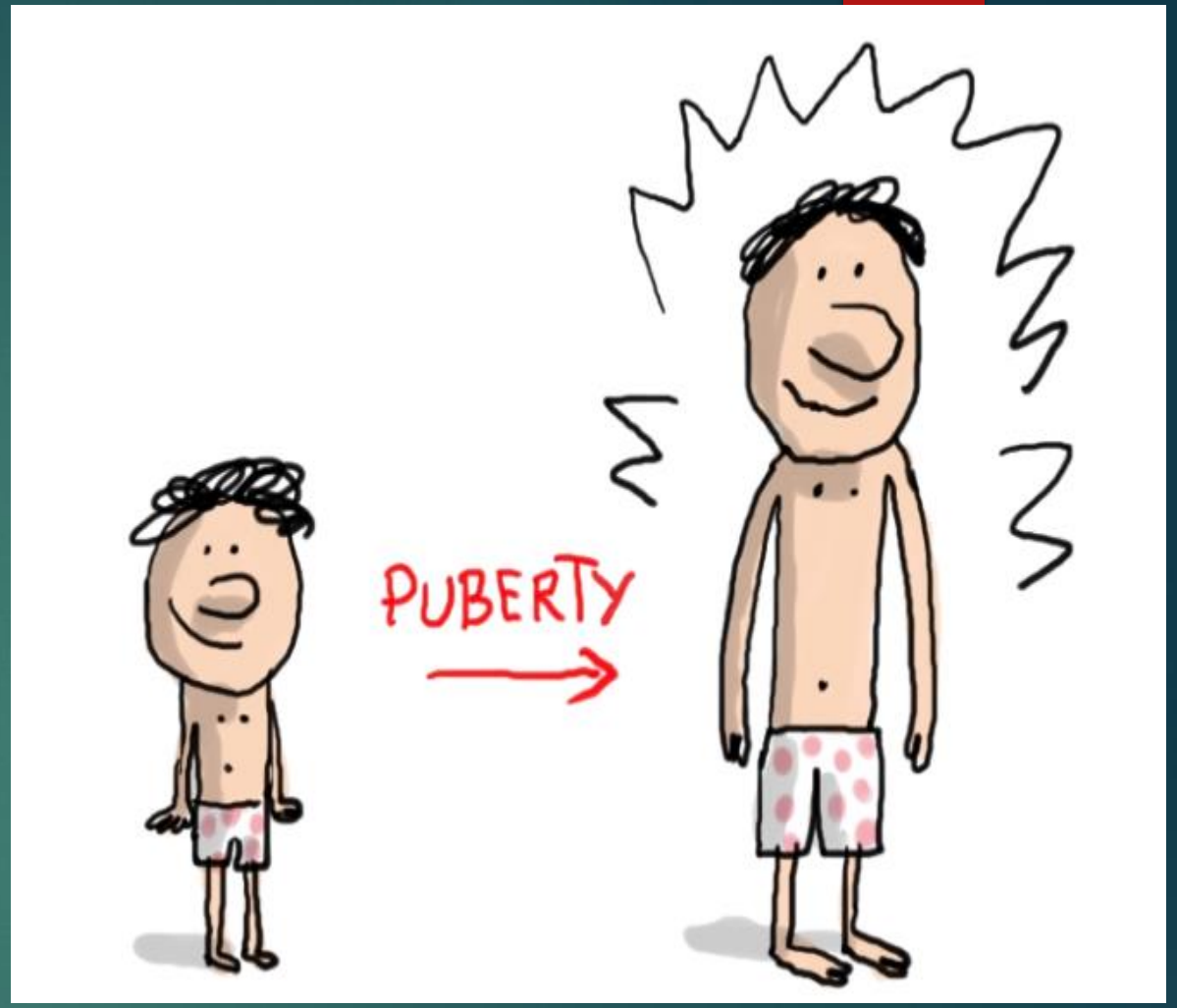

بسم الله الرحمن الرحیم

Disorders of Puberty



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PHYSIOLOGY

The onset of puberty is marked by pubarche and gonadarche.

- ***Pubarche*** results from adrenal maturation or adrenarche and is marked with the appearance of pubic hair; other features include oiliness of hair and skin, acne, axillary hair, and body odor.
- ***Gonadarche*** is characterized by increasing secretion of gonadal sex steroids as a result of the maturation of the hypothalamic-pituitary-gonadal axis.

- In males physical signs are pubic hair, axillary hair, facial hair, increased muscularity, deeper voice, increased penile size, and increased testicular volume.
- In females the physical signs are breast development, development of the female body habitus, increased size of the uterus, and menarche with regular menstrual cycles.
- The third component is the growth spurt of puberty.

typical developmental sequence:

- In girls is thelarche (due to gonadarche), followed closely by pubarche (due to adrenarche), and finally menarche 2-3 years later.
- In boys the first typical event is scrotal thinning followed by the enlargement

of testes and by the appearance of pubic hair (long diameter of the testis >2.5 cm, volume >4 mL).

