Delayed puberty in children

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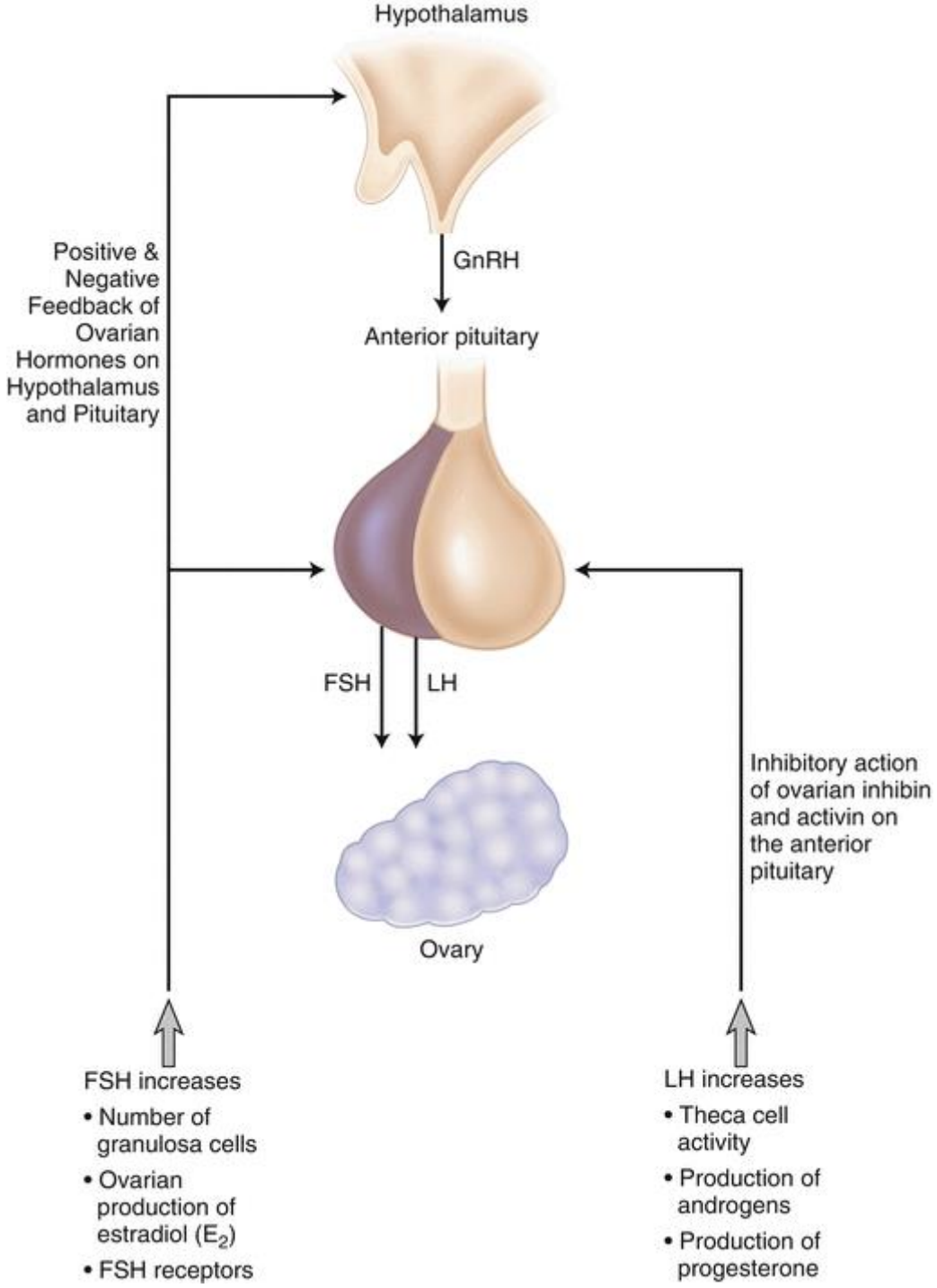
Objectives

- Normal puberty & factors affecting normal.
- Delayed puberty.
- Definition.
- Types:
  - Hypogonadotrphic Hypogonadism.
  - Hypergonadotropic Hypogonadism.
- Evaluation of delayed puberty.
- Management of delayed puberty.



Normal Puberty

- Is initiated by the onset of pulsatile secretion of (GnRH) from the hypothalamus.
- These pulses cause release of (LH) & (FSH) from the pituitary gland.
- Pituitary gonadotropins then stimulate production of sex steroids from gonads.

