Delayed puberty
Delayed puberty - definition

Initial physical changes of puberty are not present
- by age 13 years in girls (or primary amenorhoe at 16y)
- by age 14 years in boys

Lack of prog. of pub.:
M: 4.5 yr (No complete Pub.)
F: 5 yr (No mense)

Prev: 3%
Classifications

- Normal variant:
  - Constitutional delay in growth and puberty

- Pathologic:
  - Hypogonadotropic hypogonadism
  - Hypergonadotropic hypogonadism

- Female: Eugonadism (26%)
  - Mullerian Agenesis
  - Vaginal Septum
  - Imperforate Hymen
  - Androgen Insensitivity Syndrome
Constitutional delay in growth and puberty

A variation of normal

There is often a family history of father being short as a child & experiencing a late pubertal spurt.

Family history of delayed menarche or delayed secondary sexual characteristics

Height <fifth percentile, but growth rate is normal for skeletal age

The bone age is delayed & corresponds to the height age.

Onset of adrenarche is delayed

Although puberty is delayed, the final adult height and sexual development are normal.
Constitutional delay in growth and puberty

The combination of genetic short stature and constitutional delay leads to more profound short stature.

Final height is less than predicted.

Spontaneous progression into puberty occurs when the bone age reaches 12 to 13 years.
Hypogonadotropic hypogonadism

- **CNS disorders:**
  - Tumors (craniopharyngioma, germinoma, glioma, prolactinoma)
  - Congenital malformations
  - Radiation therapy
  - Other causes

- **Isolated gonadotropin deficiency**
  - Kallmann syndrome (anosmia-hyposmia)
  - Other disorders

- **Multiple pituitary hormone deficiencies**
- **Prader-Willi syndrome**
- **Laurence-Moon-Bardet-Biedl syndrome**
Craniopharyngiomas have a peak incidence in the teenage years and may cause any type of anterior or posterior hormone deficiency. Craniopharyngiomas usually calcify, erode the sella turcica when they expand, and may impinge on the optic chiasm, leading to bitemporal hemianopsia and optic atrophy.

Germinomas are noncalcifying hypothalamic or pineal tumors that frequently produce HCG, which may cause sexual precocity in boys who are of a prepubertal age (HCG cross-reacts with the LH receptor because of the similarity of structure between LH and HCG).

Other tumors that may affect pubertal development include astrocytomas and gliomas.
Isolated Gonadotropin Deficiency

- Kallmann syndrome: This disorder is caused by mutations in the KAL gene at Xp 22.3 (X chromosome).
- 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 as occurs normally.
- Isolated gonadotropin deficiency with disorders of olfaction.
- Some patients have a decreased sense of smell, others have abnormal reproduction, and some have both.
- Olfactory bulbs and olfactory sulci are often absent on MRI.
- Other symptoms include disorders of the hand, with one hand copying the movements of the other hand and shortened fourth metacarpal bone, and an absent kidney.
Idiopathic Hypopituitarism

- Congenital idiopathic hypopituitarism.
  - sporadic types are more common
  - X-linked or autosomal recessive

- Congenital hypopituitarism may manifest in a male with GH deficiency, with associated gonadotropin deficiency with a microphallus, or with hypoglycemia with seizures, especially if ACTH and GH deficiency occurs as well.
FIGURE 22-2. Micropenis and cryptorchidism in a boy with congenital gonadotropin deficiency.
Hypogonadotropic hypogonadism

- **Functional gonadotropin deficiency**
  - Chronic systemic disease: cystic fibrosis, diabetes mellitus, inflammatory bowel disease, and hematologic disease.
  - Hypothyroidism: inhibits the onset of puberty and delays menstrual periods. Conversely, severe primary hypothyroidism may lead to precocious puberty.
  - Cushing disease
  - Hyperprolactinemia
  - Anorexia nervosa and malnutrition
  - Psychogenic amenorrhea
Functional gonadotropin deficiency

- Weight loss resulting from voluntary dieting, malnutrition, anorexia nervosa or chronic disease leads to decreased gonadotropin function when weight <80% of ideal weight.
  - Primary or secondary amenorrhea frequently is found in affected girls
  - Pubertal development is absent or minimal, depending on the level of weight loss and the age of onset.
  - Regaining weight to the ideal level may not immediately reverse the condition.
- Athletic amenorrhea:
  - Increased physical activity, even without weight loss, can lead to decreased menstrual frequency and gonadotropin deficiency (exercise amenorrhea)
  - When physical activity is interrupted, menstrual function may return.
Hypogonadotrophic Hypogonadism: CM

- Adrenarche usually occurs to some degree.
- Throughout childhood and in early puberty, patients with hypogonadotrophic hypogonadism have normal proportions and growth.
- In 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.
- If a patient has concurrent GH deficiency, however, stature is exceptionally short, and the condition may have been diagnosed in infancy with a microphallus.
- May be difficult to distinguish from constitutional delay.
Fig. 12.37  Delayed development in a patient with growth hormone deficiency.

