Partial and Gonadotropin-Dependent Precocious Puberty

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Maryann N. Mugo, MD, Bert E. Bachrach, MD, and Jill D. Jacobson, MD

INTRODUCTION

Puberty is a complex biologic and psychological process marked by the appearance of secondary sex characteristics and the onset of the ability for sexual reproduction in association with skeletal maturation and a rapid increase in growth velocity. Puberty is a gradual process initiated by changes in neuronal function in the hypothalamus that trigger a cascade of neurohormonal events ultimately leading to the characteristic physical changes associated with sexual maturation. Although the neurohormonal process of puberty begins earlier, it is the appearance of body changes that is typically used to define the onset of puberty.

Several possibilities exist to describe deranged progression of puberty. Puberty may occur too early (precocious puberty) or too late (delayed puberty), or the tempo (time from onset to maturation) may be too slow or too rapid. Additionally, puberty can progress along the same prepubertal phenotypic gender (isosexual) or may cross over to the opposite gender (heterosexual, as in virilization in a female). The most common scenarios seen in clinical practice involve either early (precocious) or delayed puberty. Early puberty warrants clinical evaluation to rule out the presence of a tumor or other serious underlying causes and because of the potential association with premature closure of the growth plates, which can lead to adult short stature. Not surprisingly, precocious puberty is alarming to most families, given the associated implications of premature sexual maturation and the attendant psychosocial issues.1

This manual is the first of a two-part review of precocious puberty. This part begins with an overview of normal pubertal development and the classification of precocious puberty. This is followed by a discussion of the general clinical evaluation of precocious puberty and the specific approach to the child who presents with partial forms of precocious puberty or with gonadotropin-dependent precocious puberty (GDPP). The review continues in the next manual with a discussion of gonadotropin-independent precocious puberty (GIPP).

NORMAL PUBERTY

TIMING

The timing of normal pubertal development has come under question in recent years. In 1997, a study from the Pediatric Research in Office Settings (PROS) reported that puberty was occurring earlier in girls, with thelarche (breast development) occurring as early as age 7 years in whites and age 6 years in African-Americans.2 Based on the findings in the PROS study, the Lawson Wilkins Pediatric Endocrine Society (LWPES) initially recommended that a pathologic cause for precocious puberty be pursued only if breast and/or pubic hair development occurred before age 7 in white girls or age 6 in African-American girls.3 The validity of this new standard was called into question, however, partly because evaluation of girls in the PROS study was performed via visual inspection only, with no accompanying palpation, and because of concerns about the randomness of the selected population. Although the PROS study suggested that pubertal changes were occurring earlier in girls, the vast majority of patients in the study with early pubertal changes displayed single signs of puberty and therefore did not meet the definition of true precocious puberty. The recommendation to lower the ages of normal puberty was also criticized by several pediatric endocrinologists, who felt that serious pathology would be missed if the accepted age of puberty was lowered.4,5 Based largely on these publications, both the LWPES and The Endocrine Society issued a press release in 2001 reversing their decision and calling for further evaluation of all girls with early signs of puberty. Despite the questions about earlier onset of partial forms of precocious puberty, the age of menarche (initiation of the menstrual cycle) did not appear to have changed.

This review uses the age of puberty originally outlined by Marshall and Tanner in 1969 and 1970 (ie, 8 years in girls and 9 years in boys).6,7 These age guidelines are supported by expert pediatric endocrinologists.8,9 This conservative approach will aid the caregiver in preventing
a misdiagnosis of normal puberty in a child who may have a pathologic cause for early pubertal development.

**ENDOCRINE INFLUENCES ON PUBERTY**

Puberty involves activation of the hypothalamic-pituitary-gonadal (HPG) axis (gonadarche) and maturation of the adrenal axis (adrenarche). The HPG axis is highly active during the midfetal, neonatal, and early infancy periods. Following this phase, there is a stage of relative quiescence from approximately age 2 years to age 8 years when the HPG axis is under inhibitory influences from higher central nervous system (CNS) centers. Only very low amounts of gonadotropin-releasing hormone (GnRH) are present in the circulation and even lower amounts of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

The process of puberty begins with an increase in amplitude and frequency of the pulsatile discharge of GnRH from the hypothalamus. GnRH stimulates the pituitary gonadotrophs to release LH and FSH. Nocturnal LH secretion is augmented as is the LH response to exogenous GnRH administration. Release of LH and FSH promotes maturation of the gonads and an increase in the synthesis and release of sex steroids (estrogen and testosterone). Rising levels of estrogen and testosterone, together with increased adrenal androgens, induce the physical changes of female and male puberty. Adrenarche has been shown to be a progressive maturational event completely independent of gonadarche and may actually begin in early childhood. Adrenarche occurs in both genders and is a gradual process occurring after age 8 years in girls and after age 9 years in boys; however, the effects of adrenal androgens are not necessarily apparent in boys in the presence of the overwhelming effect of testosterone.

Recently, leptin has also been implicated as a potential inducer of puberty, especially in girls, in whom leptin levels rise dramatically during sexual maturation. The opposite is true in boys; testosterone is thought to have a role in suppressing leptin levels during male sexual maturation. In both boys and girls, skeletal maturation is closely associated with the maturation of the HPG axis.

