Precocious Puberty: Diagnosis Diagnosis & Evaluation

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Understanding Precocious Puberty

Definition

Onset of pubertal development 2 to 2.5 standard deviations earlier than population norms.

Diverse Causes

Ranges from benign developmental variants to serious pathological conditions.

Clinical Challenge

Clinicians must identify the cause and determine appropriate intervention.

Key Questions in Early Pubertal Development

Is the child too young for the the pubertal milestone?

Distinguishing normal from abnormal development based on age norms is crucial.

What is the underlying cause?

Identifying whether sex hormone effects are centrally mediated, peripherally autonomous, or exogenous.

Is therapy indicated and what type?

Tailoring intervention strategies based on the diagnosis.

Defining Precocious Puberty: Age Thresholds

- Precocious puberty is traditionally defined by specific age thresholds for the onset of secondary sexual characteristics:
- **Females:** Breast development before eight years of age.
- **Males:** Testicular enlargement before nine years of age.
- These limits represent 2 to 2.5 standard deviations below the average age of pubertal onset. While the mean age for puberty is around 10.5 years for females and 11.5 years for males, recent studies suggest a trend towards earlier onset, especially with increased body mass index.

Epidemiology and Challenges in Prevalence

- Estimating the true prevalence of precocious puberty is complex, facing several challenges:
- **Varying Prevalence Estimates**
- Prevalence differs significantly across studies and populations. Based on traditional definitions, an expected rate is ~2%. A strong female predominance in medical evaluations lacks clear biological explanation, suggesting potential referral bias.
- **Racial/Ethnic Considerations**
- Using race/ethnicity in defining precocious puberty thresholds is controversial. Associations between genetic ancestry and pubertal timing are weak and diminish with population diversification. Factors like BMI, endocrine-disrupting chemicals, and social determinants may play a larger role than race/ethnicity alone.
- Further research is needed to understand the complex interplay of genetic and environmental factors influencing pubertal timing.

Classification of Precocious Puberty by Etiology

Precocious puberty can be categorized into three main types based on its underlying cause, guiding diagnosis and treatment strategies.

Central Precocious Puberty (CPP)

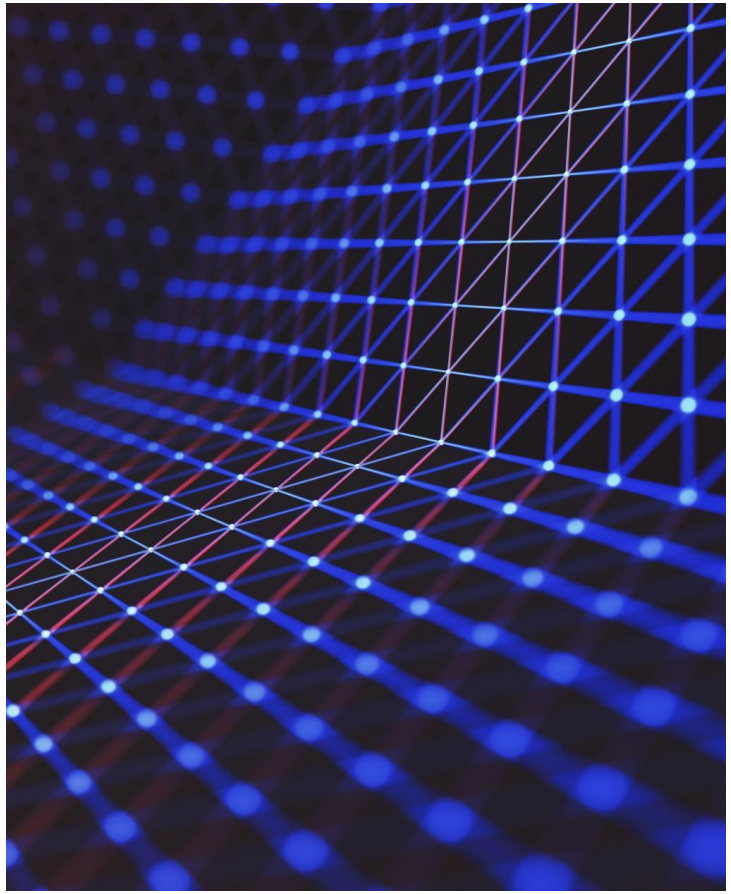
Early activation of the hypothalamic-pituitary-gonadal axis. Often idiopathic in females (80-90%) and males (25-80%).

Peripheral Precocious Puberty

Excess sex hormone secretion independent of the HPG axis (gonads, adrenals, exogenous sources, or ectopic hCG).

