Central Precocious Puberty

Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 yr in females and 9 yr in males.

Depending on the primary source of the hormonal production, precocious puberty may be classified as :-

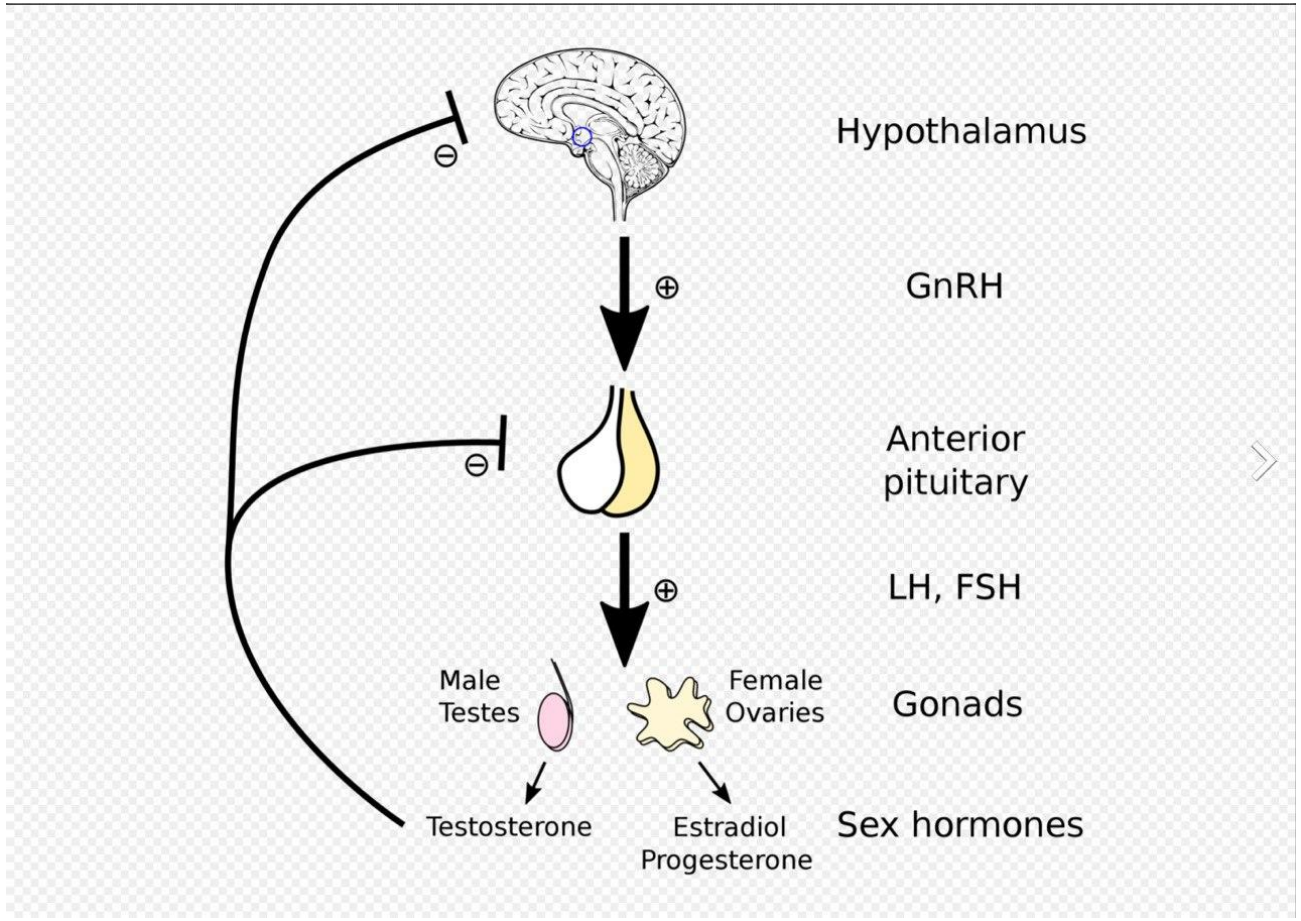
- ***central*** (also known as gonadotropin dependent, or true)
- ***peripheral*** (also known as gonadotropin independent or precocious pseudopuberty)

. Central precocious puberty (CPP) is always isosexual and stems from hypothalamic-pituitary-gonadal activation with ensuing sex hormone secretion and progressive sexual maturation.

In peripheral precocious puberty, some of the secondary sex characters appear, but there is no activation of the normal hypothalamic-pituitary-gonadal interplay. In this latter group, the sex characteristics may be isosexual or heterosexual (contrasexual)

Central Precocious Puberty

occurs 5- to 10-fold more frequently in females than in males and is usually sporadic. Although at least 90% of females have an idiopathic form, a structural central nervous system (CNS) abnormality may occur in 25–75% of males with CPP.


Hypothalamus
GnRH
Anterior pituitary
LH, FSH
Male Testes
Female Ovaries
Gonads
Testosterone
Estradiol Progesterone
Sex hormones

CLINICAL MANIFESTATIONS

Sexual development may begin at any age and generally follows the sequence observed in normal puberty. In females, early menstrual cycles may be more irregular than they are with normal puberty. The initial cycles are usually anovulatory, but pregnancy has been reported as early as 5.5 yr of age

. In males, testicular biopsies have shown stimulation of all elements of the testes, and spermatogenesis has been observed as early as 5-6 yr of age

main patterns of pubertal progression can 3 .be identified

1. Most females (particularly those younger than 6 yr of age at the onset) and a large majority of males have rapidly progressive puberty, characterized by rapid physical and osseous maturation, leading to a loss of height potential.
2. An increasing percentage of females (older than 6 yr of age at the onset with an idiopathic form), and rarely males, have a slowly progressive variant, characterized by parallel advancement of osseous maturation and linear growth, with preserved height potential.
3. Very rarely, central puberty may regress spontaneously (unsustained CPP).

