Central Precocious Puberty

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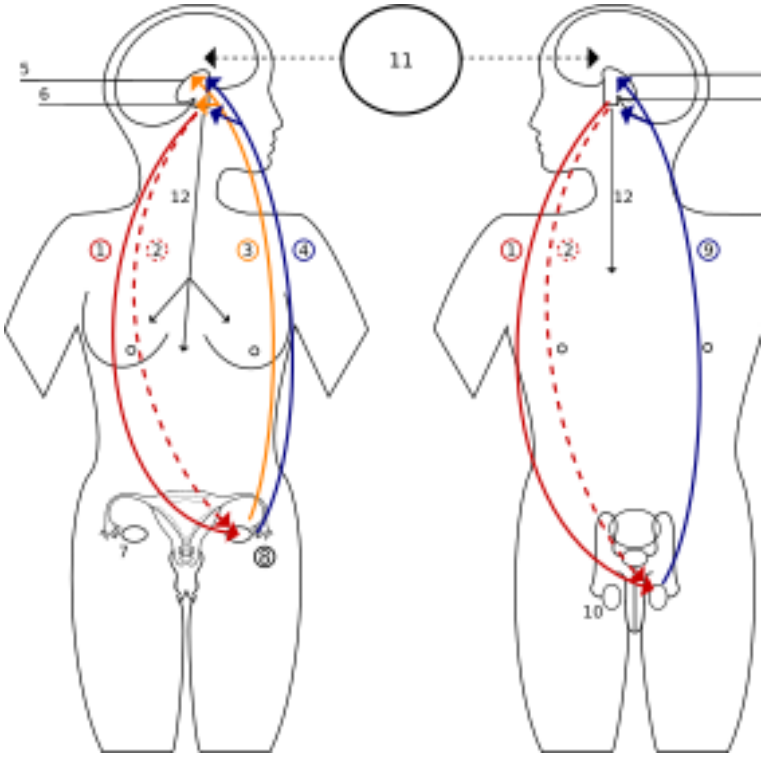


Key Points

Normal Puberty:

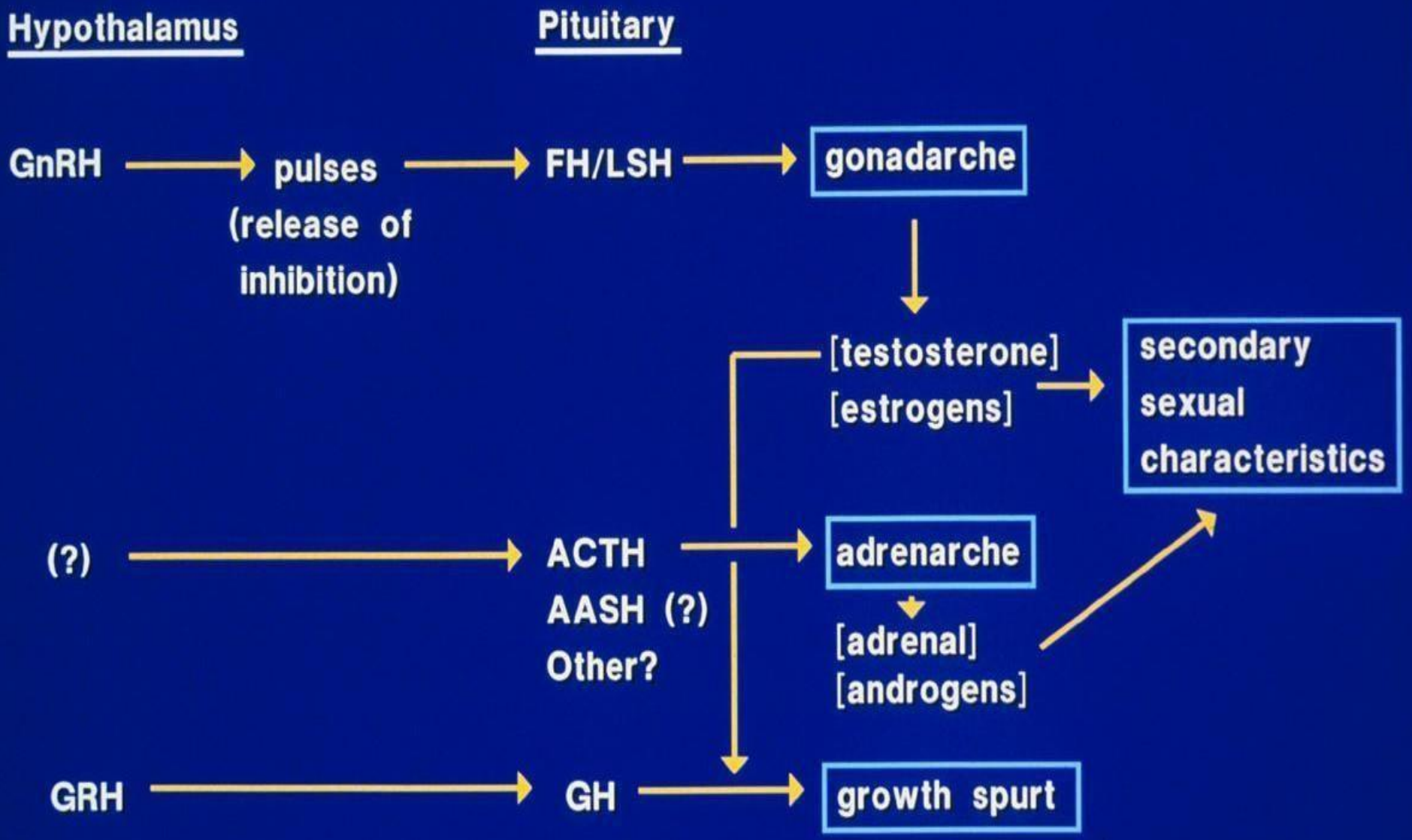
- HPG Axis.
- Factors influencing the age of puberty.
- Relationship between obesity & puberty.
- Somatic, sexual and emotional changes for both genders.
- Exogenous sources of Estrogen and early puberty.

