# Precocious Puberty in Girls

## *KIZLARDA PUBERTE PREKOKS*

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**Summary**

*The onset of pubertal development before the age of 8 years in girls constitutes precocious puberty. There are numerous causes of precocious puberty, which can be classified as central or peripheral precocious puberty. All types of precocious puberty are characterized by rapid growth and advancement of skeletal age, a short adult as a result of premature epiphyseal fusion. Treatment of peripheral precocious puberty depend on the etiology. Treatment of central precocious puberty usually involves the use of GnRH agonists.*

**Key words:** Girls, Precocious puberty

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**Özet**

*Sekiz yaşından önce pubertenin başlaması puberte prekoks olarak adlandırılır. Puberte prekoks santral ve periferal puberte prekoks olarak sınıflandırılır. Prekoks pubertenin bütün tipleri hızlı büyüme, iskelet yaşında artış ve epifizlerin prematür füzyonuna bağlı kısa erişkin boyu ile karakterizedir. Periferal prekoks pubertede tedavi etiyolojiye bağlı iken santral olanlarda GnRH agonistleri kullanılır.*

**Anahtar Kelimeler:** Kız çocukları, Puperte prekoks

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Puberty is the physiological stage that leads to reproductive capability, manifested by ovulation in the female (and spermatogenesis in the male). Major physical and psychological changes occur under neurohumoral control, which results in the development of secondary sexual characteristics, alterations in lean body mass and fat distribution, and rapid skeletal growth terminated by fusion of the epiphyses and final adult stature (1,2).

Precocious puberty is the development of secondary sexual characteristics before the age of 8 years in girls. Precocious puberty may be associated with premature and rapid skeletal maturation and closure of the epiphyseal plates, resulting in short stature compared with genetic height potential (3). Isolated early breast budding (premature thelarche), menstrual flow (premature menarche), or pubic hair development (premature pubarche) usually signify self-limited conditions which do not interfere with normal skeletal growth or the normal timing and completion of puberty (1).

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### Physiology of Normal Pubertal Development

The physical changes of puberty are under endocrine control. These endocrinologic changes represent one step of a process that begins in the fetus and continues through puberty to the attainment of full sexual maturation and fertility. The hypothalamic-pituitary-gonadal system may remain active during the first few months of life, with near adult levels of estrogen in girls during the first 1-2 years (Figure 1). The endocrine changes can be separated into two distinct processes: maturation of the go-

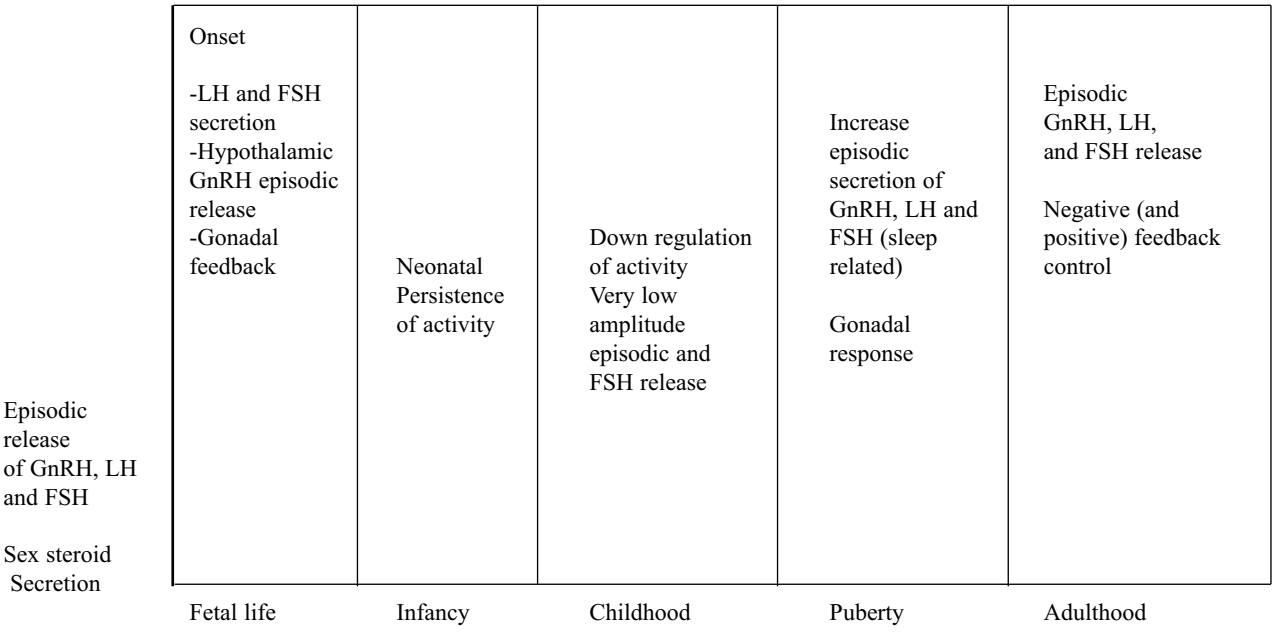


**Figure 1.** Schematic representation of the differentiation and activity of the hypothalamic-pituitary-gonadal axis at various ages