Fig. 12.38  Photograph of a patient with the Prader-Willi syndrome. Massive obesity is present.

Fig. 12.39  Photograph of an adolescent female with anorexia nervosa. This life-threatening condition is commonest in young girls. By courtesy of Dr. D. Grant.
Fig. 12.35 Photograph of an adolescent male with hypogonadotrophic hypogonadism.

Fig. 12.36 Photograph of an adolescent male with Noonan’s syndrome. The habitus resembles Turner’s syndrome.
Hypergonadotropic hypogonadism in Boys

**Common:**
- Klinefelter syndrome
- Anorchia and cryptorchidism
- Other forms of primary testicular failure: alkylating chemotherapeutic agents, Radiation of the gonads
  - Sperm preservation is possible in a boy who will undergo chemotherapy or radiotherapy

**Rare:**
- LH Resistance: male phenotype, no male secondary sexual development, gynecomastia, elevated plasma LH levels, and early pubertal plasma testosterone concentrations that did not increase after hCG administration.
- Partial deficiency of 17-hydroxylase
- Nephropathic cystinosis
Klinefelter syndrome

- Klinefelter syndrome (seminiferous tubular dysgenesis): most common cause of testicular failure.
- The karyotype is 47,XXY, but variants with more X chromosomes are possible.
- Incidence: 1 in 500 – 1000 males.
- Testosterone levels may be close to normal, at least until mid-puberty, because Leydig cell function may be spared; however, seminiferous tubular function characteristically is lost, causing infertility.
- The common observation is that LH levels may be normal to elevated, whereas FSH levels are usually more unequivocally elevated.
Figure 24.15 Adolescent boy with Klinefelter's syndrome exhibiting eunuchoid habitus and gynecomastia. (Courtesy of Gower Medical Publishing Ltd.)
Hypergonad. hypogonadism in Girls

- Turner syndrome (Syndrome of gonadal dysgenesis and its variants)
- Gonadal dysgenesis
  - Familial and sporadic XX gonadal dysgenesis and its variants
  - Familial and sporadic XY gonadal dysgenesis and its variants
- Other Causes of Primary Ovarian Failure: chemotherapy and radiation
- Noonan's Syndrome (Pseudo-Turner's Syndrome, Ullrich Syndrome)
- FSH Receptor Resistance
- Galactosemia, congenital disorders of glycosylation-1 (carbohydrate-deficient glycoprotein syndrome type la)
Turner syndrome

- Turner syndrome: common cause of ovarian failure and short stature.
- The karyotype is classically 45,XO, but other abnormalities of the X chromosome or mosaicism are possible.
- The incidence of Turner syndrome is 1 in 2000 to 5000 births.
- The features of a girl with Turner syndrome need not be evident on physical examination or by history, and the diagnosis must be considered in any girl who is short without a contributory history.
FIGURE 22-10. An adolescent with Turner syndrome demonstrating cubitus valgus.
Figure 24.13 Two patients with Turner's syndrome. Patient A has the characteristic physical features of Turner syndrome, including short stature, webbed neck, and low-set ears. Patient B shows the physical features of Turner syndrome with short stature and webbed neck.
Figure 148-5  Hypoplasia of the fourth and fifth toenails in a patient with Turner syndrome.
Diagnosis

**Hx:**
- chronic or intermittent illnesses
- growth and development details
- the patient’s sense of smell.
- labor and delivery, and birth trauma history
- Poor linear growth
- poor nutritional status during the neonatal period and childhood
- A growth chart is plotted to represent graphically the increase in stature and to assess growth velocity from birth (late onset of growth failure usually indicates a serious condition).
Physical Examination