Precocious Puberty:

- Types of precocious puberty.
- Causes.
- Central precocious puberty.
- Peripheral precocious puberty
- Approach to the diagnosis.
- Treatment of CPP (GnRH agonists).
- Safety and future gonadal functions.
- Conclusions.


PUBERTY

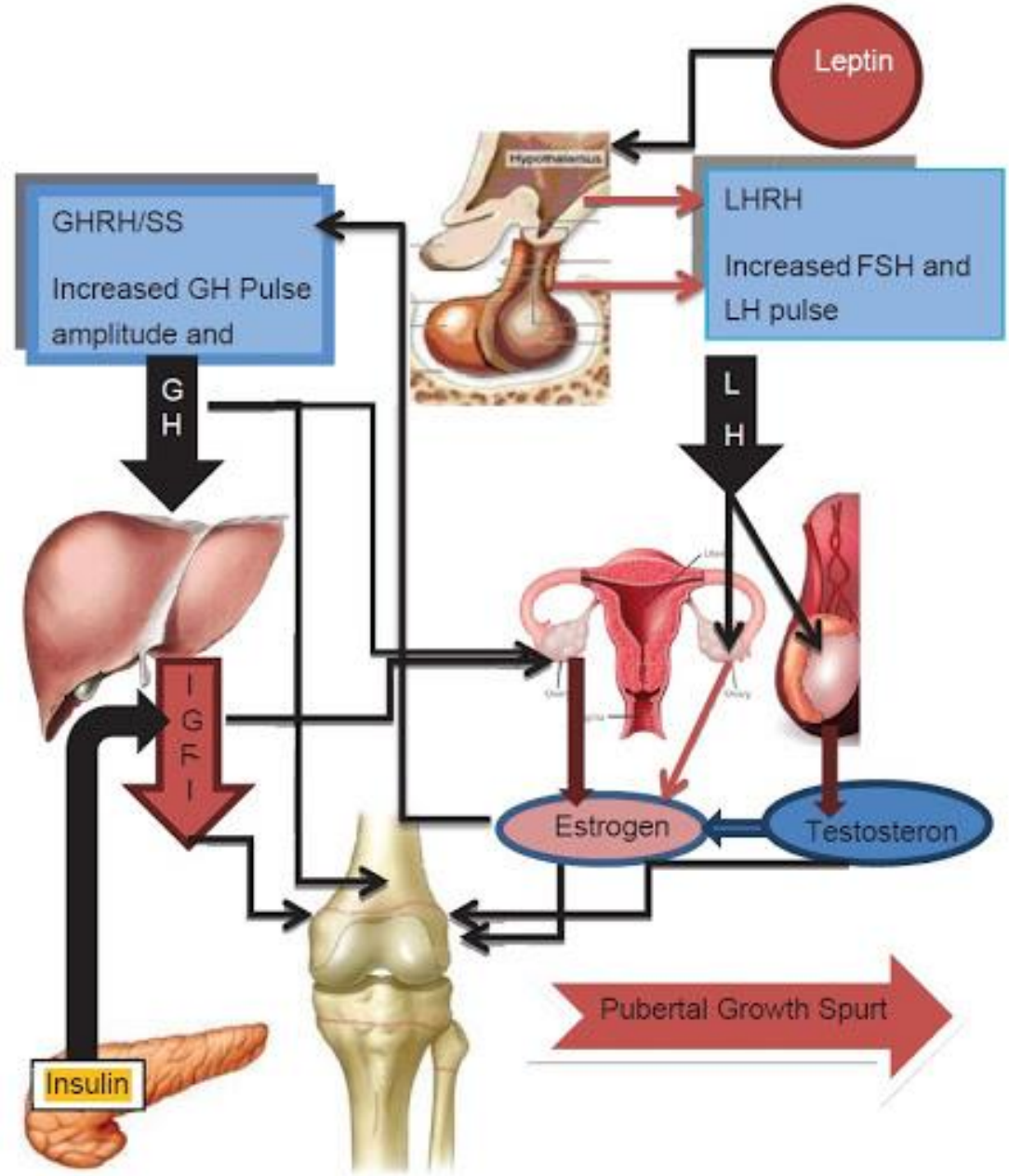
Puberty


Hypothalamus
Pituitary
GnRH
pulses
(release of
inhibition)
FH/LSH
gonadarche
[testosterone]
[estrogens]
secondary
sexual
characteristics
(?)
ACTH
AASH (?)
Other?
adrenarche
[adrenal]
[androgens]
GRH
GH
growth spurt

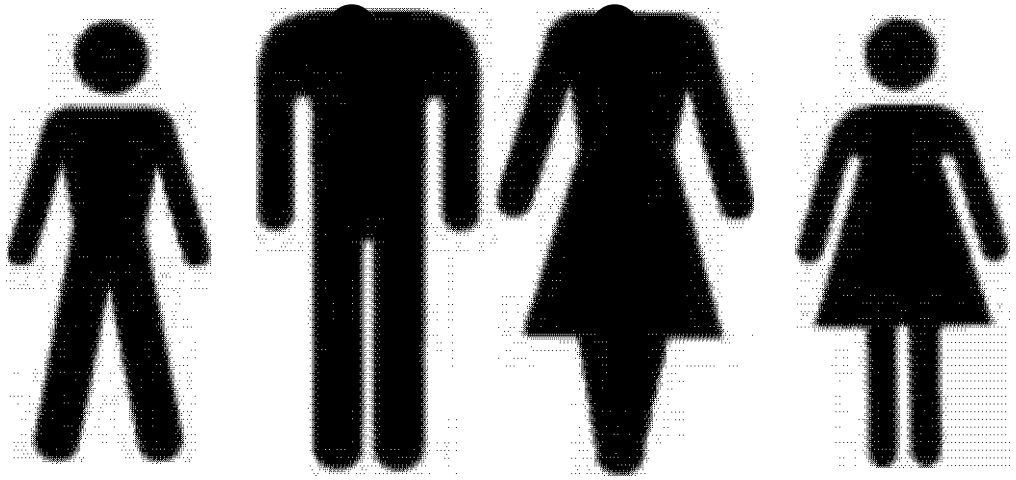
Puberty: Influencing factors

- Genetics: 50-80% of variation in pubertal timing.
- General health.
- Socioeconomic status.
- Geography: children residing closer to the equator, at lower altitudes, in cities & other urban areas generally have earlier puberty than their counterparts.
- Environmental factors: nutritional status, environmental hormonal disruptors e.g., usage of plastics, nylon or food products rich with estrogen.
- Obesity: as obese children tend to have earlier puberty as their adipose tissues produces Leptin peptide which has stimulating effects on the hypothalamus.