nads with sex steroid secretion termed gonadarche, and increased androgen secretion from the adrenals termed adrenarche. Pubic hair development is stimulated by adrenal androgens, especially growth and skeletal maturation, are the result of increased sex steroids.

Gonadarche: In order to understand the diagnosis and management of precocious puberty, it is necessary to review gonadotropine releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) secretion during fetal life, infancy, childhood, and puberty. Secretion of GnRH by the hypothalamus is under the control of the medial basal hypothalamus. This secretion begins its characteristic episodic pattern during fetal life and persists during infancy, but greatly dampens during childhood. Puberty begins after the reactivation of episodic secretion at a frequency and in sufficient quantity to upregulate pituitary gonadotropin secretion. During childhood, gonadotropin levels remain low because of lack of central nervous system (CNS) stimulation or CNS inhibitory influences on GnRH release (4). The hypothalamic-pituitary-gonadal system matures from fetal life through early, infancy. It may remain active during the first few months of life (5).

As puberty nears, the GnRH pulse generator becomes less suppressed. It has been suggested that a critical threshold level of body mass and skeletal maturation is required to reset the putative "gonadostat". This decreased sensitivity to feedback inhibition by sex steroids results in increased GnRH and gonadotropin secretion. While episodic secretion with sleep-related enhancement occurs during the prepubertal years, this pattern becomes readily apparent only as children approach the chronologic age of puberty. Thus, plasma concentrations of sex steroids rise with the onset of puberty.

GnRH stimulates pituitary production of LH and FSH. FSH stimulates formation of ovarian follicles that secrete estrogen, which then exerts negative feedback on FSH secretion. In girls, positive feedback to estrogen matures by mid-puberty. LH has little effect on the ovary until oculation occurs (1,6).

Exogenous GnRH is useful for testing the state of maturation of the hypothalamic-pituitary axis. In response to a 100 mg bolus injection, prepubertal

subjects will demonstrate low basal LH levels with a minimal rise. In contrast, during puberty, the LH response increases significantly, an even greater increase occurs in adult subjects. Girls secrete more FSH at all ages than boys. The absolute changes are relatively small, therefore FSH response to LHRH is not very informative as to the state of pubertal maturation. A pubertal LH response to LHRH indicates that the pituitary has been exposed to increased GnRH stimulation from the hypothalamus (1,2).

Adrenarche: Adrenarche refers to the maturational increase in adrenal androgens, and occurs about 2 years before the first changes in gonadotropin and sex steroid secretion (7). Plasma levels of dehydroepiandrosterone (DHEA), its sulphate (DHEAS), and androstenedione accually begin to rise above prepubertal levels, and continue to rise throughout puberty. Subjects with primary adrenal insufficiency, eg, Addison's disease, do not have adrenarche but go through puberty at a normal age. Adrenarche is dependent upon normal adrenocorticotropic hormone (ACTH) and adrenal function, but ACTH is not the sole factor responsible for adrenarche. There may be another, as yet undiscovered, pituitary hormone that stimulates adrenarche (2).

## Physical changes of puberty

Tanner staging is useful to document the extent of pubertal development in precocious puberty as in normal puberty (8). It is important to classify breast and pubic hair development separately to determine if there is a discrepancy between the two stage. Maturation of the breast, vagina and labia are under the control of estrogens. Pubic hair development is under the control of adrenal and ovarian androgens (7). Girls normally begin puberty between the ages of 8 and 13 years. Their pubertal development usually begins with the appearance of breast buds and linear growth acceleration; however, about 15% of normal girls develop pubic hair prior to breast enlargement. Girls complete puberty in 1.5 to 6 years. Axillary hair in girls appears approximately 2 years after the onset of pubic hair. The pubertal growth spurt in girls, in contrast to boys, occurs early in puberty, typically coincident with breast budding. Increase in height reaches a maximum rate during stage III. Menarche generally occurs within 2 years of the onset of breast development, with a mean age of 12.8 years and a range of 10 to 16 years (1,2,6).