DELAYED PUBERTY:

- Puberty is delayed when there is no sign of pubertal development by age 13 years in girls and 14 years in boys
- ***Hypogonadotropic Hypogonadism:***
- ***Hypergonadotropic Hypogonadism:***

Constitutional Delay in Growth and Adolescence:

- delayed onset of pubertal
- development and significant bone age delay (2 standard deviations below the mean, which is equal to a 1.5- to 2-year delay as a teenager).
- Usually height gain is below, although fairly parallel to, the normal percentiles on the growth curve.
- A family history of delayed puberty in a parent or sibling is reassuring.
- Spontaneous puberty usually begins in these patients by the time the bone age reaches 12 years in boys and 11 years in girls.

- Other causes of delayed puberty must be eliminated before a diagnosis of constitutional delay in puberty is made.
- Observation and reassurance are appropriate.
- Adult height normal for the genetic potential is generally attained.
- In some cases, boys may be treated with low-dose testosterone for a few months if the bone age is at least 11-12 years. Treatment is not required for longer than 4-8 months because endogenous hormone production usually ensues.
- Boys who do not initiate endogenous hormone production should be evaluated for other causes of hypogonadism.

Hypogonadotropic Hypogonadism:

- precludes spontaneous entry into gonadarche;
- adrenarche usually occurs to some degree.
- Throughout childhood and in early puberty: normal proportions and growth.
- When these patients reach adulthood: eunuchoid proportions may ensue because their long bones grow for longer than normal, producing an upper-to-lower ratio below the lower limit of normal of 0.9 and an arm span greater than their height.

Hypogonadotrophic hypogonadism:

- congenital hypopituitarism: such as midline defects,
- tumors,
- infiltrative disease (hemochromatosis)
- many syndromes: Laurence-Moon-Bardet-Biedl, Prader-Willi, Kallmann syndromes.
- Idiopathic hypopituitarism is the congenital absence of various combinations of pituitary hormones. Genes associated with this include HESX1, PROP1, POU1F1(PIT1), LHX3,LHX4, TBX19, SOX2, and SOX3.
- Isolated Gonadotropin Deficiency:

There are a number of additional genetic mutations associated with hypogonadism that are very rare (GnRH1, DAX1, TAC3, FGF8, and others).

- voluntary dieting, malnutrition, or chronic disease results in weight loss to less than 80% of ideal weight.
- Anorexia nervosa is characterized by striking weight loss and psychiatric disorders
- Increased physical activity, even without weight loss, (athletic amenorrhea)
- Chronic or systemic illness (e.g., cystic fibrosis, diabetes mellitus, inflammatory bowel disease, or hematological diseases) can lead to pubertal delay or to amenorrhea from hypothalamic dysfunction.
- Hypothyroidism inhibits the onset of puberty and delays menstrual periods. Conversely, severe primary hypothyroidism may lead to precocious puberty.

Kallmann syndrome:

isolated gonadotropin deficiency with disorders of olfaction.

Most cases are sporadic,

mutations in the KAL1 gene at Xp 22.3 (X chromosome), KAL2 gene (8p11.2), or KAL3 gene (20p13).

The mutation causes the GnRH neurons to remain ineffectually located in the primitive nasal area, rather than migrating to the correct location at the medial basal hypothalamus. Olfactory bulbs and olfactory sulci are often absent on magnetic resonance imaging (MRI).

Other symptoms include disorders of the hand, with one hand copying the movements of the other hand, shortened fourth metacarpal bone, and an absent kidney.

Hypergonadotropic Hypogonadism:

- **Ovarian failure**
- **Turner syndrome** is a common cause of ovarian failure and short stature.
- **Klinefelter syndrome** (seminiferous tubular dysgenesis) is the most common cause of testicular failure.

Primary Amenorrhea:

- 1-The Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome of congenital absence of the uterus occurs in 1 in 4,000-5,000 female births.
- 2-Anatomical obstruction by imperforate hymen or vaginal septum also presents with normal secondary sexual development without menstruation.
- 3-The complete syndrome of androgen insensitivity includes normal feminization, absence of pubic or axillary hair, and primary amenorrhea.