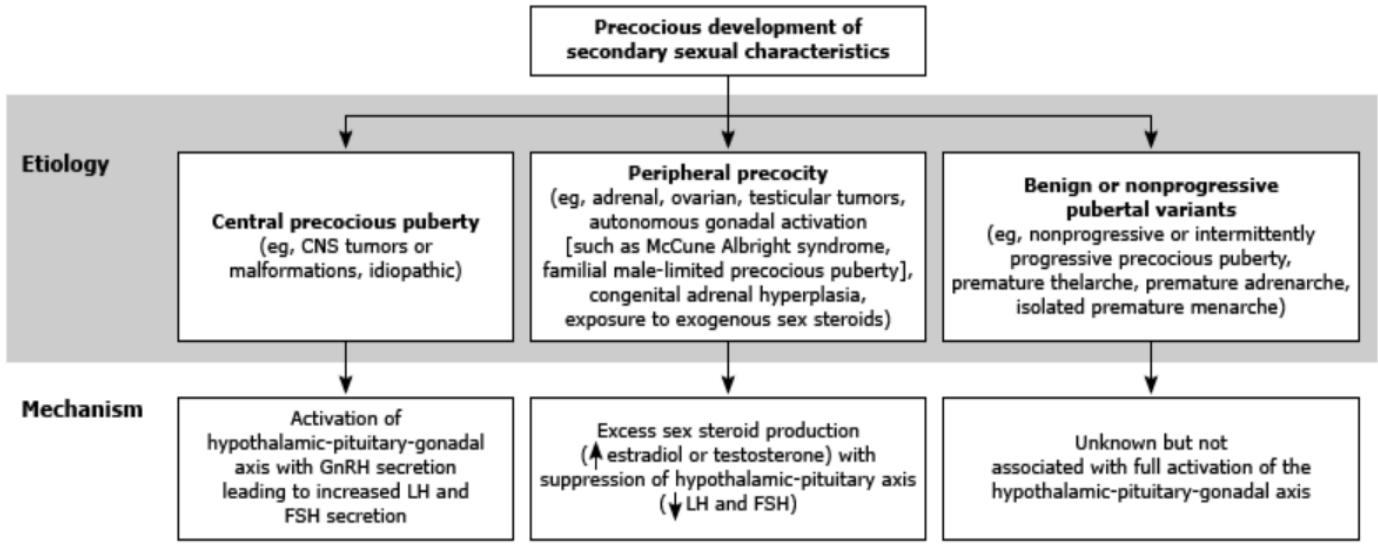
Benign Pubertal Variants

Non-progressive forms like premature thelarche or adrenarche. These require monitoring for progression.



Etiology and mechanisms of precocious puberty

Etiology and mechanisms of precocious puberty



Central Precocious Puberty (CPP): Causes

CPP arises from early maturation of the hypothalamic-pituitary-gonadal axis, leading to accelerated linear growth and advanced bone age.

Idiopathic

Most common (80-90% in females, 25-80% in males). Genetic variants may contribute to familial cases.

Central Nervous System (CNS) Lesions

Includes hamartomas (most frequent in very young children), astrocytomas, ependymomas, pinealomas, and optic/hypothalamic gliomas. CNS irradiation, hydrocephalus, and pituitary gonadotropin-secreting tumors are also rare causes.

Genetic Variants

Pathogenic variants in genes like KISS1, KISS1R, and MKRN3 are implicated. CPP can also be a feature of genetic syndromes such as Silver-Russell and Temple syndromes, or MECP2 variants.

Early Exposure to Endogenous Sex Steroids

Conditions like McCune-Albright syndrome or poorly controlled congenital adrenal hyperplasia can lead to superimposed CPP.

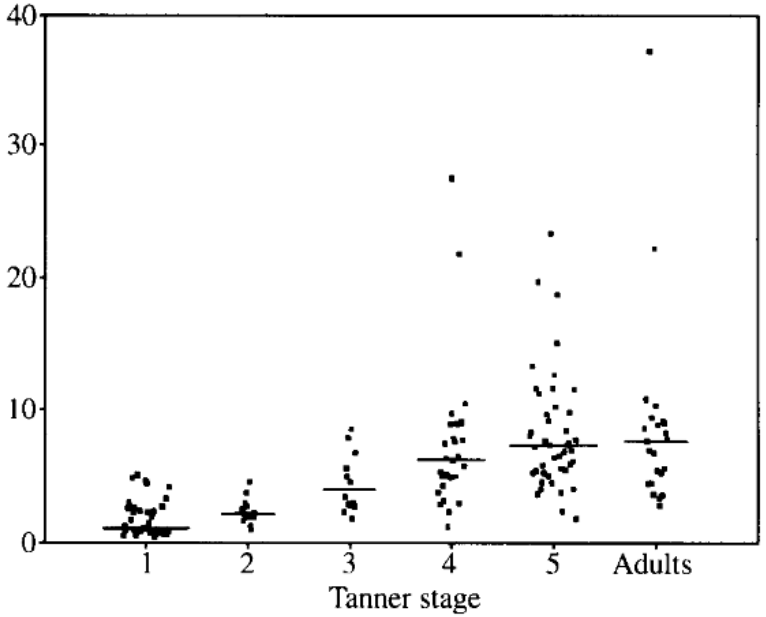
Treatment often involves GnRH agonist therapy to halt pubertal progression.

Table 2 Maturation of female internal genitalia in relation to breast development as assessed by ultrasound

Breast stage	*Uterine volume* (ml)	*Ovarian volume* (ml)	*Largest follicle* (mm)
1	1.6* (0.7–7.9)	1.2 (0.5–5.1)	4.0 (2.0–8.0)
2	2.8 (1.3–8.1)	2.2 (1.0–4.6)	5.0 (3.0–8.0)
3	8.0 (2.0–18)	4.1 (1.9–8.6)	5.0 (4.0–10)
4	37 (11–56)	6.2 (1.3–28)	7.0 (3.0–38)
5	43 (12–82)	7.3 (1.9–23)	6.0 (3.0–36)
Adult†	61 (37–130)	7.6 (2.9–37)	8.0 (3.0–36)

*Median; †adult, ≥ 19 years

OVARIAN VOLUME



UTERINE VOLUME

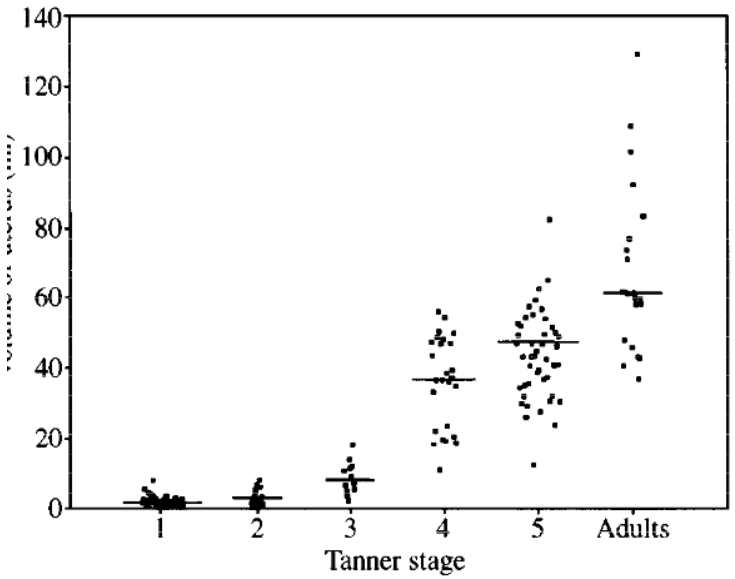


Table 1 Age, number of patients, fundus: cervix ratio, and endometrial thickness divided by breast stage

Breast stage	*Mean age (years)*	*No*	*Mean ratio of fundus: cervix (SE), range*	*Endometrial thickness (mm) (SE), range*
1	8.6	245	0.95 (0.02) 0.44-1.75	0.38 (0.07) 0-4
2	11.3	112	1.12 (0.31) 0.55-2.00	1.02 (0.15) 0-6
3	11.8	57	1.26 (0.04) 0.77-2.00	2.79 (0.28) 0-8
4	13.3	34	1.29 (0.06) 1.0-1.83	5.04 (0.63) 2-17
5	13.9	27	1.22 (0.09) 0.75-2.13	6.44 (0.81) 0-15

during the luteal phase in one study of normal women aged 21 to 25 years [9]).