Besides the maturation of secondary sexual characteristics, puberty is also characterized by dramatic changes in body composition. Lean body mass begins to increase during early puberty. In girls, muscle mass peaks at menarche and then diminished. Fat mass increases during the late stages of puberty in girls (2).

During puberty females grow an average of 25 cm. The difference in adult height between the sexes in due, in part, to the greater pubertal height gain in males but also to the later onset (about 2 years) of the pubertal growth spurt (2). The later onset of the pubertal growth spurt gives boys a longer prepubertal period of growth and thus a greater final height. In girls, acceleration of height velocity occurs early, coincident with breast budding, and reaches maximum at pubertal stage III (8). Longitudinal growth is largely complete with onset of menarche. Determining skeletal age indicates how much growth remains for a child and allows the prediction of final height. A bone age of two standard deviations (SDs) above or below the mean is considered abnormal (2).

Classification of precocious puberty: Sexual precocity is defined as the appearance of any sign of secondary sexual development more than 2.5 SDs below the mean (7). Complete isosexual, true, central or, especially, gonadotropin dependent precocity are terms to early activation of the hypothalamic-pituitary-gonadal axis. This leads to increased sex steroid secretion and sexual maturation appropriate for each sex. Incomplete isosexual, peripheral, or precocious pseudopuberty refer to sexual maturation that occurs due to a pituitary gonadotropin independent mechanism. The term heterosexual precocity is used if the sexual development is typical of the opposite sex, ie feminization in boys and virilization in girls.

A comprehensive list of the causes of precocious puberty is given in Table 1.

**Table 1.** Causes of precocity puberty

- l. Central Precocious puberty
  - Constitutional
  - Idiopatic true precocious puberty
  - CNS Tumors
    - Hamartoma of the tuber cinereum
    - Other hypothalamic tumors
      - Gliomas (often associated with neurofibromatosis)
      - Astrocytomas
      - Ependymomas
      - Craniopharyngioma
  - Other CNS disorders
    - Postinfectious
      - Meningitis
      - Encephalitis
      - Abscess
    - Head trauma: birth injury
    - Granulomas
    - Suprasellar cysts
    - Hydrocephalus
  - Secondary to peripheral precocious puberty
- ll. Peripheral (pseudo) precocious puberty
  - McCune-Albright syndrome
  - Males
    - HCG secreting tumors
      - CNS tumors (germinoma, teratoma, chorioepithelioma)
      - Hepatoma of hepatoblastoma
    - Excessive androgen secretion
      - Congenital adrenal hyperplasia (21-hydroxylase deficiency, 11-hydroxylase deficiency)
      - Virilizing adrenal neoplasm
      - Leydig cell tumor
      - Familial testotoxicosis (gonadotropin independent Leydig cell maturation)
    - Exogenous testosterone
  - Females
    - Follicular cysts
    - Ovarian tumor
      - Granulosa cell tumor
      - Lipoid tumors
      - Cystadenomas
      - Ovarian carcinomas
      - Gonadoblastoma
    - Adrenal tumor
    - Exogenous estrogen
- lll. Contrasexual development
  - Feminization in males
    - Adrenal neoplasm
    - Increased extraglandular conversion of circulating steroids to estrogen
  - Virilization in females
    - Congenital adrenal hyperplasia (21-hydroxylase, 11-hydroxylase, 3-β-OHdehydrogenase deficiency)
    - Virilizing adrenal neoplasm
    - Virilizing ovarian neoplasm
- lV. Mechanism unknown
  - Hypothyroidism
  - Chronic adrenal insufficiency
  - Russell-Silver syndrome
- V. Variations of pubertal development
  - Premature thelarche
  - Premature adrenarche
  - Premature menarche
  - Adolescent gynecomastia (in males)

*CNS= Central nervous system*

## Causes of Precocious Puberty

**1. Gonadotropin Dependent (Central) Precocious Puberty:** Most females and approximately half of males who present with precocious puberty have the central form (9). While central precocious puberty is much more common among females than males, the majority of females have an idiopathic form. Males are more likely to have an underlying central nervous system (CNS) abnormality (6).

Constitutional precocious puberty: The limits describing the onset of puberty do not include 0.6% of normal children whose onset of puberty begins before age 8 in girls and age 9 in boys but who otherwise have no evidence of a disorder. Such an individual will likely have a familial predisposition to early puberty. Typically, they will have an only modestly puberty, i.e., girls > 6 years and boys > 7 years (1).

Idiopatic precocious puberty: If no tumor or other definitive diagnosis is found, the diagnosis of exclusion is idiopatic central precocious puberty. It is the most common diagnosis in girls (1).