Evaluation:

- Serum gonadotropin levels
- differentiation between constitutional delay in growth and hypogonadotropic hypogonadism is difficult;
- the gonadotropin levels are low in both conditions.
- Sometimes observation for months or years is necessary before the diagnosis is confirmed.
- Ultrasound of the pelvic structures in females

Treatment:

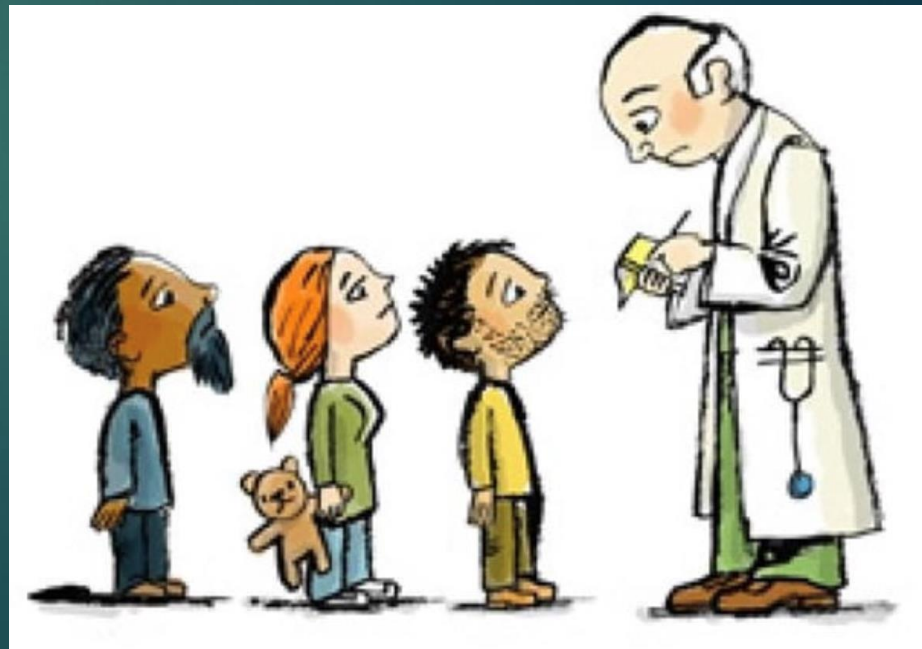
- If a permanent condition is apparent, replacement with sex steroids is indicated.
- Patients with apparent constitutional delay in puberty who have, by definition, passed the upper limits of normal onset of puberty may be given a 3- to 6-month course of low-dose, sex-appropriate gonadal steroids to see whether spontaneous puberty occurs.
- All patients with any form of delayed puberty are at risk for decreased bone density; adequate calcium intake is essential.

SEXUAL PRECOCITY:

- Sexual precocity (precocious puberty) is classically defined as secondary sexual development occurring before the age of 9 years in boys or 8 years in girls
- Central precocious puberty, resulting in gonadarche, emanates from premature activation of the hypothalamic pituitary-gonadal axis (GnRH-dependent).
- Peripheral precocious puberty, gonadarche or adrenarche, does not involve the hypothalamic-pituitary-gonadal axis (GnRH-independent).

Central Precocious Puberty:

- In central precocious puberty, every endocrine and physical aspect of pubertal development is normal but too early;
- tall stature,
- advanced bone age consistent with somatic age,
- increased sex steroid
- pulsatile gonadotropin secretion,
- increased response of LH to GnRH.



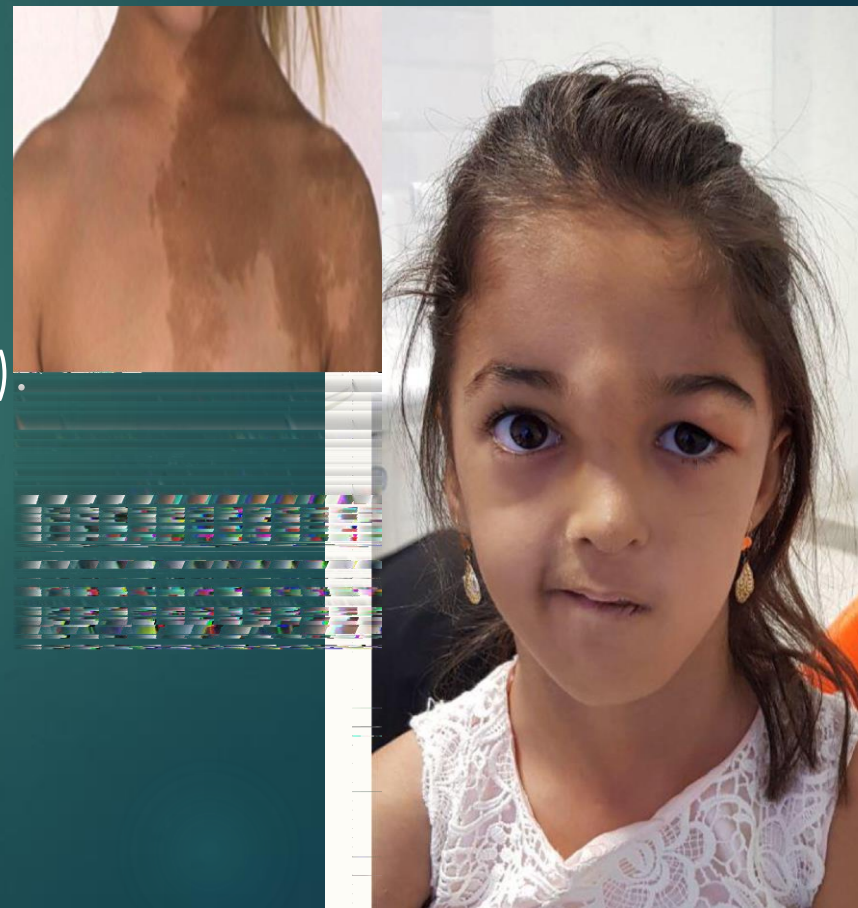
- If no cause can be determined, the diagnosis is idiopathic precocious puberty, which occurs much more often in girls than in boys.
- Obese girls have earlier adrenarche, and sometimes menarche as well, than appropriate-weight girls.
- Compared with girls, boys with precocious puberty have a higher incidence of CNS disorders, such as tumors and hamartomas, precipitating the precocious puberty.