Table 2. Ovarian volumes by age.

Age	3SD below	2SD below	1SD below	Mean ovarian vol.	1SD above	2SD above	3SD above
0	0.0	0.0	0.0	0.2	0.5	0.8	1.3
2	0.0	0.1	0.4	0.7	1.0	1.5	2.1
4	0.0	0.3	0.6	0.9	1.3	1.8	2.5
6	0.2	0.5	0.8	1.2	1.7	2.3	3.0
8	0.5	0.8	1.2	1.7	2.3	3.0	3.9
10	0.9	1.3	1.9	2.5	3.3	4.3	5.4
12	1.5	2.1	2.8	3.7	4.7	6.0	7.5
14	2.3	3.0	3.9	5.0	6.4	8.0	10.1
16	3.0	3.9	5.0	6.4	8.0	10.0	12.5
18	3.5	4.5	5.8	7.3	9.2	11.4	14.2
20	3.7	4.8	6.1	7.7	9.6	12.0	15.0
22	3.7	4.7	6.0	7.6	9.5	11.9	14.7
24	3.5	4.5	5.7	7.2	9.0	11.2	14.0
26	3.2	4.1	5.3	6.7	8.4	10.5	13.1
28	3.0	3.9	4.9	6.3	7.9	9.9	12.4
30	2.8	3.7	4.7	6.0	7.6	9.5	11.9
32	2.8	3.6	4.6	5.9	7.5	9.4	11.7
34	2.7	3.6	4.6	5.9	7.4	9.3	11.6
36	2.7	3.6	4.6	5.8	7.4	9.2	11.5
38	2.6	3.5	4.5	5.7	7.2	9.0	11.3
40	2.5	3.3	4.2	5.4	6.8	8.6	10.7
42	2.2	3.0	3.8	4.9	6.3	7.9	9.9
44	1.9	2.6	3.4	4.4	5.6	7.1	8.9
46	1.6	2.2	2.9	3.8	4.9	6.2	7.8
48	1.3	1.8	2.5	3.3	4.2	5.4	6.8
50	1.1	1.6	2.1	2.8	3.7	4.7	6.0

Central (gonadotropin-dependent) precocious puberty

Central (gonadotropin-dependent) precocious puberty

Etiology	Clinical features	Bone age	Additional evaluation
Idiopathic 80 to 90% of females with CPP 25 to 80% of males with CPP	Early progressive pubertal development, but proceeds in normal sequence.	↑↑	Increased ovarian and uterine volumes on ultrasound may help differentiate females with CPP from those with premature thelarche. Contrast-enhanced MRI to rule out CNS abnormality.
Secondary to CNS lesions (eg, hypothalamic hamartomas, other CNS tumors and lesions, cranial radiation) 20 to 75% of males with CPP 10 to 20% of females with CPP	Early progressive pubertal development that usually proceeds in normal sequence, but abnormal tempo or sequence can be seen with CNS lesions. CPP secondary to a CNS lesion occurs more commonly in males and younger children.	↑↑	
Post-early exposure to sex steroids (after treatment for peripheral precocity)	History of treatment of peripheral precocity. Progressive pubertal development with breast development in females and testicular enlargement in males.	↑↑	Basal and stimulated LH concentrations are pubertal.

CPP is characterized by basal LH concentrations >0.2 to 0.3 mIU/L and/or stimulated LH concentration post-GnRH or GnRH agonist of >3.3 to 5.0 mIU/L.

↑↑: significantly advanced for chronologic age (eg, ≥2 standard deviations); CPP: central precocious puberty; MRI: magnetic resonance imaging; CNS: central nervous system; LH: luteinizing hormone; GnRH: gonadotropin-releasing hormone.

Peripheral Precocious Puberty: Diverse Origins

Peripheral precocity results from excess sex hormone secretion independent of the HPG axis. Treatment depends on the cause, with GnRH agonists being ineffective.

Ovarian Disorders (Females)

- **Ovarian cysts:** Most common cause, often presenting with breast development and vaginal bleeding.
- **Ovarian tumors:** Rare, granulosa cell tumors (isosexual precocity) or Sertoli/Leydig cell tumors (contrasexual precocity).

Testicular Disorders (Males)

- **Leydig cell tumors:** Asymmetric testicular enlargement, typically benign and surgically curable.
- **hCG-secreting germ-cell tumors:** Activate LH receptors, increasing testosterone. Testicular size increase is often limited.
- **Familial male-limited precocious puberty:** Activating variant in LH receptor gene, leading to premature Leydig cell maturation.

These conditions can lead to either isosexual (appropriate for sex) or contrasexual (inappropriate) characteristics.

Peripheral Precocious Puberty: Systemic and Exogenous Causes

Beyond gonadal disorders, systemic conditions and external factors can also trigger peripheral precocity in both sexes.

McCune-Albright Syndrome (MAS)

A rare genetic disorder characterized by peripheral precocious puberty, irregular café-au-lait skin pigmentation, and fibrous dysplasia of bone.

Primary Hypothyroidism

Severe, long-standing hypothyroidism can cause early breast development and galactorrhea in females, or premature testicular enlargement in males (Van Wyk-Grumbach syndrome).