Puberty: Influencing factors

- Genetics: is important factor constitute 50-80% of variation in pubertal timing.
- General health: those with chronic diseases will be associated with delayed onset.
- Socioeconomical factors: adoption, migration from developing to industrialized countries, or rural to urban migration are important determinants of nutritional status.
- Geography: children residing closer to the equator, at lower altitudes, urban areas have earlier puberty than their counterparts.
- Environmental hormonal disruptors: “xenoestrogens” e.g. usage of plastics, nylon or “phytoestrogens” food products rich with estrogen.
- Obesity: contributes to earlier puberty as adipose tissues produces Leptin peptide.

There are clear racial & ethnic variations in the timing of puberty, such as earlier onset of puberty in African American females compared with their white counterparts.

Delayed Puberty

- Occurs in approximately 2% of adolescents.
- In males, delayed puberty is more common than females.
  - often constitutional “functional”.
- In females, delayed puberty is less common & often organic.

Definition

- Females: either one of the following:
  - Lack of breast development by age of 13 years.
  - Lack of pubic hair by age 14 years.
  - More than 3 years between breast growth and menstrual period.
  - Failure to menstruate by age 15-16 years.
- Females: either one of the following:
  - Testicular volume (< 4 mL) by age of 14 years.
  - Lack of pubic hair by age of 15 years.
  - More than five years to complete genital enlargement.

Types

- Physiological Delay:
  - Constitutional delay is the commonest type.
- Pathological Delay:
  - Hypogonadotrphic Hypogonadism:
    - Hypothalamic or pituitary failure results in gonadotropin deficiency.
  - Hypergonadotropic Hypogonadism:
    - Primary gonadal failure, resulting in elevated serum gonadotropin levels.

The most common cause of delayed puberty is a functional delay in the production of (GnRH) from the hypothalamic neuronal networks that synergize to initiate the episodic or pulsatile release of the GnRH.

Constitutional delay of growth and puberty

- The most common cause in both genders.
- More often seen in males (70%) than in females (30%).
- Represent the extreme of the normal physiologic variations .
- Is a diagnosis of exclusion.
- It is commonly inherited as variation in the age of onset of puberty due to genetic factors, although sporadic cases are also seen.
- Delayed skeletal maturation with potential for future growth.
- Final adult height is usually normal.

Hypogonadotropic Hypogonadism

- Characterized by deficient GnRH secretion, leads to low LH & FSH & sex hormone secretions and deficient gametogenesis.

Congenital causes:

- Isolated GnRH deficiency:
  - without or with anosmia (Kallmann syndrome).
  - associated with adrenal hypoplasia congenita.
  - associated with mental retardation/obesity (Laurence-Moon-Biedl syndrome or Prader-Willi syndrome).
  - Idiopathic forms of multiple anterior pituitary hormone deficiencies.
  - Congenital brain anomalies (associated with craniofacial anomalies).

Hypogonadotrphic Hypogonadism

Acquired causes:

- "Functional" gonadotropin deficiency (constitutional delay of growth and puberty) is the commonest cause.
- Idiopathic.
- Brain tumours:
  - Craniopharyngioma, germinomas, meningioma, glioma, astrocytoma.
  - Infiltrative diseases: granulomatous diseases, histiocytosis.
- Chronic systemic diseases.
- Malnutrition or nutritional disorders such as anorexia nervosa.
- Heavy exercise.

Hypogonadotrphic Hypogonadism

- Hypothyroidism.
- Hyperprolactinemia.
- Poorly controlled diabetes.
- Cushing's disease.
- Hemochromatosis.
- Head trauma.
- Pituitary apoplexy.
- Drugs.

Hypergonadotropic Hypogonadism

- Characterized by small gonadal size, high LH & FSH with low sex hormones.

Causes:

- Congenital causes:
  - Chromosomal abnormalities (Turner syndrome; Klinefelter syndrome).
  - Gene mutations in gonadal function.
  - Anorchia (vanishing testis).
- Acquired causes:
  - Gonadal damage from chemotherapy, radiotherapy, autoimmune or post-infectious injury, cryptorchidism, varicocele, testicular torsion , disorders of testosterone biosynthesis or medications (ketoconazole, anabolic testosterone abuse).

Evaluation of a child with delayed puberty

History

- Is pubertal development totally absent, or did it start and then “paused"?
- Is there any family history of delayed or absent puberty?
- Does the patient have any abnormal nutritional habits or a medical illness or engage in intense exercise that delayed the onset or slowed the tempo of puberty?
- Does the patient have any congenital anomalies or neurological symptoms?
- Does the patient have history of previous brain / pituitary tumours.
- Does the patient have a normal sense of smell?
- does the patient have any visual disturbances?

History

- Does the patient have any chronic illness?
- Is there any history of radiation, chemotherapy, bilateral cryptorchidism, surgery, bilateral torsion.
- Lifestyle history including nutritional habits & exercise.
- Psychosocial histories including, adoption, migration from developing to industrialized countries, or from rural to urban migration are important determinants of nutritional status.
- Medication history.

