precocious puberty

- Precocious puberty is the onset of pubertal development at an age that is 2 to 2.5 standard deviations (SD) earlier than population norms

- Precocious puberty is traditionally defined as the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys

The clinician faced with a child who presents with early development of secondary sexual characteristics should consider the following questions:

- Is the child too young to have reached the pubertal milestone in question?
- What is causing the early development?
- Is therapy indicated, and, if so, what therapy?

NORMAL PUBERTAL DEVELOPMENT

Puberty is the general term for the transition from sexual immaturity to sexual maturity. There are two main physiological events in puberty:

- *Gonadarche* is the activation of the gonads by gonadotropins (FSH and LH)
- *Adrenarche* is the increase in production of androgens by the adrenal cortex

- gonadal axis is biologically active in utero and briefly during the first week of life. It then becomes more active again during infancy, with peak activity between one and three months of age

- This state yields sex steroid levels comparable with those seen in early-to-mid puberty but without peripheral effects

- This hypothalamic-pituitary-gonadal activity during infancy is known as the "*mini puberty of infancy*"; its biologic relevance is unknown

- In boys, gonadotropin concentrations then decrease to prepubertal levels by six to nine months of age. In girls, luteinizing hormone (LH) levels decrease at approximately the same time as in boys, but the follicle-stimulating hormone (FSH) concentrations can remain elevated into the second year of life

Girls

- The earliest detectable secondary sexual characteristic in most girls is breast/areolar development (thelarche)

- Approximately 15 percent of girls have pubic hair as the initial manifestation (pubarche)

- The initial manifestation of puberty predicts body morphology and composition throughout pubertal maturation into early adulthood

- Girls with breast development as the initial manifestation of puberty have both an earlier age of menarche and greater body mass index (BMI) compared with girls who exhibit pubarche first

- Estrogen stimulation of the vaginal mucosa causes a physiologic leukorrhea, vaginal discharge typically begins 6 to 12 months before menarche

- Menarche occurs, on average, 2 to 2.5 years after the onset of puberty

BOYS

- The earliest stage of male maturation that is detectable on physical examination is an increase in testicular volume (volume ≥4 mL and length ≥2.5 cm
- The appearance of sperm in the urine and the onset of nocturnal sperm emissions occur shortly after the attainment of peak height velocity; many consider these events the male equivalent of menarche
- Mean stretched penile length is approximately 3.75 cm (±0.54 cm) at one year of age, gradually increases to 4.84 cm by late childhood, and increases sharply to approximately 9.5 cm (±1.12 cm) by late puberty

TIMING OF PUBERTAL EVENTS

- *Trends in pubertal timing*
- *Genetics accounts for the majority of the variability in the timing of pubertal onset in developed countries*
- *overall health (with poor health associated with delayed pubertal onset)*
- *social environment*
- *environmental factors, including endocrine disruptors*
- Body fat and leptin(Leptin is one of several factors that influence the activity of the GnRH pulse generator)

CLASSIFICATION

❑ *Central precocious puberty (CPP)*

- CPP (also known as gonadotropin-dependent precocious puberty or true precocious puberty) is caused by early maturation of the hypothalamic-pituitary-gonadal axis

- CPP is pathologic in up to 40 to 75 percent of cases in boys , compared with 10 to 20 percent in girls

- These children have accelerated linear growth for age, advanced bone age, and pubertal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

CAUSES OF CENTRAL PRECOCIOUS PUBERTY:

- Idiopathic
- Central nervous system lesions:

Hamartomas, other CNS tumors (astrocytomas , ependymomas, pinealomas, and optic and hypothalamic gliomas),CNS irradiation , hydrocephalus, cysts, trauma, CNS inflammatory disease, and congenital midline defects

- Genetics: Gain-of-function mutations in the kisspeptin 1 gene (KISS1) and the gene for its G protein-coupled receptor (KISS1R), loss-of-function mutations in MKRN3
- Previous excess sex steroid exposure