Obesity & Puberty

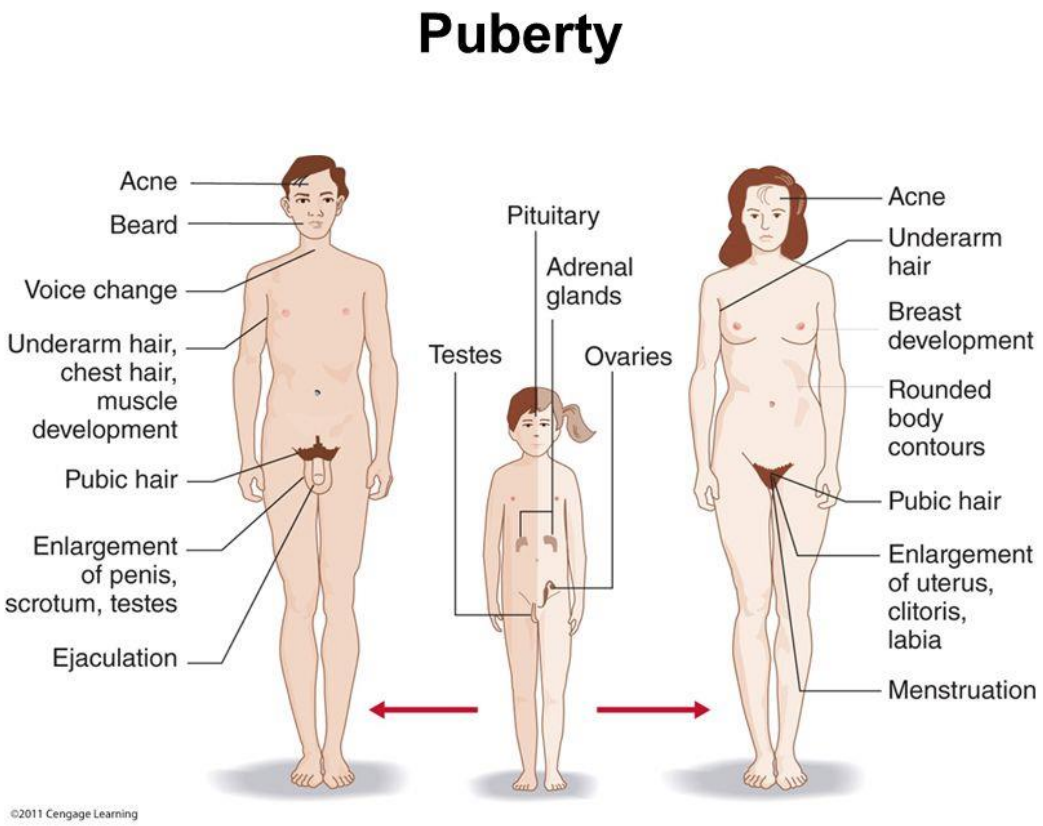


Exogenous sources of estrogens

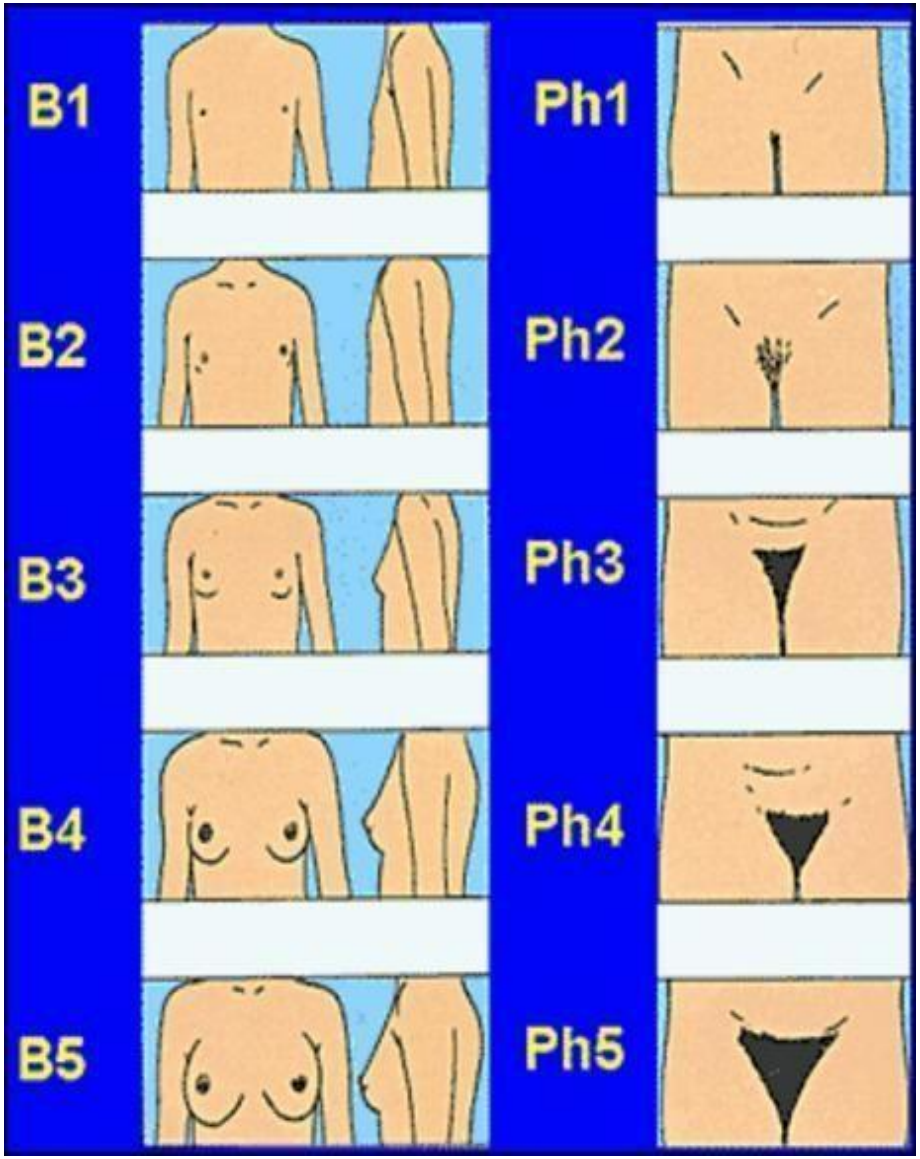


Changes during puberty