Exogenous Sex Steroids & Endocrine-Disrupting Chemicals (EDCs)

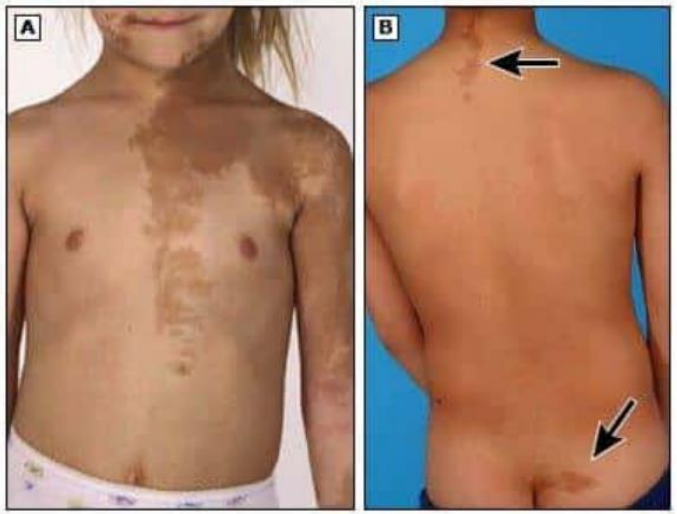
Exposure to topical estrogens (creams, ointments), certain food contaminants, phytoestrogens, and specific essential oils can induce feminization or virilization. EDCs are an active area of research.

Adrenal Pathology

Androgen-secreting tumors or enzymatic defects (e.g., congenital adrenal hyperplasia) can lead to excess androgen production. Rarely, adrenal estrogen-secreting tumors can cause feminization.

Café-au-lait spots in McCune-Albright syndrome

Café-au-lait spots in McCune-Albright syndrome



(A) A typical lesion on the face, chest, and arm of a five-year-old female with McCune-Albright syndrome, which demonstrates jagged "coast of Maine" borders and the tendency for the lesions to both respect the midline and follow the developmental lines of Blaschko (a configuration of skin lesions characterized by arcs on the upper chest, S shapes on the abdomen, and V shapes over the posterior midline, caused by patterns of X-chromosome inactivation).

(B) Typical lesions that are often found on the nape of the neck and crease of the buttocks are shown (arrows).

Peripheral precocity (gonadotropin-independent precocious puberty)

Peripheral precocity (gonadotropin-independent precocious puberty)

Etiology	Clinical features	Bone age	Additional evaluation
Females only			
Ovarian cysts	Breast development and/or vaginal bleeding. Occasionally presents with ovarian torsion and abdominal pain.	↑ to ↑↑	Pelvic ultrasound may visualize the cyst, although, in some cases, the cyst may have involuted by the time of the study. Vaginal bleeding is indicative of estrogen withdrawal. Recurrent ovarian cysts suggest McCune-Albright syndrome.
Ovarian tumor	Development of either isosexual or contrasexual sexual precocity, depending of tumor type.	↑↑	Pelvic ultrasound.
Males only			
Leydig cell tumor	Asymmetrical enlargement of the testes.	↑↑	Pubertal testosterone concentrations. Testicular ultrasound aids in diagnosis.
hCG-secreting germ-cell tumors	Symmetric testicular enlargement to an early pubertal size, but testes remain smaller than expected for degree of pubertal development. Peripheral precocity is seen only in males because hCG only activates LH receptors (estrogen biosynthesis in the ovaries requires both FSH and LH receptor activation).	↑↑	These tumors may occur in gonads, brain, liver, retroperitoneum, or mediastinum. When a tumor is identified in the anterior mediastinum, a karyotype must be performed because of an association of this finding with Klinefelter syndrome.
Familial male-limited precocious puberty	Symmetric testicular enlargement to an early pubertal size, but testes remain smaller than expected for degree of pubertal development; spermatogenesis may occur. A male-limited autosomal dominant trait. Peripheral precocity is seen only in males	↑↑	Genetic testing for mutations of the LH receptor gene.

Females and males			
Exogenous sex steroids (estradiol and testosterone creams) and endocrine-disrupting chemicals	Estrogen preparations cause feminization, while topical androgens cause virilization in both sexes.	↑ to ↑↑	Clinical history explores use of exogenous sex steroids and folk remedies by caregivers and exposure to endocrine-disrupting chemicals.
McCune-Albright syndrome (females>males)	In females, may present with recurrent episodes of breast development, regression, and vaginal bleeding. In males, sexual precocity is less common. Skin – Multiple irregular-edged café-au-lait spots. Bone – Polyostotic fibrous dysplasia.	↑ to ↑↑	Ultrasound – Ovaries enlarged, with follicular cysts. In males, testicular ultrasound can demonstrate hyper- and hypoechoic lesions (most likely representing areas of Leydig cell hyperplasia), microlithiasis, and focal calcifications. May have other hyperactive endocrine disorders, ie, thyrotoxicosis, glucocorticoid excess, and/or gigantism.
Primary hypothyroidism	Females – Vaginal bleeding, breast development, and galactorrhea. Males – Testicular enlargement. Other clinical features of hypothyroidism such as short stature.	↓	Elevated TSH.
Congenital adrenal hyperplasia (untreated)	Males have prepubertal testes with enlarged phallus and pubic hair development. Females with nonclassic congenital adrenal hyperplasia may present with early pubic and/or axillary hair and other signs of androgen excess.	↑↑	Sex hormone levels vary depending on the adrenal enzyme block. An early morning 17-OHP >200 ng/dL (>6 nmol/L) has a high sensitivity and specificity for congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency, but an ACTH stimulation test is still recommended to confirm the diagnosis for 17-OHP concentrations between 200 and 1500 ng/dL (6 to 45 nmol/L). After therapy with glucocorticoids, CPP may develop.
Virilizing adrenal tumor	Males – Pubic and/or axillary hair and penile growth with prepubertal testes. Females – Pubic and/or axillary hair, other significant signs of androgen excess (acne and clitoromegaly). May present with signs of glucocorticoid excess. May be associated with hereditary cancer syndromes.	↑↑	High DHEA or DHEAS, androstenedione, and testosterone. CT and/or ultrasound of adrenal glands to locate tumor.

Peripheral precocity is characterized by low or suppressed gonadotropin concentrations with elevated sex hormone levels. Pubertal status should be monitored for 6 months after treatment because treatment of peripheral precocity can trigger CPP.