Almost any condition that affects the CNS, including

- hydrocephalus,
- meningitis, encephalitis,
- suprasellar cysts,
- head trauma,
- epilepsy,
- mental retardation,
- irradiation,
- Hamartomas

GnRH-Independent Precocious Puberty:

- The **most common cause** of GnRH-independent precocious puberty, McCune-Albright syndrome,
- more frequent in girls than boys
- precocious gonadarche,
- polyostotic fibrous dysplasia
- hyperpigmented cutaneous macules (café-au-lait spots).



- **Adrenal carcinomas** usually secrete adrenal androgens, such as DHEA; adrenal adenomas may virilize a child as a result of the production of androgen or may feminize a child as a result of the production of estrogen.
- **familial male-limited precocious puberty:** This condition, with germ cell maturation caused by an X-limited dominant defect, produces constitutive activation of the LH receptor that leads to continuous production and secretion of testosterone without requiring LH or HCG.
- **hCG-secreting tumors** :pineal gland (dysgerminomas) or the liver (hepatoblastoma).
- **Ovarian cysts**
- **Congenital adrenal hyperplasia (CAH)**

Evaluation of Sexual Precocity:

- The first step in evaluating sexual precocity is to determine which characteristics of normal puberty are apparent and whether estrogen effects, androgen effects, or both are present.
- In boys it is also important to note whether the testes are enlarged more than 2.5 cm in length (4 mL volume), which implies gonadarche. If the testes are not enlarged but virilization is progressing, the source of the androgens may be the adrenal glands or exogenous sources.

Laboratory evaluation:

- testosterone, estradiol, DHEAS
- baseline gonadotropin
- Gonadotropin responsiveness to GnRH stimulation.
- Thyroid hormone
- MRI of the brain and pituitary with and without contrast:

1-suggestion of a CNS anomaly or a tumor

2-Boys

3- young girls (<6 years)

Treatment:

- Long-acting, super active analogs of GnRH :central precocious puberty.
- Boys with GnRH-independent premature Leydig cell and germ cell maturation:

1-inhibitor of testosterone synthesis (e.g., ketoconazole)

2-an antiandrogen (e.g., spironolactone),

3- aromatase inhibitor (e.g., testolactone or letrozole).

- hormone-secreting tumor : surgical removal
- McCune-Albright syndrome :testolactone and antiandrogens or antiestrogen, such as tamoxifen or aromatase inhibitor such as letrozole. Medroxyprogesterone acetate.

Isolated Premature Thelarche:

- unilateral or bilateral breast tissue in girls, usually at ages 6 months to 3 years.
- There are no other signs of puberty and no evidence of excessive estrogen effect (vaginal bleeding, thickening of the vaginal secretions, increased height velocity, or bone age acceleration).
- re-evaluated at intervals of 6-12 months
- no treatment other than reassurance is necessary.

Isolated Premature Adrenarche (Pubarche):

- The isolated appearance of pubic hair before age 6-7 years in girls or before age 9 years in boys is termed premature pubarche, usually resulting from adrenarche.
- Measurements of serum testosterone, 17-hydroxyprogesterone, and DHEAS are indicated to investigate the possibility of CAH.
- Ultrasound studies may reveal a hyperplastic adrenal gland or a virilizing adrenal or ovarian tumor.
- Testosterone concentrations are normal. DHEA levels usually are high.
- studies linking premature adrenarche to the development of irregular menses or polycystic ovarian syndrome (PCOS) later in adolescence.

Gynecomastia:

In males breast tissue is termed gynecomastia:

- in early puberty(45-75%): aromatization
- Klinefelter syndrome
- exogenous sources
- endogenous sources (from abnormal function of adrenal gland or ovary or from increased peripheral aromatization)


Thank you for your attention