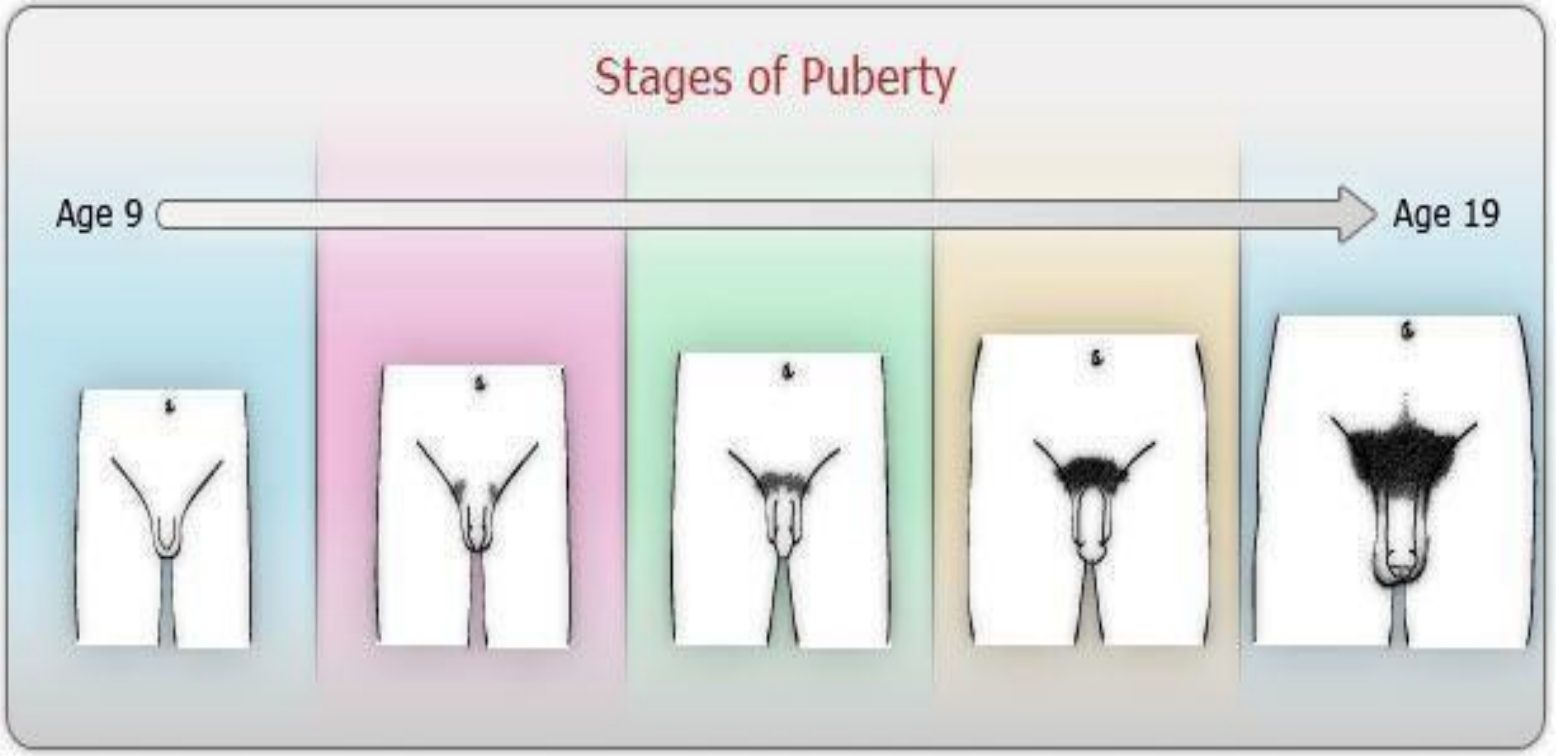
قال تعالى (فَلَمَّا وَضَعَتْهَا قَالَتْ رَبِّ إِنِّي وَضَعْتُهَا أُنْثَى وَاللَّهُ أَعْلَمُ بِمَا وَضَعَتْ **وَلَيْسَ الذَّكَرُ كَالأُنْثَى**