↑: advanced for chronologic age; ↓: delayed for chronologic age; hCG: human chorionic gonadotropin; LH: luteinizing hormone; FSH: follicle-stimulating hormone; TSH: thyroid-stimulating hormone; 17-OHP: 17-hydroxyprogesterone; ACTH: adrenocorticotropic hormone; CPP: central precocious puberty; DHEA: dehydroepiandrosterone; DHEAS: dehydroepiandrosterone sulfate; CT: computed tomography.

Clinical and laboratory characteristics of different forms of early pubertal development

Clinical and laboratory characteristics of different forms of early pubertal development

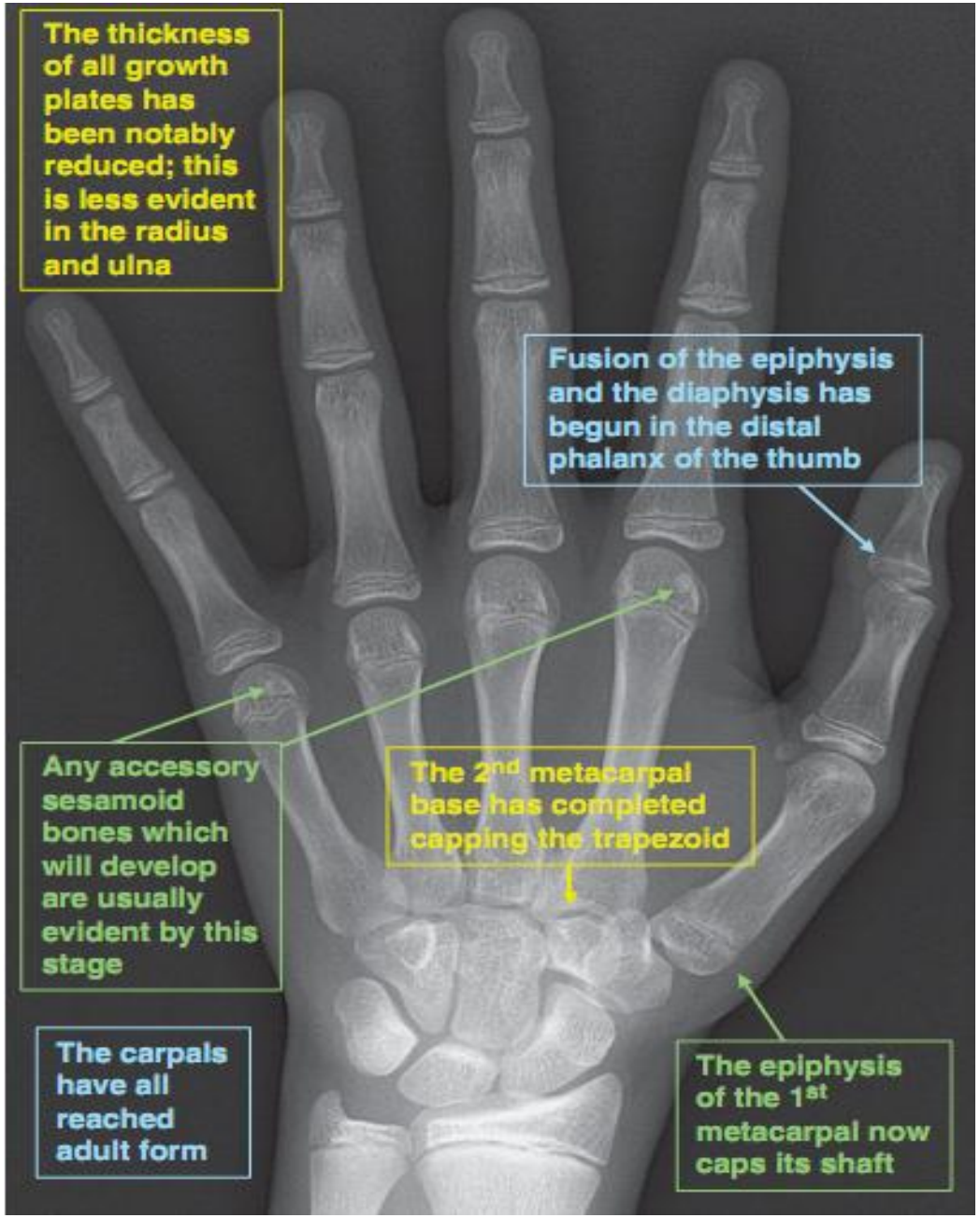
	Nonprogressive precocious puberty	Central precocious puberty	Peripheral precocity
Physical examination: Advancement through pubertal stages (Tanner stage)	No progression in Tanner staging during 3 to 6 months of observation	Progression to next pubertal stage in 3 to 6 months	Progression
Growth velocity	Normal for bone age	Accelerated (>6 cm per year)*	Accelerated*
Bone age	Normal to mildly advanced	Advanced for height age	Advanced for height age
Serum estradiol concentration (females) ¶	Prepubertal Δ	Prepubertal to pubertal	Increased in ovarian causes of peripheral precocity or with exogenous estrogen exposure
Serum testosterone concentration (males, or females with virilization) ¶	Prepubertal Δ	Prepubertal to pubertal	Pubertal and increasing
Basal (unstimulated) serum LH concentration ¶	Prepubertal Δ ◊	Pubertal ◊	Suppressed or prepubertal ◊
GnRH (or GnRH agonist) stimulation test ¶	LH peak in the prepubertal range Δ § Lower stimulated LH:FSH ratio ¥	LH peak elevated (in the pubertal range) § Higher stimulated LH:FSH ratio ¥	No change from baseline or LH peak in the prepubertal range

CPP: central precocious puberty; LH: luteinizing hormone; GnRH: gonadotropin-releasing hormone; FSH: follicle-stimulating hormone.