CNS lesions: Most CNS lesions, which cause precocious puberty, are thought to act by interfering with the inhibitory influences on the hypothalamic GnRH pulse generator that are normally exterted during childhood (7,9). They include space occupying lesions or conditions that lead to increased intracranial pressure.

Tumors of the CNS, both malign and benign,

can cause precocious puberty. Pineal tumors, for unknown reasons, have been seen only in male precocious puberty (2). The hypothalamic hamartoma-redundant CNS tissue containing GnRH secreting neurons- has become much more frequently identified, particularly among patients presenting at a very young age with precocious puberty. These hamartomas are more commonly diagnosed among males than females (6). They are best diagnosed using magnetic resonance imaging (MRI), grow little and are compatible with a normal life span. It has become clear since the advent of computed tomography (CT) and MRI that the incidence of CNS abnormalities is greater than was previously suspected. Only among patients who have a pedunculated hamartoma, which is positioned so that the surgical risk is minimal, should surgery be undertaken. Complete resection is followed by regression of gonadotropin secretion to a prepubertal state. Those patients with hamartomas not appropriate for surgery can be treated with GnRH agonist therapy (10).

**2.Gonadotropin Independent (Peripheral) Precocious Puberty**

Exogenous steroids: Exogenous estrogen exposure may occur through diet or even through contact with cosmetics that contain estrogen. Drug ingestion should be suspected when there is dark pigmentation of the nipples and breast areola, an effect of certain synthetic estrogens such as stilbestrol (2).

McCune-Albright syndrome: McCune-Albright syndrome (polyostotic fibrous dysplasia) (MAS) account for 5 % female precocity and consists of multiple disseminated cystic bone lesions which easily fracture, cafe au lait skin areas of various sizes and shapes, and sexual precocity (1,2). Variations are described with only two of these three characteristics (11). Premature menarche may be the first sign of the syndrome. Skeletal abnormalities may be become evident following the onset of puberty (1). Almost all affected individuals are girls. Most cases are sporadic and not familial. The syndrome has been associated with a high incidence of coexistent autonomous endocrine hyperfunction, such as bilateral adrenal hyperplasia, non-immune hyperthroidism, hyperparathyroidism, acromegaly and prolactinoma (1,12).

The etiology of precocious puberty in this syndrome is unknown but increasing evidence suggests that it is caused by episodic formation of autonomously functioning follicular cysts of the ovary, which secrete large amounts of estrogen. Advancement and regression of secondary sexual characteristics and episodes of menses tend to follow a cyclical pattern. In most cases, there are independent of gonadotropin secretion but correlate well with the appearance and resolution of asymmetric ovarian cysts, which correlate with plasma estrogen (12).

The protean manifestations of this disorder suggest that the pathophysiology result from a basic defect in cellular regulation at the level of either cAMP generation or protein kinase function in affected tissues (1). Most studied subjects have a suppressed gonadotropin response to LHRH stimulation and lack nocturnal LH and FSH pulses consistent with a prepubertal state. The few subjects who have been documented to have pubertal gonadotropin levels, as well as a pubertal response to LHRH, were of more advanced bone age (12). Treatment with GnRH agonists that supress pituitary secretion of gonadotropins and are very effective in controlling the progression of central precocious puberty are effective only in those girls with MAS who had a pubertal response to LHRH, i.e., their hypothalamic-pituitary-gonadal axis was activated. The subjects with a suppressed or prepubertal response to LHRH stimulation showed no response in ovarian cyst formation, deceleration of bone maturation, or regression of pubertal development (13). By contrast, therapies directed toward decreasing the availability of estrogen in the periphery, such as with the aromatase inhibitor testolactone, are effective in decreasing plasma estrogen, slowing bone maturation, and causing partial regression of pubertal changes including menses (14).

Eventual fertility is unimpaired, and adult height appears to be normal (1).

Ovarian abnormalities: Abnormalities of the ovaries can result in inappropriate secretion of

estradiol, leading to premature secondary sexual characteristics. These range from simple follicular cysts to ovarian tumors. All can cause a spectrum of feminization from premature thelarche, vaginal estrogenization, and even menses. Follicular cysts are by for the most common cause of an estrogen secreting ovarian mass in childhood (7). These children demonstrate an absence of gonagotropin pulsations, variable responses to GnRH, and a lack of suppression of puberty by a long acting GnRH agonist. The cysts may enlarge and involute, and than recur so that signs of sexual precocity and vaginal bleeding remit and exacerbate. GnRH testing is useful in differentiating the autonomous (nonreactive) cyst from those secondary to the FSH and LH stimulation of central true precocity (reactive) (1).