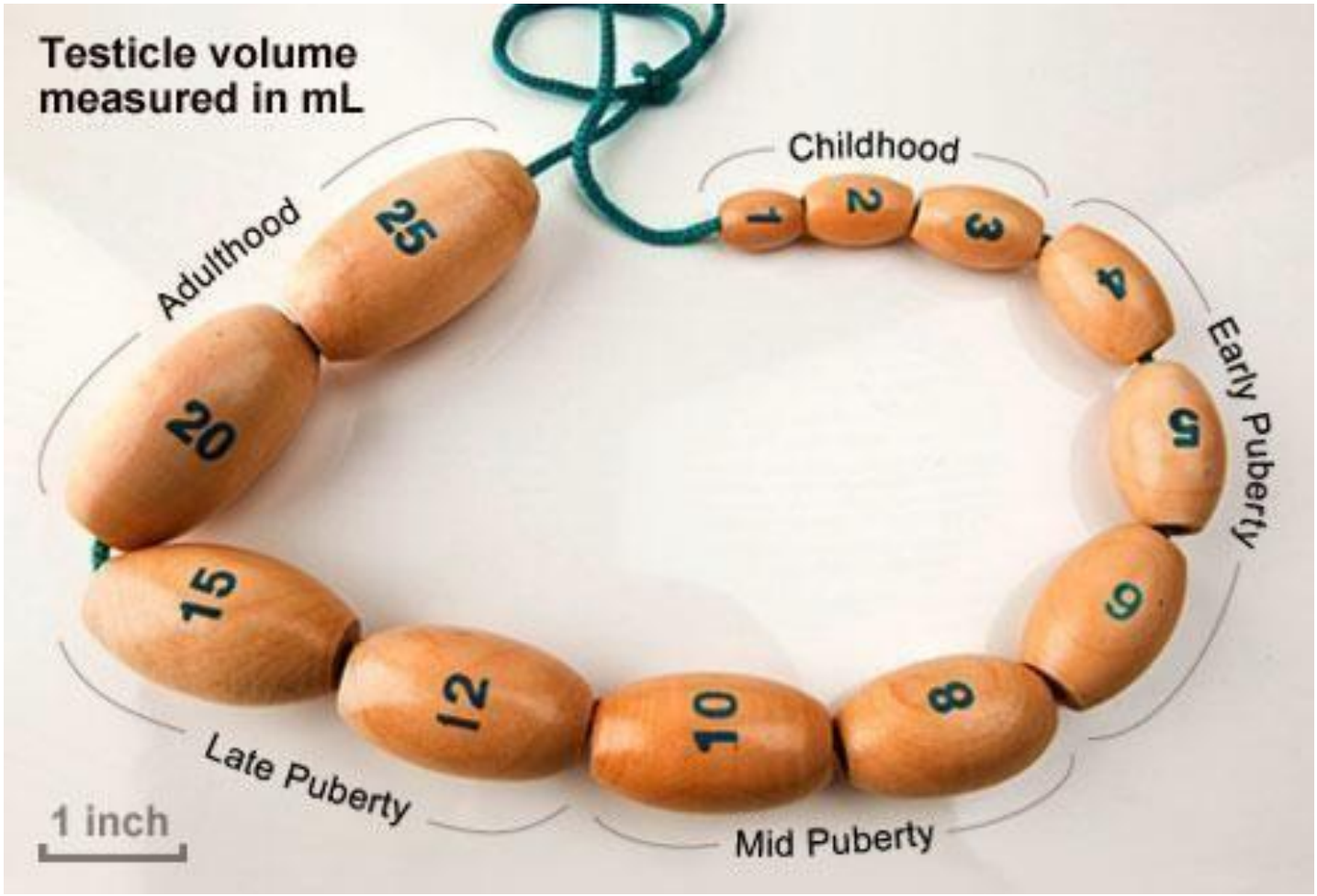
Tanner stages females



Tanner Stages: Males

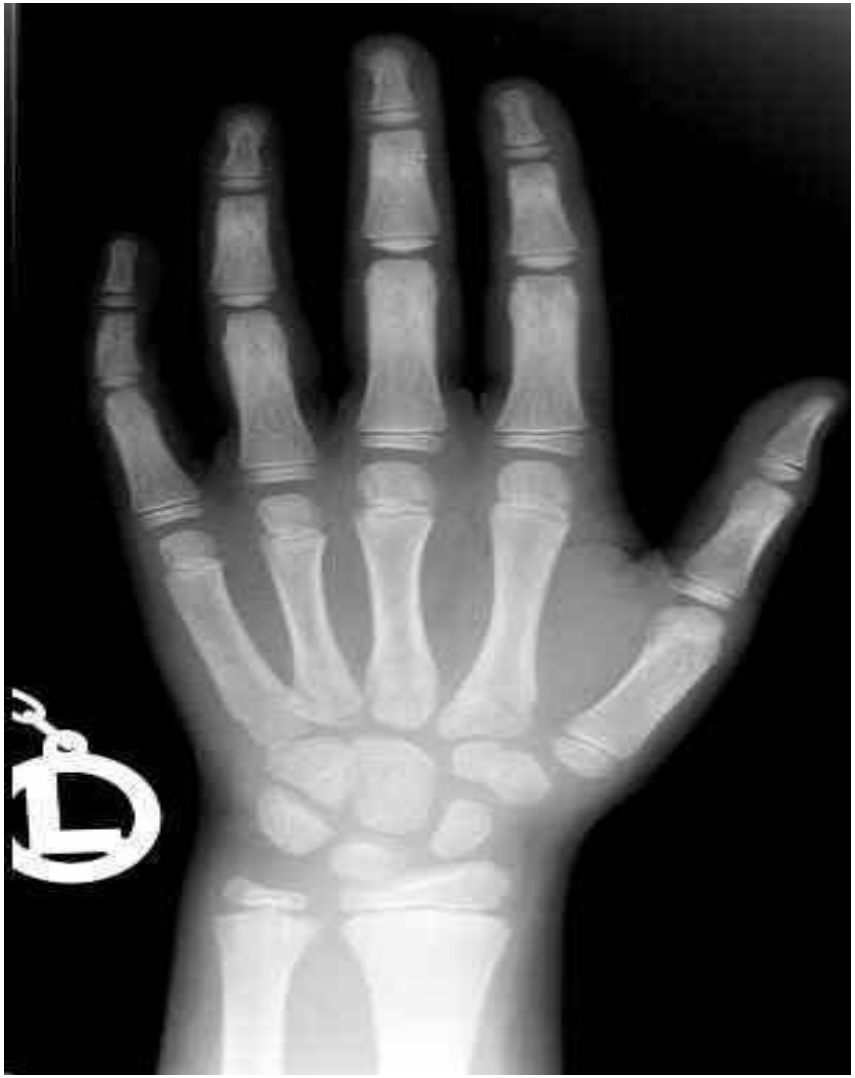


Orchidometer



Final adult height is correlated with age of puberty which is variables

- Puberty usually completed within 3 - 4 years of onset.
- Left wrist x-ray to assess bone age.
- Final adult height. results from complete fusion of epiphyses.
- Occurs approx. 1 yr. post menarche.