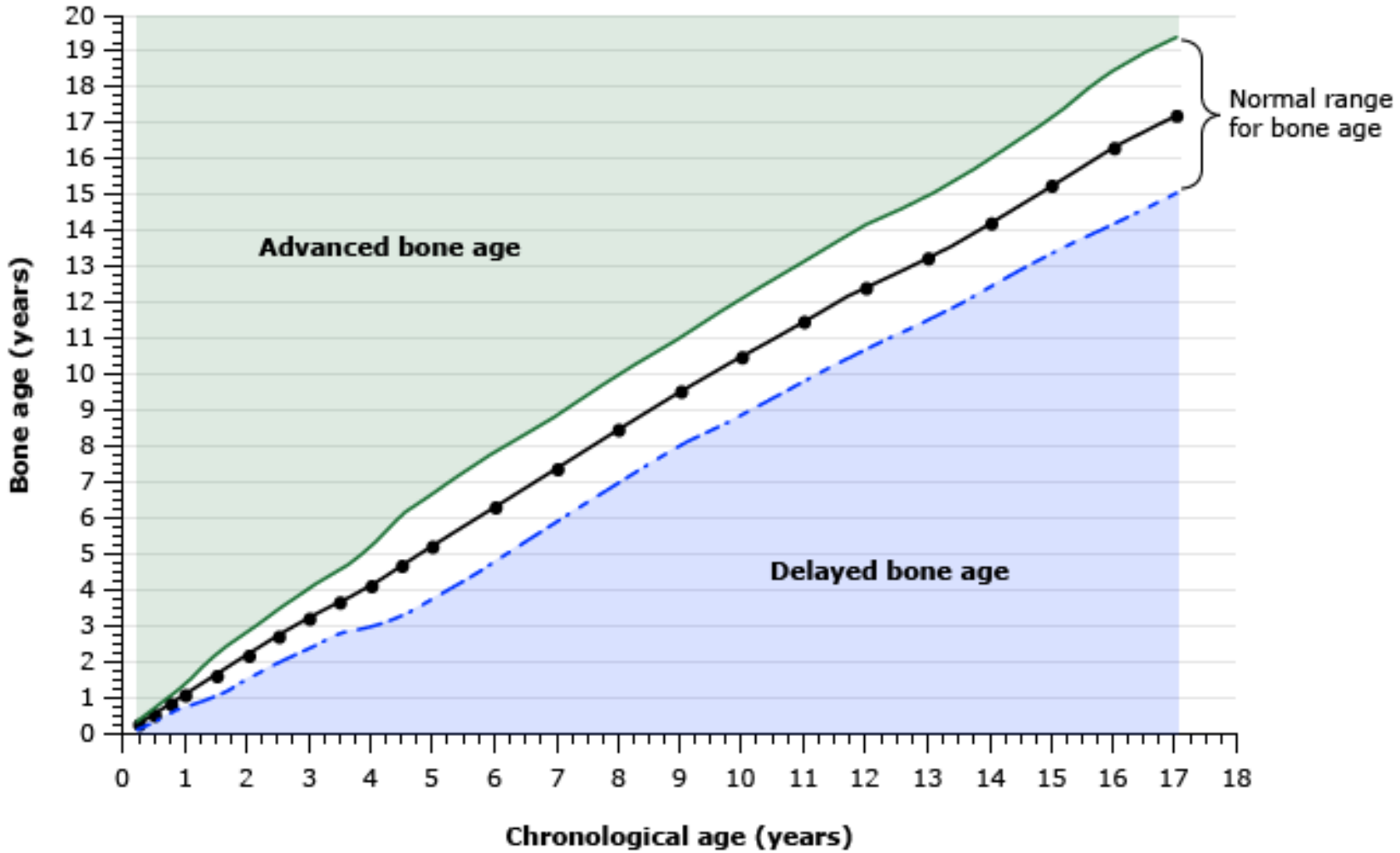
* **Unless** the patient has concomitant growth hormone deficiency (as in the case of a neurogenic form of CPP) or has already passed their peak height velocity at the time of evaluation, in which case, growth velocity may be normal or decreased for chronologic age.

¶ Using most commercially available immunoassays, serum concentrations of gonadal steroids have poor sensitivity to differentiate between prepubertal and early pubertal concentrations.

Δ In most cases, these levels will be prepubertal; however, in children with intermittently progressive CPP, these levels may reach pubertal concentrations


The thickness of all growth plates has been notably reduced; this is less evident in the radius and ulna
Fusion of the epiphysis and the diaphysis has begun in the distal phalanx of the thumb
Any accessory sesamoid bones which will develop are usually evident by this stage
The 2nd metacarpal base has completed capping the trapezoid
The carpals have all reached adult form
The epiphysis of the 1st metacarpal now caps its shaft

Chronological age versus bone age for boys



Premature thelarche (breast development)

- Most cases of premature thelarche are idiopathic and present under two years of age (and may even start at birth).

- Many cases will remit spontaneously, and most others do not progress. However, follow-up is warranted because premature thelarche can represent the initial presentation of true CPP in as many as 10 to 20 percent of children referred to pediatric endocrinology for evaluation.

Key features of premature thelarche

- Isolated breast development, either unilateral or bilateral – Typically not developing beyond Tanner stage 3
- Absence of other secondary sexual characteristics
- Normal height velocity for age (not accelerated)
- Normal or near-normal bone age
- Serum luteinizing hormone (LH) and estradiol concentrations are typically in the prepubertal range

Benign prepubertal vaginal bleeding

- Isolated, self-limited vaginal bleeding in the absence of other secondary sexual characteristics.
- The underlying etiology is unknown, but potential mechanisms include increased endometrial sensitivity to circulating estrogens or transient stimulation of the hypothalamic-pituitary-gonadal axis.
- Pelvic ultrasonography is normal, and gonadotropins are prepubertal.
- Genital or vaginal trauma, infection, and sexual abuse should be excluded. In girls with recurrent episodes of vaginal bleeding, other diagnoses (such as recurrent functional ovarian cysts or McCune-Albright syndrome [MAS]) should be considered.