**PHYSICAL CHANGES**

**Girls**

The stages of female sexual maturation according to Tanner and Marshall are shown in Table 1. The initial clinical sign of puberty in a girl usually is thelarche, occurring between the ages of 8 and 13 years; this correlates with Tanner stage 2 (breast bud palpable). During this time, the vaginal mucosa begins to change from its prepubertal reddish color (increased vascularity of the vaginal epithelium) to an estrogenized gray-pink hue (thickened vaginal epithelium). Pubarche (development of pubic hair), which is primarily controlled by the adrenal gland and to a lesser extent by ovarian-derived androgens, usually occurs approximately 1 year after initiation of breast development. Thelarche and adrenarche are independent of each other. Adrenarche is the external sign of the effect of androgens on female sexual maturation. Adrenarche is a maturational change in the adrenal gland that is responsible for the development of pubic hair, axillary hair, adult body odor, and acne via the production of androgens. The appearance of axillary hair is an even later finding, occurring about 2 years after the initiation of pubic hair. Menarche occurs at Tanner stage 4 and occurs on average 2.2 years after initiation of breast development.

Variations of normal in females can include unilateral breast development, with an up to 2-year difference in the timing of the development of one breast versus the other. Breast size is not concordant; size variance from one breast to the other is a common, normal finding. Isolated premature menarche (before age 10 years) is rare and usually associated with true precocious puberty. Vaginal bleeding in the absence of pubertal development requires evaluation to exclude other pathologic causes such as sexual abuse, foreign body, infection, sarcoma botryoides (smooth muscle tumor of the vagina), or granulosa cell tumor of the ovary. Occasionally, patients with McCune-Albright syndrome can exhibit vaginal bleeding without other signs of puberty.

**Boys**

The stages of male sexual maturation according to Tanner and Marshall are shown in Table 2. The first sign of puberty in boys is testicular enlargement, which

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**Table 1. Stages of Female Sexual Maturation According to Tanner and Marshall**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Breast</th>
<th>Pubic Hair</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prepubertal</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Breast bud palpable</td>
<td>Barely visible on mons or labia</td>
</tr>
<tr>
<td>3</td>
<td>Obvious elevation of breast tissue</td>
<td>More visible, darker, and same sites as stage 2</td>
</tr>
<tr>
<td>4</td>
<td>Areola and nipple separate on enlarging breast</td>
<td>More extensive and dark, with extension to the suprapubic area</td>
</tr>
<tr>
<td>5</td>
<td>Adult size and shape</td>
<td>Adult triangle</td>
</tr>
<tr>
<td>5+</td>
<td>Adult size and shape</td>
<td>Extension upward in midline and onto medial aspect of thighs</td>
</tr>
</tbody>
</table>

Adapted from reference 6.
normally occurs between the ages of 9 and 14.3 years. Thinning of the scrotal skin can usually be appreciated around the same time as testicular enlargement. Pubertal testes are greater than 3 mL in volume or 2.5 cm in length. A color-coded orchiometer is useful in estimating testicular size during puberty. Testosterone released from the rapidly enlarging testes results in increased length and breadth of the phallus, with progressive changes in the scrotal skin and size of the scrotum.

The staging of pubic hair development does not necessarily correlate with the staging of the phallus or testes, as pubarche in males can be secondary to gonadarche or adrenarche (ie, activation of androgen secretion from the testes or adrenal glands, respectively). However, the most useful clinical staging involves documenting the size of the testes. Of critical importance on physical examination is that the testes are usually 10 mL to 15 mL in size when the pubertal growth spurt begins.

### Definition and Classification of Precocious Puberty

The appearance of any pubertal changes at an age more than 2.5 standard deviations below established normal standards can be considered precocious. Most children with early pubertal changes, however, will display partial forms of puberty. These are considered normal variants. One of the key determinants in the evaluation of sexual precocity is whether there is a single sign of puberty or more than one sign.

#### Partial Precocious Puberty

**Isolated Premature Thelarche**

Isolated premature thelarche is breast development in the absence of pubic hair development and a growth spurt. Isolated premature thelarche is especially common and unlikely to be associated with pathology between 6 months and 3 years of age. During that age range, isolated premature thelarche is a common normal variant that may develop as the hypothalamic-pituitary-ovarian axis winds down to become quiescent. Premature thelarche differs from neonatal breast hyperplasia, which occurs at birth as a result of maternal estrogen exposure, is transient, and occurs in both boys and girls. The various etiologies for premature thelarche include heightened sensitivity to small amounts of estrogen, small functioning ovarian cysts, and enhanced FSH production.

Estrogen is now known to be responsible for advancement of skeletal age and subsequent fusion of the growth plates. As premature thelarche is a sign of estrogen exposure, girls with isolated premature thelarche are at a greater risk for advanced bone age and for adult short stature compared with girls with isolated premature pubic hair. Further, approximately 14% to 18% of girls with isolated premature thelarche will develop true precocious puberty.