Physical examination

- Growth parameters including weight, height & BMI .
- Calculate growth velocity.
- Tanner staging.
- Visual field examination & fundoscopy.
- Systemic examinations include dysmorphism.
- Evaluation of the sense of smell.
- Looking for associated congenital abnormalities (e.g. midline defects, cleft lip/palate, cryptorchidism & microphallus).

Findings	*Possible diagnoses*
Abdominal pain	Gastrointestinal disease
Anosmia	Kallmann syndrome
Asymmetric testes	Oophoritis or orchitis
Body mass index and weight (on growth charts)	Low: eating disorder, caloric insufficiency, gastrointestinal or other systemic disease
Chemotherapy, radiation treatment, brain tumor	Hypogonadism
Cryptorchidism or orchidopexy	Hypogonadism
Dysmorphic features (webbed neck, short stature, low hairline)	Turner syndrome
Enlarged thyroid	Hypothyroidism
Family history of late puberty	Constitutional delay of growth and puberty
Galactorrhea	Hyperprolactinemia

Examples of history finding & possible causes

Height (growth chart)	Short stature: Turner syndrome, constitutional delay of growth and puberty
	Tall stature: Klinefelter syndrome
Joint pain	Inflammatory disorder
Neurologic assessment (abnormal examination findings or symptoms such as headaches, vision changes)	Intracranial pathology
Red (vs. dull pink) or thin vaginal mucosa	Lack of estrogen exposure (hypogonadism)
Sexual maturity rating	Delayed pubertal development (unspecified)
Small, firm testes	Klinefelter syndrome
Temperature intolerance, gastro-intestinal symptoms, tremor, depression, palpitations	Thyroid disease
Trauma (head)	Hypogonadism
Vasomotor symptoms in girls	Ovarian insufficiency

Examples of history finding & possible causes

Investigations

- Children with delayed puberty should be evaluated for the possibility of nutritional disorders (anorexia nervosa), celiac disease, or chronic illnesses (e.g., inflammatory bowel disease, or hepatic disease) that may affect hypothalamic GnRH secretion by performing:
  - CBC, ESR, BUN, creatinine & liver function tests.
  - Tissue transglutaminase-immunoglobulin A antibodies to screen for celiac disease, which could presents with delayed growth and puberty.
- LH , FSH & estradiol (females) or testosterone (males), should be obtained to distinguish between primary & secondary hypogonadism.

Investigations

- Prolactin level to detect hyperprolactinemia which could results from prolactinoma or from any hypothalamic or pituitary disorder that interrupts hypothalamic inhibition of prolactin secretion.
- Thyroid function test.
- karyotype is to rule out “Turner syndrome” in females, while in males, to rule out Klinefelter syndrome.
- Genetic testing may be appropriate in Kallmann syndrome.
- Serum iron & ferritin for hemosiderosis as in cases of hypogonadotropic hypogonadism associated with hemoglobinopathies.

Investigations

- GnRH stimulation testing with kisspeptin is new approach to distinguish between CDGP & isolated GnRH deficiency/Kallmann syndrome.
- Serum inhibin B is biochemical index of gonadal function.
  - For boys, serial measurements of inhibin B can help to monitor pubertal progression & as supplement of measurements of testicular volume, because inhibin B and testicular size are well correlated.
  - For girls, there is no such clinical correlation.

Radiological investigations

- Bone age: to assess skeletal maturation which closely correlates with sexual development than does chronological age.
- Pelvic / scrotal ultrasound: to determine the presence or absence of internal organs.
- MRI Brain: if associated with headaches, visual disturbances, and/or midline defects.
  - if laboratory studies are consistent with hypothalamic or pituitary disease (e.g., hyperprolactinemia, central adrenal insufficiency, and/or central hypothyroidism).
  - In addition, special thin cuts through olfactory bulb to assess the presence or hypoplasia/absence of the olfactory bulb, nerves, and tracts, for possibility of Kallmann syndrome.

Management

Management of Constitutional Delay

- No intervention is usually needed but follow up by measuring serum testosterone or estrogen is recommended.
- Boys aged >14 years old whose growth is stunted or are experiencing severe distress secondary to their lack of puberty can be started on testosterone to increase their height.
- Testosterone treatment can be used to stimulate sexual development.
- Low dose of testosterone enanthate (50–100 mg given intramuscularly every 4 weeks for 3–6 months stimulate linear growth & secondary sexual characteristics without inappropriately accelerating bone age.
- Overall, studies have shown no significant difference in final adult height between adolescents treated with sex steroids and those who were only observed with no treatment.