Types of benign pubertal variants

Types of benign pubertal variants

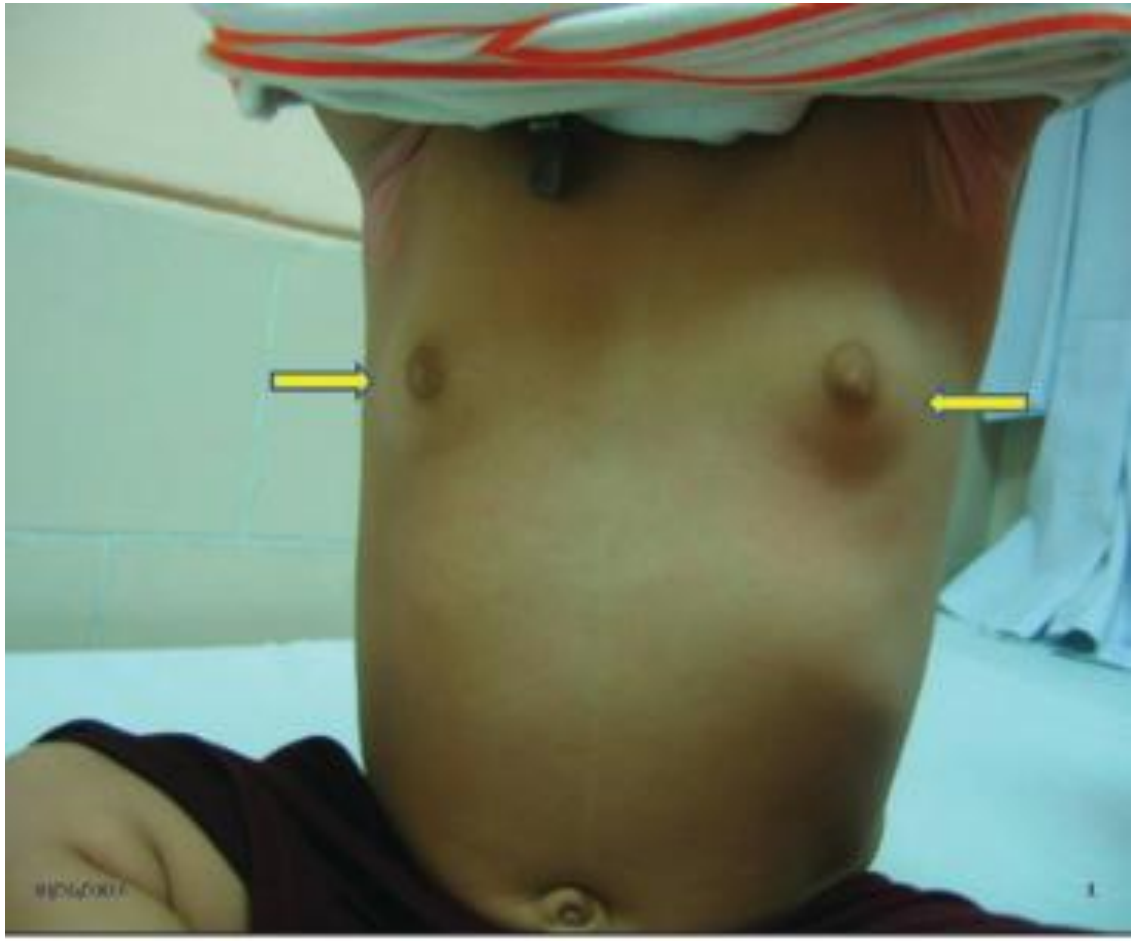
Etiology	Clinical features	Bone age	Additional evaluation
Premature adrenarche (boys or girls)	Isolated pubarche. Gonads are prepubertal in size and there is no breast development in girls. Typical age of onset 4 to 8 years. Seen more commonly in African-American and Hispanic girls and in children with obesity and insulin resistance.	↑ to ↑↑*	Further investigations needed only if there is significant progressive virilization, to help exclude peripheral precocity. Mild elevation in DHEAS for chronologic age (but appropriate for bone age). Prepubertal concentrations of 17-OHP and testosterone.
Premature thelarche (girls)	Isolated breast development with normal growth velocity. Most commonly seen in girls less than 3 years of age.	Normal (prepubertal)	No further evaluation needed in most cases, unless evidence of pubertal progression. Basal LH concentrations typically <0.2 to 0.3 mIU/L¶.
Nonprogressive or intermittently progressive precocious puberty (boys or girls)	Development of gonadarche (breast or testicular enlargement) with pubarche (pubic and/or axillary hair), with either no progression or intermittent slow progression in clinical pubertal signs.	Normal to ↑	Basal LH concentrations typically <0.2 to 0.3 mIU/L, although can be in early pubertal range in some children. Lower stimulated LH:FSH ratio compared with children with progressive central precocious puberty$^{\Delta}$. Patients with nonprogressive precocious puberty do not need treatment with GnRH agonist, because final height untreated is concordant with parental height.

