

# Puberty

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# Learning Objectives

- Understand physiology of puberty
- Causes and management approach to Precocious puberty
- Identify and investigate children with delayed puberty

# Physiology of puberty

- What is puberty?
- It is the transitional period of development during which an individual matures from childhood to physical, psychosocial, sexual & reproductive maturity

# NORMAL PUBERTAL DEVELOPMENT

- Major characteristics of puberty
  - 1-Maturation of the primary sexual characteristics  
Hypothalamic Pituitary Ovarian Axis
  - 2-Development of secondary sexual characteristics
    - Sexual hair
    - Breasts
    - Genitalia
  - 3-Dramatic growth spurt
  - 4-Psycological changes ⇒ mental & emotional maturity
  - 5-Fertility

# Endocrine Regulation of Puberty & Reproduction

- Hypothalamus releases LHRH (GnRH)
- Anterior pituitary secretes:
  - LH .
  - FSH.
- Secreted in pulsatile fashion to prevent desensitization and down regulation of receptors.
- Primary effects of LH and FSH on gonads:
  - Stimulation of spermatogenesis and oogenesis.
  - Stimulation of gonadal hormone secretion.
  - Maintenance of gonadal structure.

# Mechanism of Puberty

- GnRH stimulates pituitary gonadotropins (LH & FSH)
- During childhood pubertal Gn secretion is initially low due to downregulation
- Negative feedback of hypothalamic-pituitary-gonadal axis
- As puberty progresses, episodic release of LH
  - Increased amplitude & frequency
  - Progressive secretion extends over the 24 hr period
- Mechanism of why puberty occurs is unknown(theories?)

# NORMAL PUBERTAL DEVELOPMENT

- THE AGE OF ONSET OF PUBERTY

  - Females ----8-13

  - Males -----9-14

    - Lawson Wilkins Pediatric Endocrine Society recommended 7 for white girls/ 6 for black

- AVERAGE AGE of ONSET:

1. GIRLS 10 to 11 years (range 8 to 13 years)

2. BOYS 11 to 12 years (range 9 to 14 years)

# NORMAL PUBERTAL DEVELOPMENT

- THE TIME FROM ONSET TO COMPLETION OF PUBERTY?

Average	4.2 Y
Range	1.5-6 Y



# Factors That Affect Puberty

- Genetics
- Race/Ethnicity
- Previous nutrition
- Subcutaneous fat
- Birth weight
- Obesity
  - Increased leptin and estrogen production
  - Insulin stimulation of ovaries & uterus

# NORMAL PUBERTAL DEVELOPMENT

## INITIAL SIGNS OF PUBERTY:

**1. GIRLS – Breast Development**

**2. BOYS – Testicular Enlargement**

- **Volume  $> 3.0 \text{ cm}^3$**
- **Length  $> 2.5 \text{ cm}$**

# NORMAL FEMALE PUBERTAL DEVELOPMENT

- THE USUAL SEQUENCE OF SOMATIC CHANGES OF PUBERTY

1-Onset of growth spurt (9.6)

2-Beast development (mean 10.6 Y)

3-Pubic & axillary hair (11.2)

4-Maximal growth velocity (12)

- 5-Menarche (12.7)

# Tanner's Staging of Puberty in Girls

<b>STAGE</b>	<b>BREAST DEVELOPMENT (B)</b>	<b>PUBIC HAIR (PH)</b>
<b>1</b>	<b>Prepubertal; no breast tissue</b>	<b>None</b>
<b>2</b>	<b>Areolar enlargement with breast bud</b>	<b>A few darker hairs along labia</b>
<b>3</b>	<b>Enlargement of breast and areola as single mound</b>	<b>Curly pigmented hairs across pubes</b>
<b>4</b>	<b>Projection of areola above breast as double mound</b>	<b>Small adult configuration</b>
<b>5</b>	<b>Mature adult breast with single contour</b>	<b>Adult pubic hair distribution</b>

# Tanner's Staging of Puberty in Boys

<b>STAGE</b>	<b>GENITAL MATURITY (G)</b>	<b>PUBIC HAIR (PH)</b>
<b>1</b>	<b>Prepubertal; testes 2 ml</b>	<b>None</b>
<b>2</b>	<b>Enlargement of the testes <math>\geq</math> 4 ml; reddening of the scrotum</b>	<b>A few darker hairs at the basis of the penis</b>
<b>3</b>	<b>Lengthening of the penis; further enlargement of testes to 6-10 ml</b>	<b>Curly pigmented hairs across pubes</b>
<b>4</b>	<b>Broadening of the glands penis; growth of testis to 10-15 ml</b>	<b>Small adult configuration</b>
<b>5</b>	<b>Genitalia adult in size and shape; testes 15-25 ml</b>	<b>Adult pubic hair distribution</b>