**Isolated Premature Pubarche**

The activation of the adrenal gland (adrenarche) results in mild signs of hyperandrogenism (eg, acne, body odor) and precedes the development of pubic hair. Although premature adrenarche and premature pubarche are sometimes used interchangeably, adrenarche refers to the signs of adrenal androgens and pubarche refers specifically to the development of pubic hair. The occurrence of pubic hair prior to age 8 years in girls and 9 years in boys warrants further evaluation.

#### True Precocious Puberty

True precocious puberty is defined as breast development accompanied by pubic hair development prior to age 8 years in girls and as testicular enlargement and pubic hair development prior to age 9 years in boys. True precocious puberty is associated with a growth spurt. Precocious puberty can be classified according to whether or not it is driven by endogenous gonadotropins. Differentiating between these two main forms is important, as the etiologies and treatments are quite different. In females, 95% of cases of precocious puberty are idiopathic and GnRH dependent, whereas in males,
cases are more likely to involve an underlying pathologic cause. Thus, males warrant an extensive evaluation when determined to have precocious puberty.

**Gonadotropin-Dependent Precocious Puberty**

GDPP, also referred to as true or central precocious puberty, refers to the premature activation of the HPG axis and pulsatile release of GnRH by the hypothalamus secondary to a variety of stimuli. In GDPP, there is physiologically normal activation of the HPG axis, but it occurs at an earlier age.

There are many causes of GDPP, most of which are associated with CNS abnormalities (Table 3). CNS causes appear to interfere with the normal controls on GnRH release, by directly stimulating GnRH release or blocking the inhibitory signals for GnRH release. In addition, correction of a peripheral (gonadotropin-independent) cause of precocious puberty may result in activation of the HPG axis. For example, if one treats a patient for congenital adrenal hyperplasia (CAH) and suppresses adrenal secretion of androgen, the past hormonal exposure may have already primed the activation of the hypothalamus, resulting in physiologic, pulsatile secretion of GnRH. Classically, LH and FSH are elevated, implicating them in the pathogenesis of clinical precocious puberty. LH and FSH involvement can be demonstrated by a robust response to a GnRH stimulation test. However, as GnRH is no longer commercially available, the diagnosis is often made on clinical grounds. Obesity is prevalent in patients with GDPP.

**Gonadotropin-Independent Precocious Puberty**

GIPP, also referred to as peripheral precocious puberty or precocious pseudopuberty, refers to release of estrogen and testosterone that occurs independently of GnRH stimulation. Part 2 of this volume will discuss the approach to diagnosis and treatment of major causes of GIPP.

### APPROACH TO EVALUATION OF PRECOCIOUS PUBERTY

The approach to evaluation of a patient with precocious puberty depends upon gender and clinical signs at presentation. A practical approach is outlined in Table 4 and Table 5. Specific questions to guide this approach are: Is the child a boy or a girl? Does the child have more than one sign of puberty? Is the bone age abnormal? Is the LH prepubertal or pubertal? Is either estrogen or testosterone elevated?

A girl who presents with a single sign of puberty (ie, breast development or pubic hair) has isolated premature thelarche or isolated premature pubarche, respectively. Although both are considered benign conditions, they must be regarded as diagnoses of exclusion. More serious pathology may need to be ruled out, as true precious puberty usually starts with just one sign of puberty. A child who presents with two signs of puberty (breast development and pubic hair in a girl; testicular enlargement and pubic hair in a boy) accompanied by a growth spurt meets the definition of true precocious puberty and will require an extensive workup. The potential pathology and clinical approach differ depending on the number of signs of puberty. In clinical situations in which growth records are not available, reassurance may not be possible and more extensive laboratory evaluation may be necessary. One commonality in the approach, regardless of the presenting sign(s), is continued observation over time.

### HISTORY AND PHYSICAL EXAMINATION

A detailed history and thorough physical examination are essential for developing the differential diagnosis of precocious puberty.

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**Table 3. Causes of Gonadotropin-Dependent Precocious Puberty**

| Idiopathic |
| CNS abnormalities |
| Hypothalamic hamartoma |
| Congenital anomalies (hydrocephalus, suprasellar arachnoid or ventricular cyst, septo-optic dysplasia, empty sella syndrome, myelomeningocele) |
| Postinflammatory (encephalitis, meningitis, abscess, granulomatous disease) |
| Radiation therapy |
| Trauma or other injury (especially if associated with cerebral atrophy or focal encephalomalacia and hypoxic ischemic encephalomalacia) |
| Neoplasms (astrocytoma, ependymoma, glioma, craniopharyngioma, ganglioma, granular cell tumor, pinealomas) |
| Cysts (arachnoid, pineal, glial) |
| Various chromosomal abnormalities (trisomy X) |

**Syndromes**

- Neurocutaneous syndromes (neurofibromatosis type 1, tuberous sclerosis)
- Russell-Silver syndrome
- Williams syndrome
- Sequela of treatment of long-standing gonadotropin-independent precocious puberty

CNS = central nervous system.
Table 4. Approach to Evaluation of Precocious Puberty in Girls