Case1

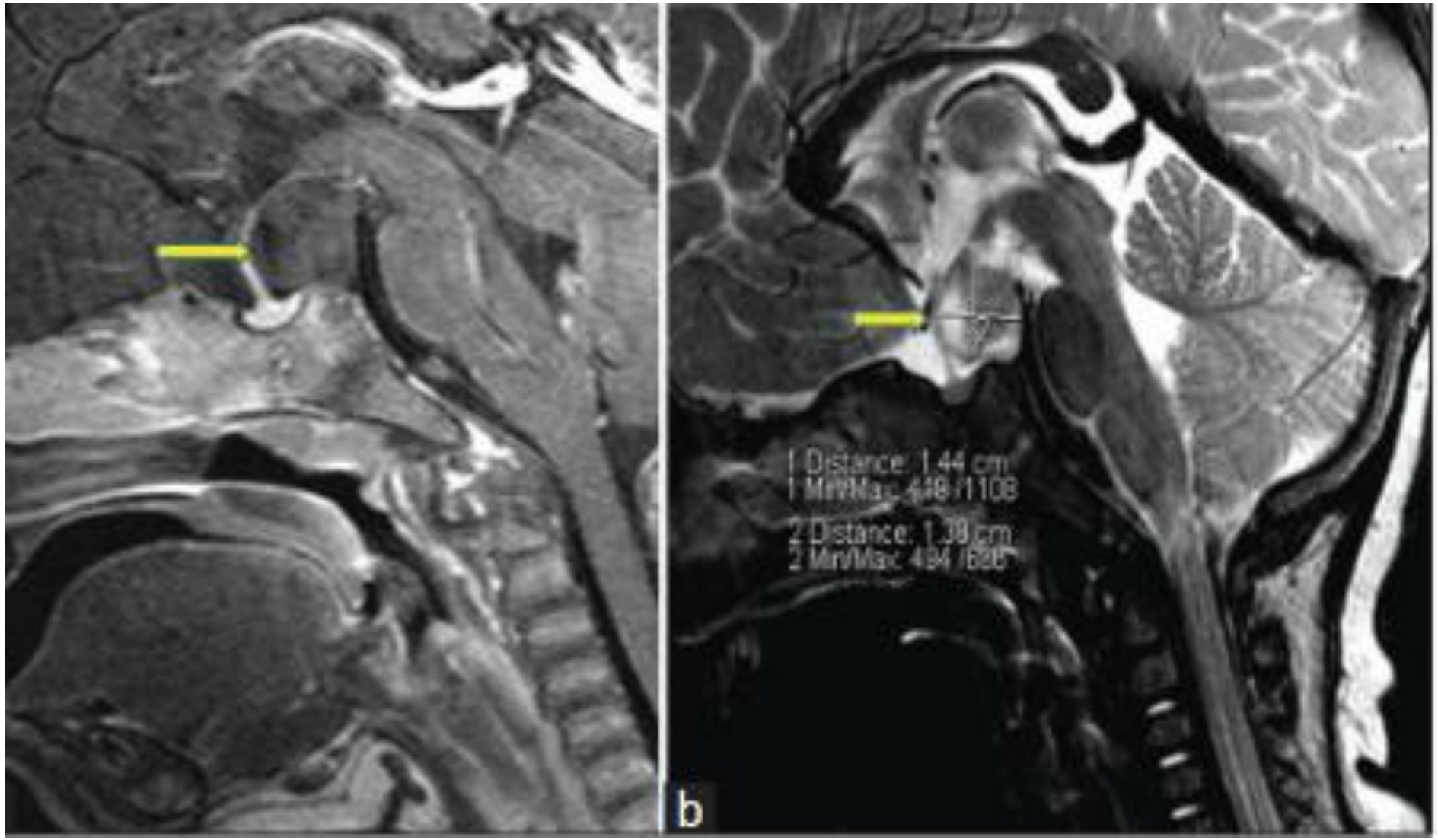
A sixteen-month-old girl was brought by her parents to

the Pediatric Endocrinology Outpatient Department

with a history of bleeding per vagina, with no previous history of genital trauma



- LH: 2.20 mIU/ mL (N < 0.6 mIU / mL)
- FSH :5.58 mIU / mL (N < 0.6 mIU / mL)
- and estradiol (E2) of 12 pg / mL (N < 9pg / mL
- bone age of 24 months
- Tumor markers such as carcinoembryonic antigen (CEA), CA 19.9, alpha-fetoprotein, and human chorionic gonadotropin (HCG)were negative.
- Uterine volume on pelvic ultrasonography was 2.2 ml, with no evidence of ovarian cyst / tumor.


1 Distance: 1.44 cm
1 Min/Max 448 /1108
2 Distance: 1.38 cm
2 Min/Max 494 /626
b

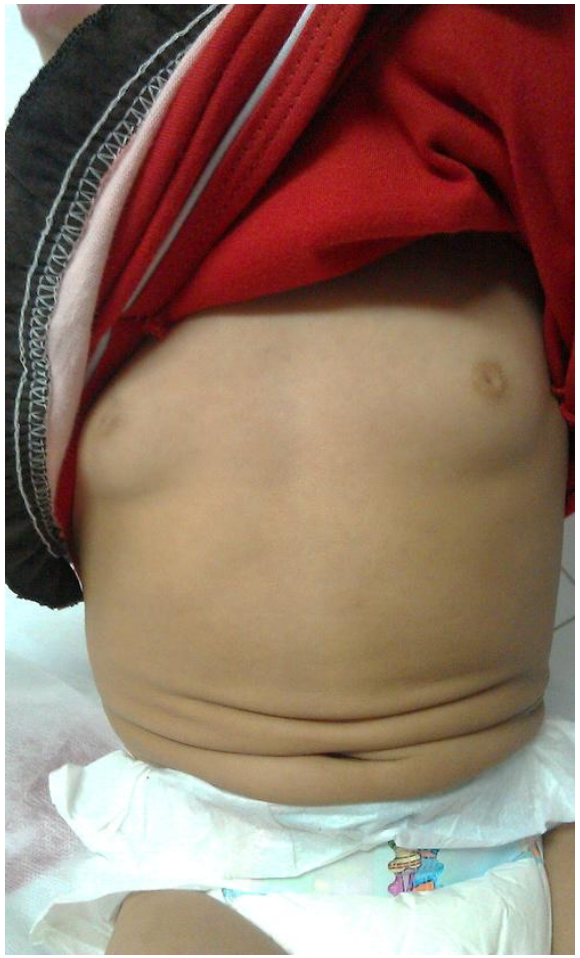
- a) Plain MRI Brain (T1W image) revealing sessile, well-defined

hypothalamic mass is intense to gray matter

- (b) MRI brain, postcontrast, revealing a hyper intense mass lesion suggestive of hypothalamic hamartoma, measuring 1.44 × 1.38 cm

Causative	Serum Gonadotropin Concentration	LH Response to GnRH	Serum Sex Steroid Concentrations	Gonadal Size	Miscellaneous
True precocious puberty	Pubertal values	Pubertal	Pubertal values of testosterone or Estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement (by sonography)	MRI scan of brain to rule out CNS tumor or other abnormality; bone scan for McCune-Albright syndrome

case2



A 15-month-old girl is referred for breast enlargement. Other examinations are normal

Height is on the 25th percentile, weight is on the 25th percentile,

- Bone age: 12 months
- LH:0.1mIU/L
- FSH:0.2 mIU/L
- Estradiol:3 pg/ml
- Uterine and ovary sono: prepubertal

- Benign premature thelarche
- Breast enlargement has been regressed

Causative	Serum Gonadotropin Concentration	LH Response to GnRH	Serum Sex Steroid Concentrations	Gonadal Size	Miscellaneous
Premature thelarche	prepubertal	prepubertal	Prepubertal or early pubertal estradiol	Ovaries prepubertal	Onset usually before 3 yr of age

TAKE HOME MESSAGE

Distinguishing normal from abnormal development based on age norms is crucial

Differentiating benign developmental variants to serious pathological conditions.

Identifying whether sex hormone effects are centrally mediated, peripherally autonomous, or exogenous.