# GROWTH SPURT

- Peak Height Velocity

- 8.1 cm/year (before puberty 3-6 cm/y)

- by the time PHV is achieved  $\Rightarrow$  90% of adult height has been achieved

- the average  $\uparrow$  in height from the onset of growth spurt to cessation of growth  
25 cm

- girls who start the growth spurt early will have a shorter adult height

# Assessment of Puberty

## History

- Parents
  - onset of puberty in parents
    - Menarche (more reliable in mothers as they remember onset)
    - Male growth spurt (as most fathers recall their pubertal progression more vaguely)
      - » Age of first shaving regularly
  - Parental heights (identify midparental height)
- **prenatal and perinatal (exposure to exogenous sex steroids in intrauterine period; birth weight, length, mechanism of delivery, perinatal pathology - resuscitation,..)**
- **concomitant illnesses, postnatal exposure to sex steroids**
- **time of first sign of puberty**
- Body changes? (important to ask about EACH)
  - Thelarche (galactorrhea)
  - Adrenarche/pubarche (body odor, axillary & pubic hair, acne)
  - Menarche
  - Gonadarche

# History cont'd...

- Important to include:
  - Past medical history (history of brain tumor, radiation, chemotherapy, known genetic disorder, chronic disease affecting growth)
  - Eating habits
    - Any evidence of disordered eating
  - Activity level
    - Is exercise excessive or is this an athlete with a high level of training
  - Growth history
    - Previous growth chart can be extremely helpful



# History

- Review of Systems
  - CNS: visual changes/visual field abnormalities, headaches, anosmia
  - Cardiac: congenital anomaly
  - Respiratory: asthma
  - Renal:
  - GI: diarrhea, blood in stools

# Physical Examination

- Examination of Growth
  - Height
  - Weight
  - Head circumference
  - Upper to lower segment ratios
- Pubertal Assessment (Tanner staging)
  - Axillary hair
  - Pubic hair & staging
  - Breast development & staging
  - Genital development & staging
- **skin, hair, thyroid**
- Neurological assessment

# Diagnostic evaluation

## Laboratory

- gonadotropins (FSH, LH) basal and peak after LHRH stimulation (prepubertal LH/FSH<1)
- estradiol
- testosterone (basal value and value after LH stimulation)
- adrenal androgens (17-OHP, A-dion,...) and ACTH

**Skeletal maturity (bone age)**

**Pelvic sonography (ovarian and uterine size)**

**CT or MRI of adrenals, CNS**

**Vaginoscopy and vaginal cytology**

**Genetic – karyotype, DNA analysis**

# Variants of normal development

## **Premature thelarché (isolated breast enlargement)**

- exclude the start of precocious puberty!

## **Premature adrenarché (pubic and axillary hairs)**

- exclude simple virilising form of CAH!

## **Premature menarché**

- exclude vaginal bleeding due to trauma of vagine or rare ovarian cyst!

**Bone age is not accelerated!**

***FSH and LH levels after LH-RH are normal***

***Gonadal and adrenal steroid levels are normal***

***Pelvic and adrenal ultrasonography is normal***

***Reassurance & f/u***

# Definition of Precocious Puberty

- ONSET OF PUBERTY BEFORE

- Females -----8 years

- Males -----9 years

- Lawson Wilkins Pediatric Endocrine Society  
recommended 7 for white girls/ 6 for black

- The prevalence

- is estimated to be between one in 5,000 to 10,000 children annually in the United States.

# Classification

## Central (true), gonadotropin-dependent

Early stimulation of hypothalamic-pituitary-gonadal axis.

## Peripheral, GnRH independent (precocious pseudopuberty)

The source of sex steroid may be endogenous or exogenous, gonadal or extragonadal, independent of gonadotropins stimulation.

# **True precocious puberty**

**(central, GnRH dependent)**

**Idiopathic, constitutional sporadic or familial (common)**

## **CNS abnormalities**

- **Congenital (hydrocephalus, arachnoid cysts, ...)**
- **Acquired pathology (posttraumatic, infections, radiation,..)**
- **Tumors (LH secreting pituitary microadenoma, glioma – may be associated with neurofibromatosis, hamartoma,..)**
- **Reversible forms - space occupying or pressure-associated lesion (abscess, hydrocephalus,...)**
- **Empty sella syndrome**

**Adopted children or children emigrating from  
developping  
countries**

- **Improved nutrition, environmental stability and psychosocial support**

# True precocious puberty (central, gonadotropin-dependent)

**Always isosexual!**

**Bone age is accelerated**

**FSH and LH elevation after LH-RH is diagnostic test  
(LH/FSH > 2)**

↓LH ⇔ LH/FSH ratio < 1 ⇔ Prepubertal

↑LH ⇔ LH/FSH ratio > 1 ⇔ Pubertal

**MRI of CNS is necessary to exclude the neoplasia**



# Treatment of true precocious puberty

- **Purpose of treatment**
  - To prevent psychosocial distress
  - To improve final height outcome
- Treat the underlying cause
- GnRH analogue
  - Lupron depot ped, leuprolide acetate
  - Desensitizes the pituitary
  - Blocks LH and FSH secretion
  - Prevents continued sexual development for the duration of the treatment

# Precocious pseudopuberty in girls (gonadotropin-independent)

## McCune - Albright syndrome

### Ovarian cysts

Isolated follicular cysts with E2 production. Self-limiting with spontaneous regression.