<table>
<thead>
<tr>
<th>Step</th>
<th>Clinical Finding(s)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial screening*</td>
<td>Breast development alone before age 8 yr</td>
<td>Bone age, estradiol, PAH</td>
</tr>
<tr>
<td></td>
<td>Pubic hair alone before age 8 yr</td>
<td>Bone age, 17-OHP, DHEA-S, testosterone, PAH</td>
</tr>
<tr>
<td></td>
<td>Breast development AND pubic hair before age 8 yr</td>
<td>Bone age, estradiol, PAH, 17-OHP, DHEA-S, testosterone, baseline and stimulated LH, unless bone age already ≥ 12 yr†</td>
</tr>
<tr>
<td>Subsequent testing</td>
<td>Elevated estradiol or testosterone with prepubertal LH</td>
<td>Evaluation for GIPP, including ovarian ultrasonography</td>
</tr>
<tr>
<td></td>
<td>LH elevated to pubertal range</td>
<td>Evaluation for GDPP, including cranial MRI</td>
</tr>
<tr>
<td></td>
<td>Elevated 17-OHP</td>
<td>High-dose ACTH-stimulation test</td>
</tr>
<tr>
<td></td>
<td>Elevated DHEA-S</td>
<td>Abdominal CT to rule out adrenal tumor</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Repeat height, weight, and pubertal status every 4–6 mo</td>
<td>If bone age advanced or PAH compromised, repeat bone age every 6 mo</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; CT = computed tomography; DHEA-S = dehydroepiandrosterone sulfate; GDPP = gonadotropin-dependent precocious puberty; GIPP = gonadotropin-independent precocious puberty; 17-OHP = 17-hydroxyprogesterone; LH = luteinizing hormone; MRI = magnetic resonance imaging; PAH = predicted adult height.

*Can be initiated by primary care provider.
†In girls, if bone age is ≥ 12 yr, baseline and stimulated LH levels may be pubertal even if the original etiology of puberty was GnRH independent. Although GnRH stimulation may not be necessary, it will be necessary to consider both GIPP and GDPP causes of puberty.

Table 5. Approach to Evaluation of Precocious Puberty in Boys

<table>
<thead>
<tr>
<th>Step</th>
<th>Clinical Finding(s)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial screening‡</td>
<td>Testicular enlargement alone before age 9 yr</td>
<td>Bone age, hCG, testosterone, PAH</td>
</tr>
<tr>
<td></td>
<td>Pubic hair alone before age 9 yr</td>
<td>Bone age, 17-OHP, DHEA-S, testosterone, PAH</td>
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<td>Testicular enlargement AND pubic hair</td>
<td>Bone age, hCG, PAH, testosterone, 17-OHP, DHEA-S, baseline and stimulated LH, unless bone age already ≥ 13 yr†</td>
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<td>Subsequent testing</td>
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<td>Elevated 17-OHP</td>
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<td>Elevated DHEA-S</td>
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<td>Repeat height, weight, and pubertal status every 4–6 mo</td>
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ACTH = adrenocorticotropic hormone; CT = computed tomography; DHEA-S = dehydroepiandrosterone sulfate; GDPP = gonadotropin-dependent precocious puberty; GIPP = gonadotropin-independent precocious puberty; hCG = human chorionic gonadotropin; 17-OHP = 17-hydroxyprogesterone; LH = luteinizing hormone; MRI = magnetic resonance imaging; PAH = predicted adult height.

‡Can be initiated by primary care provider.
†In boys, if bone age is ≥ 13 yr, baseline and stimulated LH levels may be pubertal even if the original etiology was GnRH independent. Although GnRH stimulation may not be necessary, it will be necessary to consider both GIPP and GDPP causes of puberty.

History

The history should include the current age of the child and the age at onset of the physical change (ie, breast, pubic hair, and/or external genitalia development). Additional specific information that should be gathered from the parent/guardian includes exactly when the change(s) began and, if ascertainable, at what rate of progression (eg, over 3–6 months versus 3 years). The presence or absence of other signs or symptoms (eg, headaches, visual disturbance, rapid growth, rapid weight gain) should be determined. Possible exposure of the child to any hormone-containing medications or products (eg, estrogen, testosterone creams, placental extract-containing hair products) and exposure to chemicals (eg, organochlorine pesticides) also should be determined. A history of bone fractures should be obtained, as patients with McCune-Albright syndrome or neurofibromatosis may exhibit lytic bony lesions that predispose to fractures.

Family history should address the timing of puberty and growth spurt in the parents; any history of ambiguous genitalia, familial diseases (eg, neurofibromatosis), neonatal deaths, skin spots, or other relevant anomalies as well as illness in general; and any familial use of gonadal steroids (eg, oral contraceptives, hormone creams). When evaluating timing of puberty in parents, women often will remember time of menarche or initiation of breast development. Many men do not recall the earliest event in puberty (ie, when their testes started increasing in size). However, most men recall whether they grew after high school.
Physical Examination

The physical examination similarly should encompass a specific set of assessments. Growth pattern should be assessed (eg, does it follow a steady channel or does it cross percentiles?). Calculation of the midparental height (MPH) using the following formula is extremely useful and usually is accurate within 3 in:

\[
\text{MPH in girls} = \frac{\text{mother’s height} + (\text{father’s height} - 5 \text{ in})}{2}
\]

\[
\text{MPH in boys} = \frac{(\text{mother’s height} + 5 \text{ in}) + \text{father’s height}}{2}
\]

If the MPH for a girl using the above formula is 5 ft 4.5 in, this is at the 50th percentile for an adult woman. If the girl is currently growing at the 90th percentile, this should suggest the possibility of a growth spurt and should be a red flag.