Precocious Puberty

- In girls, defined as onset of puberty “breast enlargement” before age of 8 years.
- In boys, defined as onset of puberty "testicular enlargement" before age of 9 years.
- 5 times more common in girls than boys.

Central Precocious Puberty

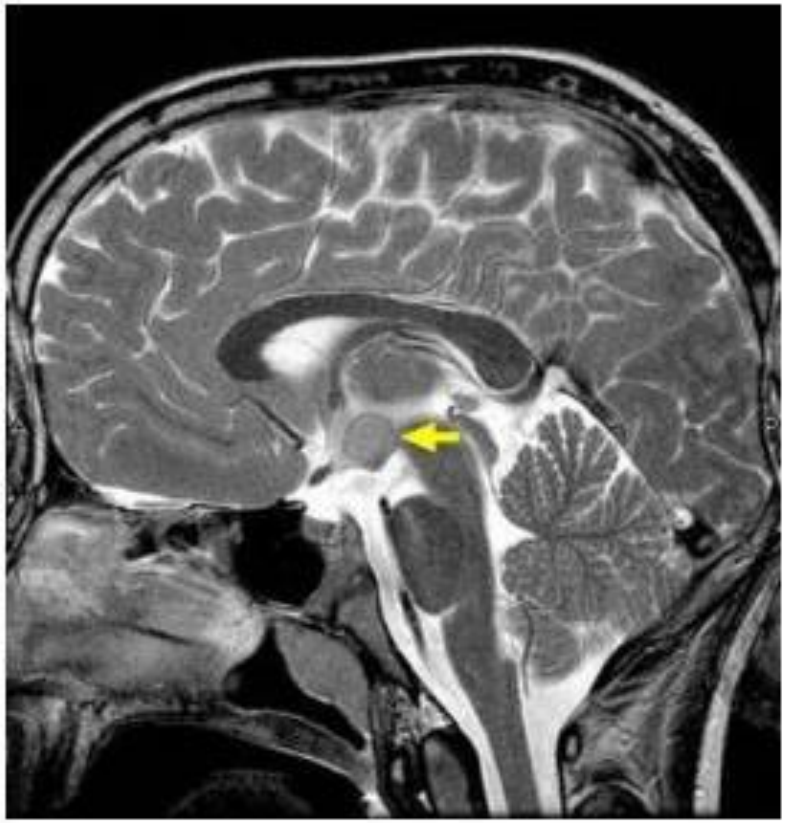
- Result from premature activation of Hypothalamic-Pituitary-Gonadal axis.
- The pulsatile GnRH secretion leads to pulsatile secretions of LH & FSH with subsequent release of sex steroids.
- Like normal mechanism but happened earlier than expected age.

Central “True” Precocious puberty

- Idiopathic (most girls in 90 % of cases)
- Secondary to CNS pathology (most boys 70-80%)

Secondary CNS causes

- Hypothalamic Hamartoma.
- Astrocytoma, craniopharyngioma, ependymoma, germinoma, glioma…..etc.
- CNS radiotherapy.
- Post pituitary surgery or head trauma.
- Inflammation (meningitis, encephalitis, Brain abscesses).
- Neurological & mental retardation.
- Hydrocephalus.
- Prolonged primary hypothyroidism (α-TSH stimulates FSH, LH, Prl).



Hypothalamic Hamartoma is the commonest Tumor causing CPP

Peripheral “Pseudo” precocious puberty

- Suppression of central axis (Hypothalamic-Pituitary-gonadal axis).
- LH & FSH levels are low (both basal & stimulated).
- Sex hormones are high.
- Gonads are small (unless tumor is present).

Pseudo precocious puberty

- Gonadal: McCune-Albright, tumor, cyst.
- Adrenal: CAH, tumors.
- Ectopic: hCG secreting tumors.
- Exogenous source of the hormone.
- Familial male dependent (Testotoxicosis).
- Chronic primary hypothyroidism (α-TSH works on α subunits of LH &FSH)

Autonomous gonadal steroid production

McCune Albright syndrome

Familial Testotoxicosis

Familial male-dependent precocious puberty (Testotoxicosis)

- Autosomal dominant.
- Male – limited.
- Mutation in LH receptors.
- Autonomous Leydig cell activity & testicular enlargement.
- Prepubertal levels of LH, FSH & pubertal testosterone.

McCune - Albright syndrome (MAS)

- First described by McCune & Albright (1937).
- Affects both sexes.
- Activating mutation of Gs α gene GNAS 1 on 20q13.2.
- Results in increased activity of the Gsα protein and cAMP in the affected endocrine tissue.
- Gonadal autonomy.
- Happen more commonly in girls.
- Menses usually happen < 2-3 years of age.

In girls, the presenting feature is often menses with / without thelarche.

Abnormalities in McCune-Albright syndrome

Endocrine

- Precocious Puberty ++++
- Goitre / Hyperthyroidism +++
- Acromegaly/ Gigantism ++
- Cushing's syndrome +
- Hyperprolactinemia +
- Hypophosphatemic rickets +

Abnormalities in McCune-Albright syndrome

Non-endocrine

- Cafe-au-lait spot. ++++
- Fibrous dysplasia of bone. ++++
- Facial asymmetry. ++
- Elevated hepatic transaminases. ++
- G.I polyposis. +
- Cardiomyopathy. +
- Arrhythmias. +

Variants of normal puberty

Isolated benign Thelarche

Isolated benign Adrenarche (Pubarche)

Isolated Benign Thelarche

- Premature breast enlargement with the absence of growth spurt.
- Bone age is not accelerated.
- Prepubertal pelvic U/S findings.
- Onset between 6m to 4 y of age.
- Increased sensitivity of the breast tissue to a low level of estradiol.
- Benign nature.
- Need no therapy.