❑*Peripheral precocity*

Peripheral precocity (also known as gonadotropin-independent precocious puberty) is caused by excess secretion of sex hormones (estrogens or androgens) from the gonads or adrenal glands, exogenous sources of sex steroids, or ectopic production of gonadotropin from a germ-cell tumor (eg, hCG)

Peripheral precocity may be appropriate for the child's gender (isosexual) or inappropriate, with virilization of girls and feminization of boys (contrasexual)

Girls

Ovarian cysts:

- A functioning follicular cyst of the ovaries is the most common cause of peripheral precocity in girls
- Affected patients often present with breast development, followed by an episode of vaginal bleeding, which occurs due to estrogen withdrawal once the cyst has regressed
- These cysts may appear and regress spontaneously, so conservative management is usually appropriate
- Large cysts may predispose to ovarian torsion

Ovarian tumors:

- Ovarian tumors are a rare cause of peripheral precocity in girls
- Granulosa cell tumors, the most common type, typically present as isosexual precocity
- Sertoli/Leydig cell tumors (arrhenoblastoma), pure Leydig cell tumors, and gonadoblastoma may make androgens and cause contrasexual precocity

Boys

- Leydig cell tumors

- Human chorionic gonadotropin-secreting germ-cell tumors: These tumors occur in the gonads, brain (usually in the pineal region), liver, retroperitoneum, and anterior mediastinum

- Familial male-limited precocious puberty

Both girls and :

- Primary hypothyroidism
- Exogenous sex steroids and endocrine-disrupting chemicals
- Adrenal pathology
- McCune-Albright syndrome

Benign or nonprogressive pubertal variants

- Isolated breast development in girls (premature thelarche)
- Isolated androgen-mediated sexual characteristics such as pubic and/or axillary hair, acne, and apocrine odor in boys or girls (premature adrenarche)
- Both of these conditions can be a variant of normal puberty
- Repeat clinical examination is warranted to ensure there is no rapid and/or expanded pubertal progression and that the diagnosis is correct

EVALUATION

- ***Medical history*** :when the initial pubertal changes were first noted, timing of pubertal onset in the parents and siblings, headaches, changes in behavior or vision, seizures, or abdominal pain , previous history of CNS disease or trauma, exposure to exogenous sex steroids (medicinal or cosmetic sources) or compounds with sex steroid-like properties
- ***Physical examination*** :height, weight, and height velocity (cm/year),assessment of visual fields and examination for café-au-lait spots

- **Pubertal staging**

- **Bone age** :A significant advance in the bone age (greater than approximately 2 standard deviations [SD] beyond chronologic age) is more likely to be indicative of either CPP or peripheral precocity rather than a benign pubertal variant

- **Basal serum luteinizing hormone** — A good initial screening test to identify activation of the hypothalamic-pituitary-gonadal axis Results are interpreted as follows:
- LH concentrations in the prepubertal range (ie, <0.2 mIU/mL) are consistent with either peripheral precocity or a benign pubertal variant such as premature thelarche
- LH concentrations greater than 0.2 to 0.3 mIU/mL can identify children with progressive CPP with high sensitivity and specificity
- LH concentrations are less informative: nonprogressive precocious puberty, intermittently progressive precocious puberty, early pubertal range in some children

Basal serum follicle-stimulating hormone

- Basal FSH concentrations have limited diagnostic utility in distinguishing children with CPP from those with benign pubertal variants
- Like LH, FSH concentrations are typically suppressed in children with peripheral precocity

Serum estradiol

- Very high concentrations of estradiol, with associated suppression of gonadotropins, are generally indicative of peripheral precocity, such as from an ovarian tumor or cyst
- Most estradiol immunoassays, however, have poor ability to discriminate at the lower limits of the assay between prepubertal and early pubertal concentrations
- Estradiol pubertal level >9 pg/ml

Serum testosterone —

- Elevated testosterone concentrations are indicative of testicular testosterone production in boys, or of adrenal testosterone production or exogenous exposure in both sexes
- Very high concentrations, with associated suppression of gonadotropins, are generally indicative of peripheral precocity
- Measurement of other adrenal steroids (eg, dehydroepiandrosterone sulfate [DHEAS]) may be necessary to help discriminate between adrenal and testicular sources of the androgens
- In children with CPP, testosterone immunoassays cannot always distinguish between prepubertal and early pubertal testosterone concentrations, but tandem mass spectroscopy methods are more discriminative