The precise stage of puberty also should be assessed. In boys, it should be noted whether there is pubic hair without testicular enlargement. In girls, it should be noted whether the vaginal mucosa is prepubertal (reddish) or estrogenized (pink) and whether there is breast development without any signs of pubic hair or acne. The child should also be examined for any neurologic, visual, or other endocrine findings (eg, hypothyroidism or signs of androgen excess [acne, hirsutism]) as well as for pigmented birth marks (eg, café au lait spots in neurofibromatosis and McCune-Albright syndrome) or hypopigmented skin lesions (eg, tuberous sclerosis). Any abdominal (hepatic) or pelvic masses should be noted. Finally, blood pressure should be evaluated, as it can be abnormal in certain forms of CAH.

SPECIFIC TESTING

Bone Age

Bone age assessment via radiography of the left hand and wrist and comparison to the standards of Greulich and Pyle\(^5\) is essential. Bone age within 2 standard deviations of chronologic age is considered normal; a difference greater than this is considered abnormal and warrants further evaluation, especially if associated with signs of precocious puberty. Bayley Pinneau tables can be used to determine the standard percentage of growth completed and remaining at each bone age as well as the predicted adult height (PAH) for the child.\(^6\) Endocrinologists can compare the PAH based on the Bayley Pinneau method with the MPH that is based on the parents’ heights. If the PAH is more than 3 in below the MPH, excessive hormone exposure must be suspected. On the other hand, perfect concordance between the PAH and MPH can be reassuring. The reading of bone age is highly operator dependent and must be carried out by someone experienced in the field. This issue is even more critical when serial bone age testing is used to monitor patients with suspected precocious puberty.

Growth Curve

Evaluation of the gender-appropriate growth curve to identify any increase in growth velocity is essential in management of the patient. A growth chart containing multiple historical points is invaluable in evaluating precocious puberty.

Biochemical Testing

Several biochemical tests are available to evaluate precocious puberty. It is not necessary to perform biochemical tests in all suspected cases; however, testing is appropriate when the suspicion is strong and the growth curves and bone age support this suspicion. The tests used depend on gender as well as presentation. This testing can be initiated by the primary care provider.

Girls with premature thelarche should have estradiol levels measured (in addition to bone age assessment). Boys and girls with premature adrenarche should have 17-hydroxyprogesterone (17-OHP) and dehydroepiandrosterone sulfate (DHEA-S) levels measured. Boys and girls with true precocious puberty (2 signs of puberty in girls; testicular enlargement and growth spurt in boys) should have free thyroxine and thyroid-stimulating hormone levels measured. Patients with hypothyroidism can occasionally exhibit early puberty, but thyroid hormone levels are an excellent way to screen for a hypothalamic-pituitary defect. Boys with testicular enlargement before age 9 should have human chorionic gonadotropin (hCG) levels measured. hCG binds to the LH receptor, and hCG-secreting tumors can cause precocious puberty in boys. Measurement of hCG is unnecessary in girls, as girls need both LH and FSH stimulation to enter puberty.

Patients with true precocious puberty, premature menarche, or advanced bone age may require GnRH stimulation to assess the status of the HPG axis (pubertal versus prepubertal). GnRH-stimulated LH and FSH testing is still the gold standard. Although the standard GnRH preparation previously used in stimulation testing is no longer available, several centers now use a GnRH superagonist (leuprolide) in stimulation testing. Two forms exist, a short-acting aqueous leuprolide (given subcutaneously) and a long-acting depot leuprolide (given intramuscularly). Both have proven useful in diagnostic testing. Generally, a single injection is followed 30 to 40 minutes later by LH measurements.
by immunochemiluminescent assay. The advantage of the depot form is that a single injection can be used for therapeutic effect and for determination of therapeutic efficacy. The thresholds to distinguish prepubertal LH levels are not as well established using these preparations as with older GnRH. One published study used a peak LH of up to 2.3 IU/L after aqueous leuprolide to define prepubertal levels, whereas another used a peak of 1.4 IU/L. With either the aqueous or depot form, a level greater than 8 IU/L is diagnostic of GDPP. With stimulation, prepubertal children will have a predominantly FSH response, while pubertal children will have a LH-predominant response, with the LH:FSH ratio often greater than 1. A sensitive LH assay should actually be able to distinguish between prepubertal and early pubertal gonadotropin levels even without GnRH stimulation. Although the older radioimmunoassays were not sensitive enough to ensure this discrimination, the newer immunochemiluminescent assays are very sensitive, and an unstimulated LH greater than 0.3 IU/L generally indicates a central process.