### Ovarian tumors

*Acceleration of bone age*

*FSH and LH are low after LH-RH stimulation*

*Estrogens are elevated*

# Precocious pseudopuberty in boys

(gonadotropin-independent)

## Congenital adrenal hyperplasia (CAH)

Undiagnosed or inadequately treated simple virilising form of CAH caused by 21-hydroxylase deficiency.

Neonatal screening?

## Testotoxicosis

Activating mutation of LH receptor. AD inherited.

## Tumors

- Gonadal (testosterone-secreting Leydig cell tumor)
- Adrenal (adenoma, carcinoma)

**Exogenous androgens** (anabolic steroids – iatrogenic, doping)

## McCune Albright Syndrome

*Acceleration of bone age*

*FSH and LH are low after LH-RH stimulation*

*Testicular or adrenal steroids are elevated*

# Precocious puberty-treatment

## Gonadotropin-dependent PP

- **Idiopathic**
  - GnRH (LH-RH) analog (triptorelin) to block LH-RH receptor in gonadotroph of pituitary gland
- **Organic – tumor or cysts**
  - Surgery

## Gonadotropin independent (pseudopuberty)

- testicular, ovarian or adrenal tumors –surgery
- CAH – substitution of corticosteroids
- autonomous steroid secretion-estrogens receptor antagonists (tamoxifen), steroid synthesis inhibitors (ketoconazole), aromatase inhibitors (testolacton)

# Delayed puberty - definition

**Initial physical changes of puberty are not present**

- **by age 13 years in girls  
(or primary amenorrhoe at 15.5-16y)**
- **by age 14 years in boys**

**Pubertal development is inappropriate**

**the interval between first signs of puberty and menarche in girls/completion genital growth in boys is > 5 years**

# GnRH or gonadotropin dependent I.

## **Idiopathic**

sporadic or familial (associated with constitutional growth delay)

## **Chronic diseases**

with bone age delay and growth retardation due to different pathophysiological mechanisms (malnutrition, anemia, acidosis, hypoxia,...anorexia nervosa, cystic fibrosis, chronic renal insufficiency,..)

## **Psychosocial deprivation**

# GnRH or gonadotropin dependent II.

## Hypogonadotropic hypogonadism

### Gonadotropin deficiency

LH only (fertile eunuch syndrome)

FSH and LH

- Congenital (genetic, syndromes) - Kallman syndrome –mutation of KAL gene,  
mutation of DAX1 gene, Prader-Willi syndrome ,...
- Acquired - cranial irradiation, hemosiderosis, granulomatous disease

### Associated with others pituitary hormones deficiencies

- Congenital – empty sella syndrome, genetic-transcription factors, disruption  
of pituitary stalk (breech delivery),...
- Acquired – tumors, inflammation, irradiation, trauma....

# Syndromes Associated with Pubertal Delay

- Prader-Willi syndrome
- Laurence Moon syndrome
- Septo-optic dysplasia
- Bardet-Biedl syndrome



# **Gonadotropin independent (hypergonadotrophic)**

## **Boys**

### **Congenital**

**Anorchia**

**Chromosomal abnormalities (Klinefelter syndrome,  
Noonan syndrome...)**

### **Acquired**

**Autoimmune inflammation (APS)**

**Radio or chemotherapy**

**Traumatic**

**Surgery**

# **Gonadotropin independent (hypergonadotrophic hypogonadism)**

## **Girls**

### **Congenital**

**Bilateral ovarian torsion**

**Chromosomal abnormalities (Turner syndrome, pure gonadal dysgenesis, Noonan syndrome...)**

### **Acquired**

**Autoimmune inflammation (APS)**

**Radio or chemotherapy**

**Traumatic**

**Surgery**

# Investigating Delayed Puberty

- Investigations depend on clinical presentation, but may include
  - Bone age
  - Hormone levels (FSH, LH, estradiol, testosterone,, TSH)
  - Karyotype
  - Hormone stimulation tests
    - GnRH stimulation test
  - Imaging
    - MRI if gonadotropins high & no obvious cause of hypogonadotropic hypogonadism

# Treatment of delayed puberty

- Treat underlying cause
- Testosterone
- estrogen