- Height
- Stage of puberty
  - BP: HTN: 17 α def.
- Galactorrhea
- Neurologic examination (optic discs and visual field, olfaction)
- The stigmata of gonadal dysgenesis (Turner’s syndrome) or the small testes and gynecomastia of Klinefelter’s syndrome may suggest one of these diagnoses.
- Mental ret.: PWS, Noonan Sx
Figure 148-6  Complete absence of breast development in a 15-year-old girl presenting with delayed puberty. Arm span was 8.3 cm greater than height and upper-to-lower body segment ratio was 0.7, confirming a "eunuchoid habitus." Karyotype was 46,XY.
Fig. 12.33  Photograph of brothers with constitutional delayed adolescence. The brothers have chronological ages of 17 and 20 and bone ages of 13 and 15 respectively.
Laboratory studies

- LH and FSH
- Testosterone /estradiol
- Measurement of the rise in LH level after LHRH administration
- T4 and prolactin
- Na,K
- Progestational Challenge test
- Bone Age
- Sonography
MRI: Hypogonadotropin hypogonadism (after R/O CDGP)

KARYOTYPE: Hypergonadotropin hypogonadism
Eugonadism
(Differential Diagnosis)

- primary amenorrhea
  - an anatomic defect may be responsible; presents with normal secondary sexual development without menstruation.
  - the Mayer-Rokitansky-Kuster-Hauser syndrome
    - congenital absence of the uterus
    - 1 in 4000 to 5000 female births.
  - imperforate hymen
  - vaginal septum
  - syndrome of androgen insensitivity
AIS

- The complete syndrome of androgen Insensitivity:
  - normal feminization,
  - absence of pubic or axillary hair
  - primary amenorrhea.
  - all müllerian structures, including ovaries, uterus, fallopian tubes, and upper third of the vagina, are lacking;
  - the karyotype is 46,XY
  - intra-abdominal testes.
Treatment
Treatment of Delayed Puberty

- Depends on the diagnosis and the nature of the disorder.

- Patients with constitutional delay in growth and adolescence ultimately have spontaneous onset and progression through puberty.

- If a permanent condition is apparent, replacement with sex steroids is indicated.
  - BOYS: Initial therapy: at 13 yr of age, Begin replacement therapy in boys with suspected hypogonadotrophic hypogonadism by bone age ≤14 yr
  - GIRLS: Begin hormonal therapy at 12-13 yr of age
THERAPY OF CDGP

andatory but not anxious or socially handicapped adolescent:

- Reassurance and follow-up (tincture of time)
- Repeat evaluation (including serum testosterone or estradiol) in 6 mo

Psychosocial handicaps, anxiety, highly concerned:

- Therapy for 4 mo with
  - Boys: testosterone enanthate 100 mg IM every 4 wk at 14-14.5 yr of age, or overnight transdermal testosterone patch
  - Girls: ethinyl estradiol 5-10 μg daily by mouth or conjugated estrogens 0.3 mg daily by mouth or overnight ethinyl estradiol patch at 13 yr of age
- No therapy for 4-6 mo; reevaluate status including serum testosterone or estradiol; if indicated repeat treatment regimen.
Girls

Initial therapy: ethinyl estradiol 5 μg or conjugated estrogen 0.3 mg (or less) PO daily for 4-6 mo or preferably estradiol transdermally

- After 6 mo of therapy (or sooner if “breakthrough” bleeding occurs) begin cyclic therapy:
  - Estrogen: first 21 days of month
  - Progestagen: 12th to 21st day of month (e.g., medroxyprogesterone acetate 5 mg/day)

Gradually increase dose of estrogen over next 2-3 yr to conjugated estrogen 0.6-1.25 mg or ethinyl estradiol 10-20 μg daily for first 21 days of month or estradiol patch
Treatment of Delayed Puberty

- **BOYS**:
  - Initial therapy: at 13 yr of age, testosterone enanthate (or other long-acting testosterone ester) 50 mg intramuscularly every month for about 9 mo (6-12 mo)
  - Over the next 3 to 4 yr: gradually increase dose to adult replacement dose of 200 mg every 2-3 wk
  - *To induce fertility* at appropriate time in hypogonadotropic hypogonadism: pulsatile GnRH or FSH and hCG therapy
Treatment of Delayed Puberty

- All patients with any form of delayed puberty are at risk for decreased bone density; adequate calcium intake is essential.
- In hypogonadotropic hypogonadism: to induce ovulation at appropriate time: pulsatile GnRH or FSH and hCG therapy
- Subjects with hypergonadotropic hypogonadism, whether Turner syndrome or Klinefelter syndrome, have by definition a primary gonadal problem and are unlikely to achieve spontaneous fertility.
- Patients with Turner syndrome have had successful pregnancies after IVF with a donor ovum and endocrine support
امام صادق عليه السلام:

آنیه برایی خود نمی پسندی برای حاکم‌ران هم نپسند.