Estrogen results should be interpreted relative to the clinical situation. Estradiol levels in GDPP are appropriate for the Tanner stage of development, whereas in estrogen-producing tumors the estradiol concentrations are markedly elevated. Levels of inhibin A and inhibin B appear to be elevated in GDPP.

Breast ultrasonography is useful in both boys and girls when unilateral breast growth is difficult to distinguish from a tumor. Ultrasonographic assessment of the size of the uterus and ovaries can be used as an adjunct to diagnosing precocious puberty. Measurement of uterine and ovarian volumes by pelvic ultrasonography has been found to be sensitive and specific for differentiating between early premature thelarche and early GDPP, which can present similarly. The presence of masses or cysts suggests a cause for GPP, whereas pubertal/maturational changes in the ovaries (increased size with mature follicles) suggests GDPP.

Magnetic resonance imaging (MRI) of the brain should be used to rule out a CNS lesion as an etiology for GDPP. In boys, a search for a CNS cause of GDPP is imperative, while in girls there is still debate on whether imaging is always required. Abdominal computed tomography is the best way to search for an adrenal mass as an etiology for premature adrenarche. Pelvic or testicular ultrasonography is useful in seeking gonadal sources of excess hormone production. An evidence-based diagnosis rule for use of imaging studies in girls was recently developed and is widely used in Europe.

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**PARTIAL PRECOCIOUS PUBERTY**

**CASE 1 PRESENTATION**

An African-American girl, aged 7 years, 7 months, is brought by her mother for evaluation of early breast development. This was first noted approximately 6 months ago by the mother. The patient’s twin sister is currently being followed in the clinic for early breast development, which began about 3 months earlier in that child. The mother believes that the child being seen today has recently begun developing pubic hair as well. She also believes that both girls are growing too fast.

Past medical history is significant for a twin pregnancy. There is no history of birth marks or bone fractures. There is no family history of diabetes, thyroid disease, or neurologic conditions. The mother is roughly 5 ft 7 in and had menarche at age 10 years. The father is 6 ft and reportedly had normal pubertal development.

Review of the growth curve shows that the patient has been tracking between the 90th and 95th percentiles for height and between the 50th and 75th percentiles for weight. Vital signs are normal. Breast examination reveals moderate glandular tissue (firm and resistant to compression). The vaginal mucosa is reddish pink. There is no clitoral enlargement. Pubic hair is Tanner stage 1, with vellus hair present but no terminally differentiated hair. Neurologic examination is normal. There are no café au lait spots.

- **What is the most likely diagnosis?**

Breast tissue growth is driven primarily by estrogen, and this may be gonadotropin dependent or independent. The differential diagnosis for this child’s early breast development includes GDPP (as the initial presentation before pubic hair), an estrogen-producing tumor (eg, granulosa cell tumor, functioning ovarian cysts or tumor, teratoma), and isolated premature thelarche. Obese children often have fatty tissue in the breast area that may mimic the appearance of breast tissue on visual inspection. Palpation is critical in differentiating firmer true breast tissue from the softer fatty tissue.

A key feature of this child’s history is that her breast development is of recent onset and is occurring close to the normal time of puberty. The child’s growth pattern has not shown any recent acceleration that would suggest long-standing effect of estrogen, and there are no other signs of excess estrogen, such as changes to the vaginal mucosa or vaginal bleeding. The absence of both a growth spurt and pubic hair rules out true...
precocious puberty. Like her twin sister, this patient most likely has isolated premature thelarche.

- What management approach would be appropriate for this child? Is further evaluation indicated?

The initial evaluation of the patient with suspected premature thelarche should include obtaining a bone age (radiograph of the left hand and wrist) and consulting the Bayley Pinnue tables to determine whether the patient is on track to reach her MPH. Depending upon the timing of the premature thelarche and physical examination findings, baseline estradiol, LH, and FSH measurements also may be indicated. Unfortunately, estrogen levels in girls with premature thelarche are not easily quantified because of poor sensitivity of the current estradiol assays. Several different methods to improve upon this have been tried including an ultrasensitive recombinant cell bioassay. However, premature thelarche has been shown to be associated with enhanced follicular development similar to that in early puberty, and this is thought to be under the influence of FSH.

Rarely, premature thelarche may be associated with growth hormone (GH) therapy. Some rare conditions have also been associated with premature thelarche, including the Coffin-Siris syndrome and Rubinstein-Taybi syndrome. In some girls, premature thelarche or fluctuating thelarche may be the earliest sign of McCune-Albright syndrome, which is caused by an activating mutation of the GNAS1 gene. Aromatase excess syndrome is a familial condition associated with feminization of both sexes, leading to premature thelarche and macromastia in girls and peripubertal gynecomastia in boys.

If isolated premature thelarche is diagnosed based on the initial clinical assessment, the patient should be monitored closely and return at 4- to 6-month intervals for evaluation to rule out other pathology that may become apparent later. Follow-up visits will be necessary to document a normal growth velocity, lack of continued progression into puberty, and normal bone age. Lack of progression will continue to support the diagnosis of isolated premature thelarche. Imaging other than the influence of FSH.