Isolated Benign Adrenarche

- Occurs when adrenal androgens are turned on prematurely in the absence of gonadal activation.
- Premature appearance of pubic & axillary hair, acne, body odor & oily skin.
- Idiopathic & Benign in nature.
- No treatment.
- Only observation for progression to precocious puberty.

Isolated Benign Adrenarche

- Elevated adrenal androgens
- Normal LH / FSH & gonadal steroids
  - Need to exclude late-onset CAH.
  - Need to exclude adrenal tumors.
  - Need to exclude PCOS.

Evaluation of Precocious Puberty

- History & physical examination.
- Current height percentile.
- Calculation of target height.
- Bone Age assessment.
- Predicted adult height (PAH).
- Crucial Investigations should include initially:
  - Basal LH, FSH and sex steroids
  - GnRH stimulation test

Other investigations !!

- hCG : hepatoblastoma, germ – cell tumor.
- Inhibin : ovarian granulosa cell tumor.
- 17 OHP : non - classical CAH.
- Radiological investigations depending on type of precocious puberty.
  - MRI Brain: hypothalamic Hamartoma, optic glioma, other CNS tumores.
  - U/S Testes
  - Pelvic & Adrenal U/S

Treatment of central Precocious Puberty

- How early is the onset of puberty?
- How much advancement of the bone maturation?
- What is the predicted adult height (PAH)?
- Comparison of PAH to MPH ?
- How fast the progression of physical changes?
- Familial / social issues.

GnRH agonist

Treatment of underlying pathology

Central precocious puberty (CPP)

- Early activation of the hypothalamic-pituitary-gonadal (HPG) axis.
- Occurs in 1 in 5000 to 10,000 children.
- CPP is far more common in girls, in whom it is usually idiopathic.
- Safe and effective treatment of CPP in the form of long-acting GnRH analogs has been available for many years.

Central precocious puberty (CPP)

- The earliest clinical manifestation in girls is usually breast development (thelarche), followed by pubic hair (pubarche).
- The pubertal growth spurt occurs during Tanner stage II-III.
- Menarche occurs at Tanner stage IV.
- In boys, the initial clinical sign of central puberty is testicular enlargement, and the pubertal growth spurt happens later than in girls.

Evaluation of Precocious Puberty

- History & physical examination.
- Tanner's staging assessments.
- Current height percentile.
- Calculation of target height.
- Bone age assessment.
- Predicted final adult height (PAH).

Investigations

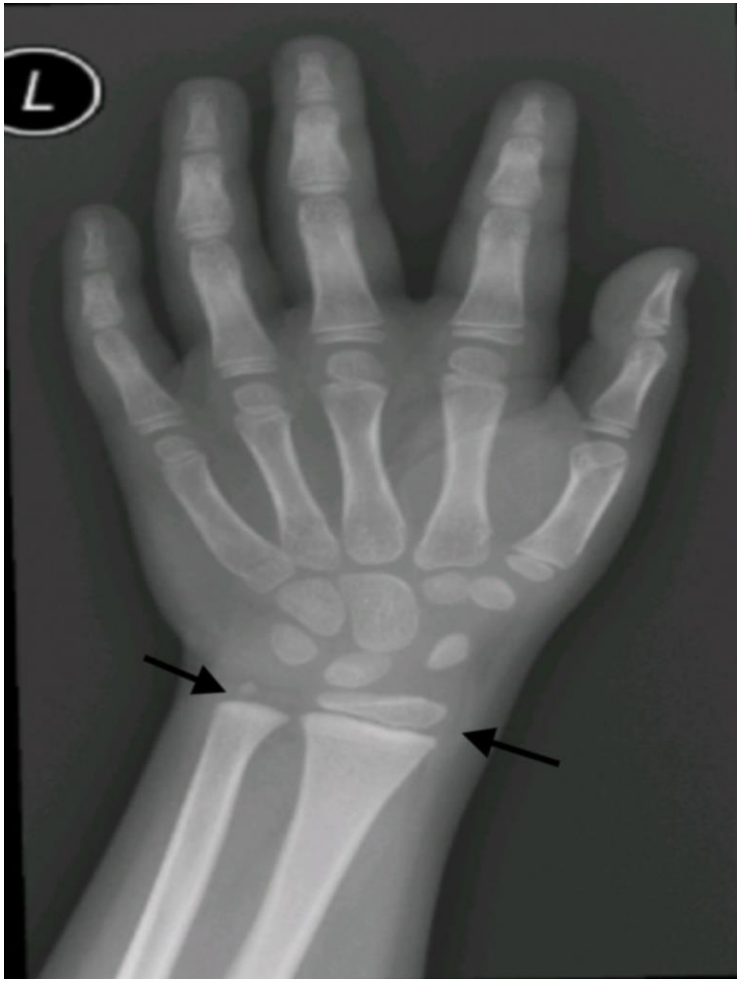
- Crucial Investigations should include:
  - Basal LH, FSH and sex steroids.
  - GnRH stimulation test.
- hCG : hepatoblastoma, germ – cell tumor.
- Inhibin : ovarian granulosa cell tumor.
- 17 OHP : non - classical CAH.
  - Pelvic & Adrenal U/S

Basal Vs GnRH stimulation

- A GnRH stimulation test has long been considered the gold standard for the diagnosis of CPP.
- While precise cut-offs are difficult to establish, a peak stimulated LH of >~8 mIU/mL after GnRH after GnRHa is considered indicative of CPP.
- An LH/FSH ratio of ≥2 is also consistent with CPP.
- An alternative diagnostic approach has been the measurement of basal ultrasensitive LH, typically <0.3 IU/L in prepubertal children.
- Even if the laboratory evaluation is unremarkable, patients should continue to be monitored over time and retested as indicated if clinical suspicion is high

Radiological Investigations of CPP

- MRI Brain: hypothalamic Hamartoma, optic glioma, other CNS tumores.
- The role of the brain (MRI) in the evaluation of patients with CPP has been debated:
  - Boys are more likely to have a pathological cause, MRI has an essential tool in their evaluation.
  - When female CPP patients without neurological symptoms are screened with MRI, the incidence of positive findings is approximately 15 %.
  - However, some of the abnormalities that are found may be incidental and unrelated to the CPP.
  - It has been suggested that brain MRI scanning may not be necessary for girls older than age 6 years who have no neurologic symptoms.