Differenting benign follicular cysts from ovarian neoplasms can be difficult because of the wide degree of clinical overlap. Estrogen levels tend to be higher in association with neoplasms, and estrogen levels may wax and wane in concert with changes in cyst size (7).

Eleven percent of girls with precocious puberty have an ovarian tumor. The granulosa-theca cell tumors are the most common ovarian neoplasms associated with precocious puberty (15). Five percent of granulosa cell tumors and 1% of theca cell tumors occur before puberty. However, gonadoblastomas (usually in associated with streak gonads of gonadal dysgenesis), teratomas, lipoid cell tumors, cystadenomas and even ovarian cancers have been reported as causes of precocity (1,7). Arrhenoblastomas can also cause sexual precocity in association with virilization (1). A pelvic mass is readily palpable in 80% of cases. Pathological identification (by laparotomy or laparoscopy) is indicated when a cystic mass is highly suspicious for neoplasm, i.e., > 3 cm in size, enlarging in size over time or associated with rapid progression of sexual development or bone age (1,16).

Adrenal abnormalities: Congenital adrenal hyperplasia (CAH) due to an inborn error of steroidogenesis may result in excess adrenal androgen production and sexual precocity with virilization. CAH with associated deepening voice, pubic hair development, and clitoral enlargement. Virilization may also occur in conjunction with Cushing's syndrome (1). In contrast to other causes of peripheral precocious puberty, it is characterized by growth failure due to the excess glucocorticoids (7).

Adrenal tumors tend to secrete large amounts of androgens, especially the 17 ketosteroids, androstenedion, DHEA, and DHEAS, and produce rapidly progressive virilization and cause contrasexual precocious development (2). A feminizing adrenal tumor is very rare (1% of cases) and associated with increased blood levels of DHEA (1,2).

Mechanism unknown: Rare cases of precocious puberty have been reported in associated with hypothyroidism (17) and chronic adrenal insufficiency (2). Uniquely, in contrast to the other forms of precocious puberty, hypothyroidism causes a retardation of bone age instead of a acceleration. The increase in gonadotropin secretion in both syndromes is thought to be caused by overlap in the hormonal feed-back mechanism at the pituitary level, rather than due to premature maturation of the hypothalamic-pituitary axis. In support of this is the resent demonstration that elevated gonadotropin levels are unresponsive to exogenous LHRH stimulation. In addition, replacement of thyroxine to hypothyroid subjects returned gonadotropins to prepubertal levels with regression of secondary sexual development (18).

Secondary to peripheral causes: It has been suggested that the central mechanisms that controls the onset of puberty is activated after a critical level of somatic development has been reached due to the premature production of sex steroids (19). At that point, the pubertal process becomes self-perpetuating, driven by increasing GnRH pulsatile secretion of an activated "gonadostat" and can not be stopped by reversal of the underlying lesion that caused excess sex steroid secretion in the first place, eg, surgical removal of an adrenal adenoma. It is, however, responsive to measures which repress the hypothalamic-pituitary-gonadal axis in central precocious puberty.

## Variations of Pubertal Development

Premature thelarche: Premature thelarche is a benign self-limited condition of unilateral breast development that occurs usually in a girl under 3

**Table 2.** Diagnostic evaluation of precocious puberty

| |
|---|
| Clinical assesment |
| History of menses, acne, erections, behavior |
| Growth rate, height, and weight percentiles |
| Tanner stage breasts, pubic hair, testicular volume |
| Complete physical exam |
| Radiologic evaluation |
| Bone age |
| Pelvic / testicular US |
| Adrenal US or CT / MRI |
| Head CT or MRI |
| Bone survey or bone scan (if MAS suspected |
| Laboratory evaluation |
| Basal LH, FSH, estradiol, or testosteron |
| LHRH stimulation test: peak FSH and LH |
| dehydroepiandrosterone sulphate |
| Cortrosyn stimulation test: 17-OHP, 11-S bhCG |
| Thyroid stimulating hormone |
| Vaginal or urinary smear for cytology |

US=ultrasound
CT= computed tomography
MRI= magnetic resonance imaging
MAS=McCune-Albright syndrome
LH= luteinizing hormone
FSH=follicle-stimulating hormone
βhCG=human chorionic gonadotropin, β subunit

years of age (1,2). It is to three times more common than precocious puberty. There are minimal or no other signs of estrogen effect such as dulling of the vaginal mucosa, an there is little nipple development. Serum estradiol values are often low. There is no alteration in the time of onset or progression of the other signs of normal pubertal development (2). For unclear reasons, there is usually a marked FSH predominant response to LHRH stimulation (3, 20).