CASE 1 CONCLUSION

Bone age is assessed at 7 years, 10 months (at a chronologic age of 7 years, 7 months), which is within 2 standard deviations of normal. The patient’s PAH based on this bone age is 5 ft 8.5 in, which is within 3 in and actually higher than her calculated MPH of 5 ft 7 in. At this point, reassurance is indicated, with plans for close follow-up of both sisters.

CASE 2 PRESENTATION

A 5-year-old Caucasian girl is brought by her parents, who report noting pubic hair growth over the last 6 months. The parents have not noted any breast or axillary hair development or any excess hair on the child’s face or on any other part of her body. They report that the child has been growing well up to this point. Since starting kindergarten, she has gained some weight as a result of decreased activity compared with what she had had in preschool. The family has not noted salt cravings, and there is no history of polyuria or polydipsia.

On physical examination, the child is at the 95th percentile for weight and at the 80th percentile for height. Blood pressure is normal for age, and other vital signs are normal. She has no breast buds. The vaginal mucosa is red, there is no clitorimegaly, and the external genitalia are otherwise normal. Skin examination reveals no acne and no acanthosis nigricans. Evaluation of the growth curve reveals a normal pattern.

- What is the differential diagnosis for this child’s presentation?
- What tests would be indicated at this time?

Although most likely a benign condition, isolated premature pubarche must be differentiated from pathologic and potentially treatable causes such as CAH, adrenal tumor, exposure to exogenous testosterone creams, hyperinsulinism, ovarian tumors, and (in boys) familial male-limited precocious puberty (testotoxicosis). Girls with obesity and early adrenarche are at increased risk for development of polycystic ovary syndrome (functional ovarian hyperandrogenism) in adolescence and adulthood, along with its attendant cardiovascular disease risk.

The initial evaluation for patients with suspected isolated premature pubarche includes bone age assessment to screen for excessive hormone exposure, a random 17-OHP level (for the most common form of CAH), 21-hydroxylase deficiency, and a DHEA-S level (for adrenal tumor). An elevated DHEAS level that is appropriate for the Tanner staging will support a diagnosis of benign premature adrenarche. A complete biochemical evaluation is not necessary unless physical examination findings, bone age, and linear growth suggest a pathologic process. If all findings are normal, having the patient return at 4- to 6-month intervals for reevaluation of the physical examination, linear growth, and bone age will suffice. If weight gain accelerates or acanthosis nigricans appears, it may be necessary to perform an oral glucose tolerance test. Supportive evidence for a benign process include a normal linear growth, lack of acceleration of the bone age,
and absence of other signs of puberty, such as breast development or increasing testicular size.

CASE 2 CONCLUSION

The child is found to have a mildly elevated DHEAS level appropriate for degree of pubic hair, with no elevation in 17-OHP. The diagnosis of isolated premature pubarche is made. The physician recommends monitoring the child every 6 months with a clinical examination and bone age assessment. Nutrition education, increased activity, and weight loss management are also recommended.

GONADOTROPIN-DEPENDENT PRECOCIOUS PUBERTY

CASE 3 PRESENTATION

A Caucasian girl, aged 8 years, 4 months, is referred by her pediatrician and presents with her mother for evaluation. The pediatrician reported that she recently evaluated the child (at age 7 years, 11 months) and noted her to be in the earliest stages of breast and pubic hair development. She then received a call from the mother 5 months later, reporting that her child just experienced menstrual bleeding. The pediatrician initiated a work-up and referred the child for evaluation.

History reveals that the patient has been healthy. She was hospitalized once at age 20 months for a head injury from a fall. She experienced dehydration related to recurrent vomiting after that injury. There were no other known sequelae to this incident. There is no history of bone fractures. Family history reveals that the mother is 5 ft 6 in and the father is 5 ft 11 in, giving the patient a calculated MPH of 5 ft 6 in.

The mother had menarche at age 12 years.

Review of growth records reveals that the patient was tracking between the 75th and 90th percentiles until 24 months of age and then, between the ages of 4 and 6 years, crossed down to between the 25th and 50th percentiles. She subsequently had a growth spurt. On current evaluation, the child’s height is above the 75th percentile. Her weight also has recently increased.

Physical examination reveals normal vital signs. The main findings are Tanner stage 3 pubic hair and Tanner stage 3 breast development. There is no acne, and there are no changes in skin pigmentation.

Bone age is assessed as 12 years (at a chronologic age of 8 years, 4 months), giving the patient a PAH of 4 ft 11 in. Initial laboratory studies reveal normal thyroid function, a 17-OHP level of 181 ng/dL, and an adrenocorticotrophic hormone (ACTH)–stimulated 17-OHP level of 206 ng/dL. The remainder of the CAH work-up is negative.

- What is the differential diagnosis for this child’s presentation?