Subsequent laboratory testing :

- Serum LH concentrations after GnRH agonist: In children in whom the clinical picture is discordant with the initial baseline investigations (ie, ongoing pubertal progression with basal LH level <0.3 mIU/mL),
- Serum adrenal steroids

- Other biochemical tests — In boys, human chorionic gonadotropin (hCG) should be measured to evaluate for the possibility of an hCG-secreting tumor leading to peripheral precocity.
- If a tumor is found in the anterior mediastinum, a karyotype should be performed to evaluate for Klinefelter syndrome because of its association with mediastinal germinoma
- A thyroid-stimulating hormone (TSH) concentration should be measured if chronic primary hypothyroidism is suspected as the underlying cause for the sexual precocity.

- **Imaging:**
- •Brain magnetic resonance imaging (MRI): recommend performing a contrast-enhanced brain MRI for all boys with CPP and for girls with onset of secondary sexual characteristics before six years of age because of higher rates of CNS abnormalities in these groups of patients
- •Pelvic ultrasound –

Treatment

CENTRAL PRECOCIOUS: gonadotropin-releasing hormone (GnRH) agonist

- This treatment can be used for patients with idiopathic or neurogenic CPP , or for secondary activation of CPP
- When CPP is caused by an identifiable central nervous system (CNS) lesion, therapy is also directed toward the underlying pathology when possible

Decision to treat — The decision of whether to treat CPP with a GnRH agonist depends upon:

- the child's age,
- the rate of pubertal progression
- height velocity
- and the estimated adult height as determined from the rate of bone age advancement

Formulations and dosing:

- Sustained-release formulations of several GnRH agonists have been developed: depot preparations for monthly, three-, or six-monthly dosing and a subcutaneous implant that is surgically inserted every 12 months

Monitoring :

- Evaluation of pubertal development and growth every three to six months
- Effective GnRH agonist therapy should result in a decrease in height velocity, cessation of menses, and arrest pubertal progression.
- Periodic bone age measurements (eg, every 6 to 12 months), looking for a reduction in the bone age advancement
- If this testing shows incomplete suppression of the pituitary-gonadal axis, the GnRH agonist dose should be increased or the interval between doses decreased

- Within the first weeks after the initial dose of the GnRH agonist, vaginal bleeding may occur due to estradiol withdrawal because the treatment initially stimulates estradiol production before suppressing the pituitary-gonadal axis

- If vaginal bleeding occurs later in the course of treatment, this either indicates lack of suppression of the pituitary-gonadal axis or an alternative diagnosis to CPP (eg, a cause of peripheral precocity).

- Pubic hair stage may advance due to adrenarche despite effective treatment with GnRH agonists because these agents have no effect on adrenal androgen production

Treatment duration

- The duration of GnRH agonist therapy should be long enough to optimize final adult height
- allow progression of pubertal characteristics at an age that is concurrent with the individual's peers
- When GnRH agonist therapy with monthly depot preparations is stopped, normal puberty returns, on average, within 12 to 18 months

- Recommended to continue treatment until approximately age 11 years in girls and age 12 years in boys

Safety

- Adverse effects include pain and local reactions at the injection sites, and, although uncommon, sterile abscess formation

- Regarding long-term outcome of GnRH agonist therapy for CPP:
- Treatment with GnRH agonists appears to have no significant long-term effects on the pituitary-gonadal axis
- Although earlier pubertal development is associated with obesity, long-term treatment with GnRH agonists does not appear to cause or exacerbate obesity in adolescence or adulthood

- While bone mineral density may slightly decrease during GnRH agonist administration, these changes are not sustained, with preservation of peak bone mass accrual after discontinuation of therapy

- Overall, there is no clear evidence that GnRH agonist treatment increases the risk for polycystic ovary syndrome