Premature adrenarche: Premature adrenarche is a benign self-limited appearance of a small amount of pubic hair, comedones, or axillary hair or odor that may occur usually after the age of 6 years. The normal rise in adrenal androgens such as DHAS occurs earlier in children with this condition. The rest of pubertal development, such as breast development, occurs normal age. There may be an increase in rate of growth along with a slight advancement of bone age (1,2).

Premature menarche: This rare condition has been described in girls from 1-9 years old whom no other signs of sexual development were present. Most had just one or several menses, although some had recurrent bleeding for up to 6 years. Height and bone age were normal (21). Normal pubertal development, with normal menses, occurred at the normal age of puberty. No cause for this condition has been determined (2). Other causes for isolated vaginal bleeding due to precocious estrogen secretion, hypothyroidism, neoplasm, infection, foreign body, or trauma (child abuse) must be ruled out before this diagnosis can be made (22).

## Diagnostic Evaluation of Sexual Precocity

### *Clinical Assessment*

The diagnosis of precocious puberty is made by documenting early and progressive sexual development on the history, physical examination, and laboratory evaluation (Table 2). It is important to obtain a history of menses, acne, or behavior changes if present. A family history of neurofibromatosis, familial poliposis, CAH, or early pubertal development and growth spurt may suggest the correct diagnosis (1). A complete physical examination with particular attention to the Tanner stage of breast, pubic hair, as well as growth rate and height and weight percentiles, will provide needed information (1,2,6). Tanner staging is useful to document the extent of pubertal development in precocious puberty as in normal puberty. The isolated breast development of premature thelarche and the isolated pubic hair development of precocious adrenarche rarely develop beyond stage lll. Heterosexual development (clitoromegaly or other signs of virilization in girls) suggests a peripheral mechanism, such as CAH or a gonadal tumor. Signs of both estrogen and androgen effects in a female (eg, breast development and pubic hair development) likely imply true central precocious puberty, although it may be secondary to a peripheral cause. Hypothyroidism would be accompanied by other signs of severe myxedema, such as growth retardation and immature bone age. In addition to short stature, galactorrhea may be present (1,2). Abnormal physical findings that may be diagnostically useful are given in Table 3.

**Table 3.** Abnormal physical findings that potential diagnostic usefulness in precious puberty

| Finding | Associated diagnosis |
|---|---|
| Hypertension* | 11-hydroxylase deficiency or adrenal tumor |
| Hyperpigmented skin spots | McCune-Albright syndrome$^{\Psi}$ or neurofibromatosis$^{f}$ |
| Adrenal mass | Adrenocortical carcinoma |
| Ovarian mass | Ovarian tumor or McCune-Albright syndrome $^{\xi}$ |
| Testicular mass | Testicular tumor or adrenal rest tumor of the testis |
| Bone deformity | McCune-Albright syndrome |
| Neurologic abnormality | Central nervous system lesions |

* Blood pressure must be elevated for height age, not chronologic age (to allow for the expected increase resulting from increased body size)

$^{\Psi}$ The McCune-Albright syndrome is the unexplained triad of hyperpigmented skin spots, polyostotic fibrous dysplasia, and precocious puberty. The skin spots have irregular borders ("coast of Maine")

$^{f}$ The spots have smooth borders ("coast of California")

$^{\xi}$ Patients with McCune-Albright syndrome frequently have large unilateral ovarian cysts (up to 4 cm in diameter) which may raise unwarranted concern about an ovarian malignancy

### *Radiologic Evaluation*

Although plain skull X-rays are included on most list of recommended studies, the CT scan of the head has largely supplanted the more traditional study, and MRI studies offer the promise of even greater resolution in the representation of structural details within the CNS. The price to be paid, other than the obvious cost burden associated with the newer technology, is that the bones of the skull can not be seen on an MRI scan, and changes in the basal skull bones may be the only identifiable abnormality in some cases of MAS (22).

Bone age is critical in the evaluation of sexual precocity because the degree of skeletal maturation is an excellent measure of the integrated exposure to sex steroids over time. Patients with benign syndrome, such as precocious adrenarche or thelarche, will have normal or a minimally elevated bone ages into the upper range of normal. Although the exact hormonal determinants of bone maturation have not been defined, an abnormally advanced bone age is usually strong evidence of progressive sexual precocity (1). In contrast to other causes of precocious puberty, hypothyroidism and glucocorticoid excess are characterized by growth failure and immature bone age. Following the bone age over time is extremely useful in estimating the exposure to sex steroids and for monitoring the effects of therapy.