With both breast and pubic hair development and a growth spurt occurring before age 8 years, this patient meets the definition of true precocious puberty. The documented decrease in height percentiles between the ages of 24 months and 4 years is highly unusual. Most children do not cross percentiles beyond 19 months of age. This might raise the suspicion of GH deficiency. Pathologic central processes can often result in GH deficiency in combination with precocious puberty. These two conditions can mask each other, resulting in a normal growth velocity.

- What can be surmised from the initial test results?
- What further tests would be indicated at this time?

The normal thyroid function in this patient argues against a major hypothalamic-pituitary defect. Although the baseline 17-OHP was elevated, the ACTH-stimulated 17-OHP value of just 206 ng/dL rules out 21-hydroxylase deficiency as well as the carrier state. The discrepancy between the patient’s PAH (4 ft 11 in) and her calculated MPH (5 ft 6 in) indicates hormone excess leading to advanced bone age, and a work-up for the source of hormone excess is indicated. Because of the close relationship between skeletal maturation and central puberty, it would be expected that gonadotropin levels would be pubertal in a girl with a bone age of 12 years, regardless of whether the original etiology of sexual precocity was GnRH dependent or GnRH independent. In other words, once the bone age is advanced to 12 years by any mechanism, the GnRH pulse generator will be activated. Thus, when the bone age is greater than 12 years, peripheral etiologies of sexual precocity should remain in the differential diagnosis. On the other hand, GnRH-stimulation tests may not be helpful or even necessary in these cases, as they do not aid in the differential diagnosis. Pelvic ultrasonography and brain MRI should be performed. For GDPP, if a CNS mass or tumor is causing the condition, surgery or other appropriate therapy (eg, radiation) may be needed.

CASE 3 CONTINUED

Results on further biochemical studies are: LH, 0.3 IU/L (low pubertal range); FSH, 2.9 IU/L; testosterone, 26 ng/dL (normal, 14–76 ng/dL); DHEAS, 101 µg/dL (normal, 35–43 µg/dL); estradiol, 11 pg/mL; peak GH, 20.2 ng/mL (normal). Pelvic

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ultrasonography shows a pubertal uterus and multiple follicles in the ovaries. Brain MRI is normal, suggesting an idiopathic etiology.

- How should this patient be treated, and what is her prognosis?

Failure to treat this patient would result in reduced final height and the risk for psychosocial problems. Most girls younger than 10 years are not emotionally equipped to deal with menstrual bleeding.

Treatment of idiopathic GDPP is nonsurgical. The mainstay of therapy is the use of leuprolide, a GnRH agonist that can slow the sexual maturation as well as improve final height potential. Several GnRH analogs are currently available for intramuscular injection (every 4 to 12 weeks) or daily subcutaneous injection. GnRH analogs work by initially stimulating the LH receptor, which then becomes down-regulated until it is no longer functional.

Leuprolide is usually administered as depot (intramuscular) injections (at a dose of 0.3 mg/kg every 28 days). The dose will require titration based on the child’s growth pattern and the effect on puberty. Once the child has reached an acceptable final height prediction and her peers are undergoing puberty, treatment can be discontinued to allow her to proceed through puberty (around age 11 for girls and age 12 for boys). The child’s prognosis is good if she is monitored closely during treatment, with adjustments made according to her progress. This raises the question of how to adjust dosing. Brito et al. used a peak LH response of 6.6 IU/L 2 hours after depot leuprolide dosing to define acceptable suppression. In another recent study, the investigators measured LH 40 minutes after a therapeutic dose of depot leuprolide; they considered a peak LH response of 6.6 IU/L too high and empirically used a threshold of 5 IU/L to define adequate therapy.

In some patients started on GnRH analogs, the growth velocity is so markedly reduced that it impairs final height potential. In these patients, GH has been shown to significantly improve final height when added for 2 to 4 years while a child is on treatment with GnRH analogs. Controversy still exists and more data are needed on the issue of combination GH and GnRH agonist therapy, as a large number of patients on GnRH analogs cannot be recommended widely. A significant determinant of growth during therapy with a GnRH agonist is senescence of the growth plate, secondary to the exposure to estrogen, prior to the initiation of therapy.

CASE 3 CONCLUSION

The patient is started on intramuscular leuprolide injections (11.25 mg every 28 days). After 1 year of treatment, her breast tissue has regressed but she maintains Tanner stage 3 pubic hair, and her PAH has increased slightly to 5 ft 0 in.

CONCLUSION

The evaluation and management of precocious puberty need not be complicated, and with a pragmatic approach, the appropriate diagnosis and management can be implemented. The gender of the patient, age of onset and progression of symptoms, and associated signs assist in determining whether the condition is a variant of normal not requiring treatment or a more serious entity, such as a brain tumor requiring surgical intervention. An important factor often missed is the family history, as this is a powerful modifier of the differential diagnosis. Obesity appears to play a role especially in adrenarche and to some degree in GDPP, and a preventive approach in toddlers may need to be implemented to avoid later problems. A shift in apparent age of onset in the partial forms of puberty especially in Western communities may lead to a paradigm shift in the management of these patients in the future. Nonetheless, an aggressive and vigilant approach to patients with true precocious puberty should remain the standard of care.

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Part I and Gonadotropin-Dependent Precocious Puberty


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