- ***LABORATORY FINDINGS***
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serum estradiol concentrations are low or undetectable in the early phase of sexual precocity in females, as they are in normal puberty.

- In males, ***serum testosterone*** levels are usually detectable or clearly elevated by the time the parents seek medical attention, provided that an early morning blood sample is obtained.

- With the use of highly sensitive immunofluorometric and chemiluminescent assays, ***serum LH concentrations*** are undetectable in prepubertal children in random blood samples but become detectable in 50–75% of females and a higher percentage of males with CPP.

Measurement of ***LH in serial blood samples obtained during sleep*** has greater diagnostic power than measurement in a single random sample, and it typically reveals a well-defined pulsatile secretion of LH.

Administration of ***gonadotropin-releasing hormone (GnRH stimulation test, intravenously) or a GnRH agonis***t is a helpful diagnostic tool, particularly for males, in whom a pubertal LH response (LH peak >5 IU/L) with predominance of LH over (FSH) tends to occur early in the course of precocious puberty. In females with sexual precocity, however, the nocturnal LH secretion and the LH response to GnRH or GnRH agonist may be quite low at breast stages II to early III (LH peak, <5 IU/L), and the LH to FSH ratio may remain low until mid-advanced puberty. In such females with low LH response, the central nature of sexual precocity can be proven by detecting pubertal levels of estradiol (>50 pg/mL) 20-24 hr after stimulation with leuprolide.

Osseous maturation is variably advanced, often more than 2-3 SD.

Pelvic ultrasonography in females reveals progressive enlargement of the ovaries, followed by enlargement of the fundus and then of the whole uterus to pubertal size.

An ***MRI*** scan usually demonstrates physiologic enlargement of the pituitary gland, as seen in normal puberty; it may also reveal CNS pathology

differential diagnosis

For females

- tumors of the ovaries
- functioning ovarian cysts
- feminizing adrenal tumors
- McCune-Albright syndrome,
- exogenous sources of estrogens.

- ***males***
- congenital adrenal hyperplasia, adrenal tumors
- Leydig cell tumors,l
- human chorionic gonadotropin(hCG)–producing tumors
- exposure to exogenous androgens, familial male precocious puberty should be considered.

Treatment

The observation that the pituitary gonadotropic cells require pulsatile, rather than continuous, stimulation by GnRH to maintain the ongoing release of gonadotropins provides the rationale for using GnRH agonists for treatment of CPP.

These GnRH agonists (after a brief period of stimulation) desensitize the gonadotropic cells of the pituitary to the stimulatory effect of endogenous GnRH and effectively halt the progression of central sexual precocity. Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentration of the drug for weeks or months, constitute the preparations of choice for treatment of CPP.

In ***the United States, the available preparations include:***

- (***a***) leuprolide acetate (Lupron Depot Ped), in a dose of 0.2-0.3 mg/kg (7.5-15 mg) intramuscularly once every 4 wk;
- (***b***) longer-acting preparations of depot-leuprolide, allowing for injections (11.25 or 30 mg IM) every 90 days;
- (***c***) histrelin (SupprelinLA), a subcutaneous 50-mg implant with effects lasting at least 12 mo; and
- (***d***) triptorelin (Triptodur), 22.5 mg IM every 6 months. Other preparations such as goserelin acetate (Zoladex) are approved for treatment of precocious puberty in other countries.

Treatment results

1. decrease of the growth rate, generally to age appropriate values,
2. decrease of the rate of osseous maturation. Some children may show marked deceleration of their growth rate and an arrest in the rate of osseous maturation.
3. enhancement of the predicted height, although the actual adult height of patients followed to epiphyseal closure has, historically, been approximately 1 SD less than their mid–parental height.

In females

1. breast size may regress in those with Tanner stage II-III development but tends to remain unchanged in females with late stage III-V development or may even increase slightly because of progressive adipose tissue deposition. The amount of glandular tissue decreases.
2. Pubic hair usually remains stable in females or may progress slowly during treatment, reflecting the gradual increase in adrenal androgens.
3. Menses, if present, cease.
4. Pelvic sonography demonstrates a decrease of the ovarian and uterine size

. ***In males***

1. decrease of testicular size
2. variable regression of pubic hair
3. decrease in the frequency of erections.

Except for a reversible decrease in bone density (of uncertain clinical significance), no serious adverse effects of GnRH analogs have been reported in children treated for sexual precocity. If treatment is effective, the serum sex hormone concentrations decrease to prepubertal levels (testosterone, <10-20 ng/ dL in males; estradiol, <5-10 pg/mL in females).

Therapy is typically discontinued at a pubertal chronological age, after which puberty resumes promptly. In females, menarche generally appears at an average of 18 mo (range 6-24 mo) after cessation of IM therapy and somewhat earlier after removal of the histrelin implant.

Recurrent sterile fluid collections at the sites of injections are an uncommon local side effect and occur in less than 1–3% of patients treated with depot-leuprolide.

Thank you