Bone age X-ray is a crucial investigation in pubertal assessment & prediction of the final adult height

Treatment of Central Precocious Puberty

- How early is the onset of puberty?
- How much advancement of the bone maturation?
- What is the predicted adult height (PAH)?
- Comparison of PAH to MPH?
- How fast does the progression of physical changes?
- Familial/social issues.

GnRH agonist

Treatment of underlying pathology

Goals of CPP Treatment

- Decrease the progression of pubertal changes.
- Decrease bone maturation.
- Increase the predicted final adult height.
- Psychosocial & behavioral therapy.

Treatment could be with GnRH agonist alone or with combined GnRH agonist and GH depending on predicted adult height calculation and how advanced bone age.

GnRH agonists

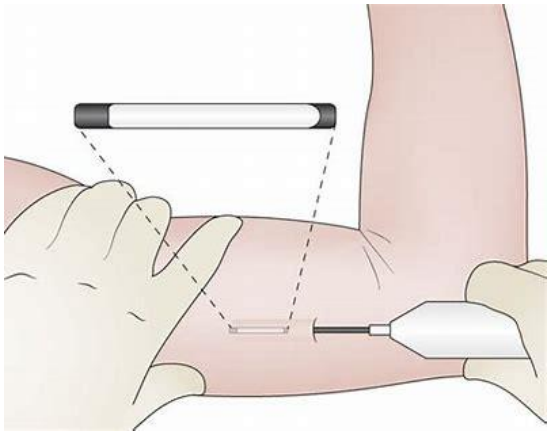
- First reported in 1981.
- The treatment of choice of central type.
- Alteration of peptide sequence of native GnRH with more potency, and affinity to the receptors.
- Acts continuously with downregulation of GnRH receptors.
- Depot. “slow-release” preparations.
- Various brands available:
  - Leuprorelin acetate (Lucrin): 0.3 mg / kg
  - Triptorelin (Decapeptyl) 50-100 mcg/kg
  - Goserelin (Zoladex)

Extended-Release GnRHa Preparations

Three-Monthly Depot GnRHa

- FDA approval of a 3-monthly form for Pediatric use 2011.
- Clinical indices of pubertal suppression have been reassuring, the 11.25-mg 3-monthly dose resulted in 100% HPG-axis suppression in several studies.
- No differences in adult height between girls treated with monthly vs 3-monthly triptorelin at the 11.25-mg dose.
- Six- monthly preparations form of 22.5mg of Triptorelin is as well approved for CPP in Pediatric age group.
- One - year - GnRH agonist implants “Histrelin” is also approved for the treatment of CPP in children.

Various preparations of Extended-release GnRH agonist preparations



Safety of GnRHa

- GnRHa preparations have an admirable safety profile.
- The most reported adverse events are:
  - injection-site reactions are “mild and self-limited”.
  - Sterile abscess formation has been reported in the setting of IM injections and the histrelin implant.
- Although some children may experience weight gain while on therapy, the preponderance of evidence suggests that GnRHa does not affect body mass index in patients being treated for CPP.
- Bone mineral density is typically increased for age at diagnosis and progressively decreases during GnRHa treatment.
- It is important during GnRHa, vitamin D supplantation.
- Follow-up of patients several years after cessation of therapy reveals BMD within the normal range compared with the population.

Monitoring of Treatment

- Auxologic indices including, weight, height, and growth velocity.
- Tanner staging evaluation and whether there is pubertal progression.
- Bone age assessment yearly.
- Follow-up of ultrasensitive LH, FSH & sex hormones values frequently to be kept in the pubertal range.
- If treatment failure is suspected on clinical grounds, a GnRHa stimulation test is recommended.

When to discontinue Treatment?

- There are essentially no studies in which age at treatment cessation has been standardized.
- However, cumulative evidence suggests that optimal height gains are realized when treatment is stopped at a bone age of 12 years in girls and;13 years in boys.
- Regardless, the decision of when to stop therapy is individualized and incorporates numerous patient-specific characteristics including:
  - predicted final adult height.
  - Opened epiphyseal growth plate.
  - psychosocial factors.
  - pubertal stage.
  - family preferences.

Future Gonadal Function

- Long-term outcomes of patients treated with GnRHa with respect to gonadal function is reassuring.
- Menstrual cycles are reported to be normal with respect to duration and timing and mean ovarian volumes like those in the general population.
- There have been no perceived health consequences to offspring of mothers who were treated with GnRHa and no increased need for assisted reproductive technology.
- Limited follow-up in adolescent boys previously treated with a GnRHa for CPP reveals similarly normal testicular function and sperm counts within the normal range , although more data in men are needed.

Conclusion

- Therapeutic usage of GnRH agonists for the treatment of children with CPP has rapidly expanded over the last 2 decades owing to environmental induced early puberty particularly in females.
- Various GnRH agonists are available particularly newer extended-release GnRHa formulations.
- GnRHa preparations have an admirable safety profile.
- FDA approval of a 3-monthly form for Pediatric use 2011.
- Clinical indices of pubertal suppression have been reassuring, the 11.25-mg 3-monthly dose resulted in 100% HPG-axis suppression in several studies.
- No differences in adult height between girls treated with monthly vs 3-monthly triptorelin at the 11.25-mg dose.
- Long-term outcomes of patients treated with GnRHa with respect to gonadal function is reassuring.


Thanks