness of behavioral changes and physical signs of sexual abuse (Table 14.3). If desired, parents may choose to start their adolescent female on contraception and immunize her against human papilloma virus as a means to prevent some of the complications of sexual abuse [2].

Challenges in the Office Visit Regarding Puberty in Females with Cognitive Difficulty

A female with a cognitive disability may provide challenges in the office visit. One challenging factor is that the female may not be able to participate in the medical interview. At times these difficulties can be overcome by providing the child with

Table 14.3 Signs and symptoms of abuse

Behavioral indicators	Physical indicators
Significant changes in behavior such as aggression	Difficulty walking or sitting
Social withdrawal	Torn or bloody underwear
Sleep disturbances	Genital or anal trauma
Sudden avoidance of specific individuals or situations	Genital or anal itching or pain
Shying away from touch	Ongoing, unexplained medical problems such as stomachaches or headaches
New or detailed understanding of sexual behavior	

Data from Reproductive health care for adolescents with disabilities: supplement to guidelines for adolescent health care. Second edition. Washington DC: The American College of Obstetricians and Gynecologists; 2012

materials in pictorial formats or in simple, basic, straightforward language [2]. Ultimately, the level of cognitive difficulty will determine the level of involvement of the patient. Performing a physical exam on females with cognitive difficulties may also be challenging. Adaptations in the office visit may be necessary in order to make examination comfortable for the patient. Gynecologic evaluation should never be accomplished by physical force or inducement of fear in any patient. If the patient is unable to tolerate the genital examination or becomes combative during the exam, the provider may consider proceeding with an examination under anesthesia [2].

Treatment of Abnormalities in Puberty in Females with Cognitive Difficulty

The treatment of both precocious puberty and delayed puberty in children with cognitive difficulty is not different than in children with normal cognitive function. The treatment goals of puberty abnormalities in the patient with cognitive difficulties are to achieve the final projected genetic height and to develop normal secondary sexual characteristics. However, these children may have additional medical comorbidities that may limit the treatment options. The medical providers should work as a multidisciplinary team in order to coordinate medical care in these situations with consideration of the risks and benefits of the different medical therapies.

One area of particular interest in children with severe cognitive difficulties is growth attenuation. In 2006, a case study was published describing the "Ashley" treatment which consisted of a prophylactic hysterectomy followed by high dose estrogen therapy to result in growth attenuation [4]. The case study led to national media attention and an ethical debate as no studies currently address this type of management. Although the "Ashley" treatment [4] was a deliberate medical treatment to cause

growth attenuation, in clinical experience many parents of children with severe cognitive disability may choose to allow precocious puberty to progress without intervention to indirectly cause growth attenuation. Similarly, parents of children with delayed puberty may refuse treatment to prevent the development of secondary sexual characteristics and menarche. The parents must be counseled that untreated delayed puberty may lead to a hypoestrogenic state which can result in a decreased bone density [5]. In general, patients with delayed puberty should be treated with hormone replacement in order to maximize bone health [5].

Puberty in Females with Physical Disability

Females with physical disabilities in general do not have an increased risk of pubertal abnormalities. These females should be monitored in a manner similar to the general population for height, weight, and pubertal development, although difficulties with hygiene may arise. In the rare cases of females born with cloaca with concurrent difficulties with ambulation, these patients should be evaluated for mullerian anomalies as they are common [6].

Challenges During the Office Visit Regarding Puberty in Females with Physical Difficulty

An office visit for a young female with physical disability may require more preparation than for the typical young female. Prior to the visit, consider scheduling additional time for the visit. The patient should be seen in the most accessible exam room possible with sufficient support staff. At the first visit, the provider should ask the parent(s) and the patient about exam preferences. The patient should be transferred to the exam table in a safe manner if possible. Alternative exam positions may need to be utilized as well. The skin should be examined during the exam for evidence of ulceration due to pressure or assistive devices.

When evaluating for puberty, a pelvic or rectal exam is not typically indicated. However, if either exam is undertaken, care must be taken in females with spinal cord lesions. This is due to possible autonomic hyperreflexia which is a loss of control of the hypothalamic control over the sympathetic spinal reflexes [2]. This is a medical emergency characterized by severe hypertension and bradycardia. Since this is often the first pelvic or rectal exam a young female may have had, the provider should monitor the patient closely for physical signs of autonomic hyperreflexia. Typical symptoms include sweating, piloerection, nausea, and nasal congestion. If symptoms occur, the exam should be stopped and the patients head elevated. Blood pressure should be monitored and symptomatic relief given.

Treatment of Abnormalities in Puberty in Females with Physical Difficulty

Females with physical difficulties may be immobile. The treatment of delayed puberty with estrogen may cause concern given the potential for thrombotic risk [7]. There are minimal data available in regard to the risk of venousthrombosis with the use of estrogen in this population. Clinicians should assess the patient for hypercoaguability by obtaining a careful extended family history prior to prescribing estrogens. Exercise of the extremities should be encouraged in patients who are able to participate for any patient for whom an estrogen therapy is considered. Ultimately, the risk versus benefits of the therapy should be weighed carefully and individualized [7].

Summary

Puberty is a time of both physical and psychological changes where patients have increasing special needs regarding sexual education, prevention of sexual abuse, and prevention of pregnancy and sexually transmitted infections. Patients with both cognitive and physical disabilities need the same reproductive health care as women without disabilities, but may also need specialized care depending on the underlying disability.

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