Ultrasound examinations of the pelvis and in some cases the adrenal glands have become a part of the basic evaluation of the child affected by peripheral precocious puberty (22). Normal uterine and ovarian size for age make it highly likely that the diagnosis is premature adrenarche and thelarche. Large, adult size ovaries with uterine enlargement is seen in true precocious puberty and large ovaries with dominant follicular cyst in MAS (1). Symmetrically enlarged ovaries are consistent with central precocity and unilateral enlargement with tumors, whereas cyst can be found in any situation (6).

### *Laboratory Evaluation*

The basic laboratory evaluation consists of thyroid function studies, basal FSH and LH levels, gonadal steroid levels, serum chorionic gonadotropin levels, and a vaginal smear or a fleshly collected an processed urine sample for cytologic analysis (22).

GnRH stimulation test is very sensitive and specific in differentiating prepubertal subjects from these with pubertal activation of the hypothalamic-pituitary axis (23). There are no restrictions to the time of day when the test can be performed, and whether the patient is in the fed or fasted state is irrelevant. A standard dose of 100 mg of the peptide may be administered either intravenously or subcu-

**Table 4.** Objective of the management and treatment of true precocious puberty

| |
|---|
| Detection and treatment of an expanding intracranial lesion |
| Arrest of premature sexual maturation until the normal age of onset of puberty |
| Regression of secondary sex characteristics already present |
| Attainment of normal mature height; suppression of the rapid rate of skeletal Maturation |
| Prevention of emotional disorders and handicaps and alleviation of parental anxiety; Promotion of understanding by counseling early sex education, and acceleration of social age |
| Reduction of risk of sexual abuse and of early sexual debut |
| Prevention of pregnancy in girls |
| Preservation of future fertility |
| Diminishing the increased risk of breast cancer associated with early menarche |

tanously after a baseline blood sample. Subsequent blood sample should be drawn at 15 minute intervals for a period of 1 hour. The hallmark of the activation of the hypothalamic-pituitary-gonadal axis is an augmented response in secretion of the gonadotropins, beginning with an FSH dominant pattern as pubertal development proceeds. A pattern displaying a peak response, however, which is twofold to threefold greater than the baseline value, is indicative of activation of the control axis. The pattern of responses reported in the literature for central precocious puberty patients is qualitatively similar to those seen in normal puberty (22). If the LHRH test is prepubertal or immunoreactive LH is elevated but unresponsive to LHRH, then an hCG secreting tumor must be suspected and should be confirmed by an immunospesific assay for hCG. The new supersensitive gonadotropin assays are reported to be sensitive enough to ultimately eliminate the need for GnRH testing. This method is too new to abandon the classic GnRH test (24). CT or MRI should be used to screen the CNS (including spine), liver, and other locations for neoplasm (1). If isolated precocious adrenarche, thelarche, or menarche is suspected clinically, a prepubertal response to LHRH is strongly supportive evidence (6).

In the setting of a prepubertal LHRH test and virilization, an adrenal or gonadal source of androgens is suspected. DHEAS is now often used instead of urinary 17-ketosteroids to differentiate between adrenal and gonadal sources of androgens. Elevated DHEAS indicates an adrenal source (1).

## Management of Precocious Puberty

Management of precocious puberty is directed first at treating the underlying cause if possible. When no treatable cause is found, medical therapy is required. The goal of treatment then becomes the attainment of effective and selective suppression of gonadal sex steroid secretion or action that will arrest the premature sexual maturation. In addition, treatment should aim toward attaining a normal final height by suppressing the rapid rate of skeletal maturation. Prompt reversal of the suppression after treatment is discontinued and avoiding toxicity during chronic administration are important considerations. Strategies of treatment can be divided into those effective in central precocious puberty and those effective peripheral precocious puberty. Psychological support is helpful to both children with precocious puberty and their parents. Menstruation in a girl may be extremely distressing to parents of further significance is the possibility the these patients may become targets of sexual abuse, and there is the additional element of potential fertility (1). The rationale for treating precocious puberty is given in Table 4.

The normal variations of pubertal development, such as premature thelarche or premature isolated menses in girls and premature adrenarche, the benign and self-limited conditions. They deserve careful follow-up but do not require treatment (1,2,22).