Management of various causes of delayed puberty

- If a specific underlying disorder can be identified, therapy should be targeted at that disorder.
  - Thyroid hormone replacement in hypothyroidism.
  - Dopamine agonist treatment of lactotroph adenomas.
  - Excision of craniopharyngiomas.
  - For patients with primary gonadal failure (e.g. Turner or Klinefelter syndrome) sex hormone therapy is component of management.
  - In patients with coeliac disease, an early diagnosis & establishment of gluten-free diet prevents long-term complications which allows restoration of normal maturation.
  - Effective therapy of inflammatory bowel disease is important.

Females with Hypogonadism

- Requires lifelong sex steroid replacement therapy.
- In females with primary ovarian failure:
  - Estrogen should be started when puberty is supposed to start.
  - Start with conjugated estrogen 0.3 mg po daily for 3-6 months with gradual increases in dose 3-6 monthly providing adequate time for pubertal growth, and gradual breast development up to 1.25 mg once daily (this dose to be reached over 2 years).
  - Progestins are usually added after acceptable breast growth, or 12 - 24 months after starting estrogen, as starting treatment with progestin too early can negatively affect breast growth.
  - Progestins “Provera (medroxyprogesterone) at dose of 5 –10 mg / day in the last 10 days of each calendar month.

Males with Hypogonadism

- When hypogonadism is diagnosed at a prepubertal age, testosterone therapy may be started as early as a bone age of 11–12 years.
- Testosterone enanthate , administered by intramuscular injection, is the most common method of pubertal induction and maintenance .
- Starting dose of 50 mg every 4 week, is usually sufficient to achieve early virilization & growth over time (i.e., three to six months duration), without unduly advancing epiphyseal maturation (bone age).
- When pubertal growth spurt is well established, the dose should be gradually increased to full adult dose of 250 mg every 2 -4 weeks depending on sexual maturation &testosterone level.

Males with Hypogonadism

- Although exogenous sex steroid administration accelerates epiphyseal maturation , most studies indicate that low doses of sex steroids for limited periods of time does not adversely affect adult height.
- The use of testosterone gel transdermal has not yet been approved or even widely studied in males younger than age 18 years.

Beneficial effects:

- decline in total plasma cholesterol and LDL concentrations, increased lean body mass. decreased risk of osteoporosis.

Side effect:

- acne, and gynecomastia, fast skeletal maturation leading to impaired adult height, excessive aggressiveness, excessive stimulation of libido, priapism, polycythaemia, obstructive sleep apnoea mainly in obese subjects

Males with Hypogonadotropic Hypogonadism

- Boys aged older than 12 years old with hypogonadotropic hypogonadism are most often treated with short-term testosterone while males with testicular failure will be on life-long testosterone.
- Although testosterone therapy alone will result in the start of puberty, to increase fertility potential, they may need pulsatile GnRH or hCG with rh-FSH replacement.
- hCG can be used in hypogonadotropic hypogonadism & rh-FSH can be added in cases of low sperm count after 6 to 12 months of treatment.
- If puberty has not started after 1 year of treatment, then permanent hypogonadotropic hypogonadism should be considered.

Males with Hypogonadotropic Hypogonadism

- Human chorionic gonadotropin has the biologic activity of LH but a longer half-life in the circulation, stimulates the Leydig cells of the testes to synthesize & secrete testosterone.
- hCG is used to replace LH in males who have secondary hypogonadism and desire to become fertile, (for fertility reasons, testosterone could be replaced with the following):
  - hCG dose starting of 2000 U three weekly, either SC or IM, for 6 months (same days of week) then to add rh-FSH (always hCG precedes FSH replacement) .
  - Recombinant human follicle-stimulating hormone (rh-FSH) dose of 75 units three time / week (could be added in same syringe), dose could be increased to 150 units three times / week after 6 months if sperm count less than 10 million .
- The use of hCG appears to be more physiologic and potentially safer than testosterone However, HCG is more expensive and requires multiple injections.

Conclusions

- Delayed puberty occurs in approximately 2% of adolescents.
- In males, delayed puberty is more common than females and often constitutional.
- In females, delayed puberty is less common & often organic.
- In hypogonadotropic hypogonadism, low GnRH secretion with low LH & FSH & sex hormones.
- In hypergonadotropic hypogonadism, small gonadal size, high LH & FSH with low sex hormones.
- Low dose of testosterone enanthate (50–100 mg given intramuscularly every 4 weeks stimulate linear growth & secondary sexual characteristics without inappropriately accelerating bone age.
- hCG can be used in hypogonadotropic hypogonadism & rh-FSH can be added in cases of low sperm count after 6 to 12 months of treatment.

Thanks