### *Treatment of central precocious puberty*

A conservative approach to the hypothalamic hamartoma is generally called for since the central

precocious puberty associated with it can be treated medically, surgery is not curative and can lead to devastating complications. An exception may be the pedunculated lesion that is easily approached surgically. In children with central precocious puberty, GnRH agonists are used, both in those with CNS lesions that persist with pubertal gonadotropin secretion-whether or not the lesion are amenable to surgical removal-and in those whose central precocious puberty is idiopatic in origin (10). Pineal and other CNS hCG secreting dysgerminomas respond well to radiation therapy, which is the treatment of choice (1). The current treatment of choice for central precocious puberty is to administer long-acting GnRH agonists (GnRH-A). GnRH agonist therapy has supplanted progestational agents for the treatment of central precocious puberty and results in decreased gonadotropin levels and estrogen secretion. Breast size may decreased in girls. Growth rates and skeletal maturation rates decrease as well (6). The earlier the bone age at which therapy is initiated, the better the ultimate height prognosis, taking into account a person's genetic potential (19). The investigators also observed that posttherapy growth has been more significant when treatment was stopped before bone age exceed 13 years.

Episodic secretion of GnRH results in pulsatile gonadotropin secretion. Constant infusion of GnRH causes a decrease in pituitary response to GnRH, leading to decreased gonadotropin secretion. Structural modifications that increase the potency and duration of action of GnRH have provided GnRH agonists, which have increased receptor affinity and increased resistance to enzymatic degradation, prolonging their effectiveness. Chronic administration of these GnRH agonists result in "down regulation" of pituitary GnRH reseptors, and desensitization of pituitary gonadotrops. To maintain effectiveness, these agents must be administered every day or more recently sustained release depot preparations have been employed (2,24).

GnRH-A are available in subcutaneous injectable, intranasal aerosol, and depot intramuscular preparations (24). Erratic and inefficient absorption intranasally has been associated with poor results (1,25). Intramuscular slow release leuprolide and tryptorelin are now available and appear as effective as subcutaneously administered analogs in suppressing gonadotropin and sex steroid secretion (26).

With adequate dosing, gonadotropin secretion is promptly suppressed, demonstrable within 1 month of the first dose. To verify that adequate suppression has been achieved, monitoring of GnRH-A therapy is best accomplished with a GnRH stimulation test. Obtaining basal estradiol levels is also useful. Once the hypothalamic-pituitary axis has been suppressed, patients should be reevaluated every 6 months for dosage requirements (25).

Few side effects of GnRH-A therapy have been reported. They include pain at the injection side and cutaneous reaction. Cutaneous reactions have been successfully treated with antihistamines and do not require termination of therapy. Generalized allergic response to GnRH-A has been rare (1,22,27). No deleterious effects of GnRH therapy on reproductive function have been reported. The suppressive effects of GnRH-A on the hypothalamic-pituitary-gonadal axis appears to be reversible (24). Pretreatment levels of gonadotropins and sex steroids return within 3-12 month of ending therapy (19). Uterine bleeding following GnRH-a treatment in premenarchal girls with CPP is common, and may be massive and recurrent, since most episodes resolved spontaneously and necessitated no further treatment, careful advice should be given to girls and their families prior to treatment initiation, in an attempt to avoid unnecessary anxiety and achieve better compliance (29).

If an inadequate dosage of GnRH agonist is used, there will be stimulation of the hypothalamic-pituitary-gonadal axis rather than suppression.

### *Treatment of peripheral precocious puberty*

Tumors of the gonads and adrenals should be resected. An exception is the large follicular cysts in MAS. Cysts are likely to reoccur, and excellent medical therapy is now available (1). It may be difficult, however, to differentiate a large cyst from a granulosa cell tumor and consideration toward a pathologic diagnosis by laparatomy or laparascopy should be given if the lesion exceeds 3 cm (1).

Gonadotropin-releasing hormone analogs have been unsuccessfull in treating peripheral forms of precocious puberty except where secondary central precocious puberty has been shown to occur (2,6). Medroxyprogesterone acetate (MPA) is used to treat recurrent ovarian follicular cysts, MAS. MPA is a progestational agent that can suppress gonadotropins. Side effects associated with the use of MPA are related to its structural similarity to glucocorticoids. Thus, with long-term use, it may cause adrenal suppression. Cushingoid features result from the use of higher doses (2).

Testolactone is a competitive inhibitor of the enzyme aromatase, which converts androgens to estrogens (eg, androstenedione to estrone and testosterone to estradiol). When used to treat McCune-Albright syndrome patients, it has been effective in decreasing estrogen levels, ovarian volume, frequency of menses, growth rate and rate of skeletal maturation. In a preliminary series, testolactone at 20-40 mg/dL in divided doses was effective in reducing plasma estradiol and was associated with a decrease in menstrual bleeding and ovarian volume (14). These effects quickly reversed with cessation of therapy. In McCune-Albright syndrome, traditional therapy has employed cyproterone acetate, which in addition to being an antiandrogen, also has antiestrogenic activity (7).

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