PRECOCIOUS PUBERTY

FLAME LECTURE: 203

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LEARNING OBJECTIVES

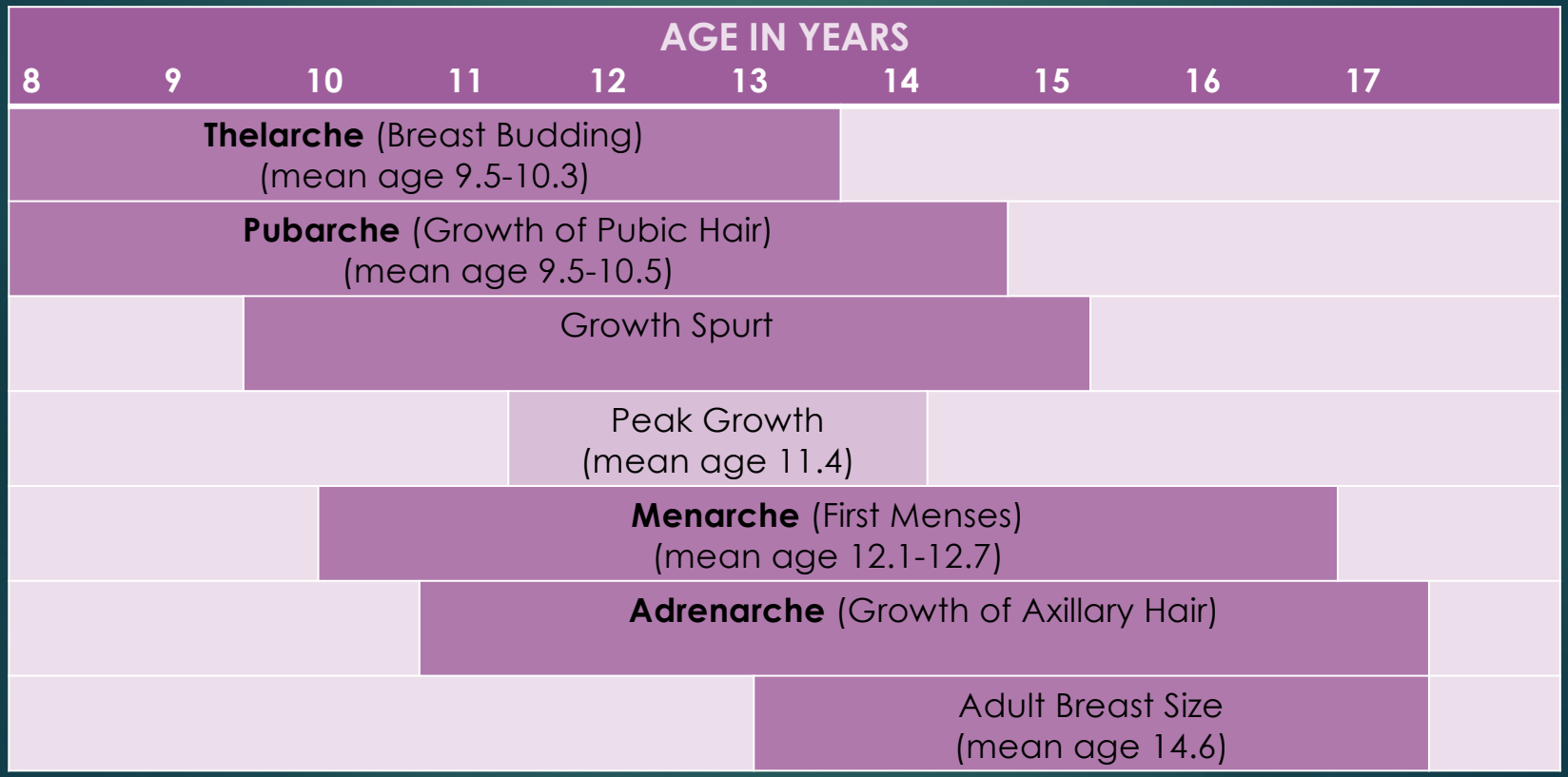
- To define precocious puberty and differentiate its etiologies
- To describe the treatment modalities for precocious puberty
- Prerequisites:
  - NONE
- See also – for closely related topics
  - FLAME LECTURE 204: Delayed Puberty

BACKGROUND

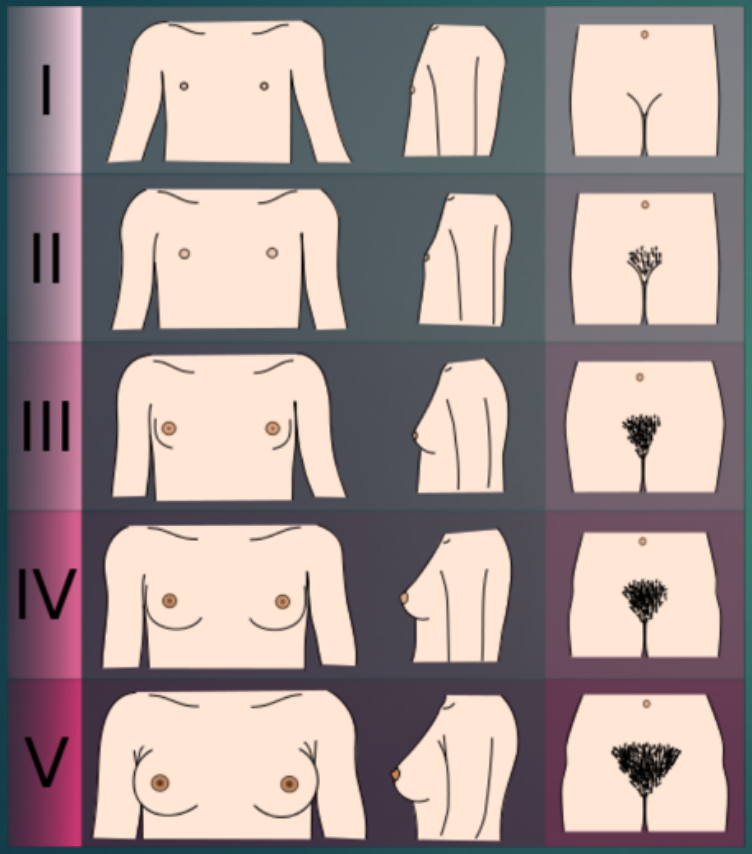
- For girls, precocious puberty is defined as the appearance of physical and/or hormonal signs of puberty before 8 yrs old (mean age of normal puberty onset is 11.5 yrs)
  - Physical signs include:
    - **Thelarche** – Tanner Stage III breast < 8 yrs old
    - **Adrenarche** – pubic/axillary hair development (+ breast budding) < 8 yrs old
    - **Menarche** – menstruation < 8 yrs old
    - Bone age > 2 years advanced from chronological age
  - Hormonal signs include: elevated LH or FSH, elevated estrogen
  - 10 times more common in females than males

Medscape. "Precocious Puberty" 2017.

SEQUENCE OF NORMAL PUBERTY



TANNER STAGING



I	No sexual hair No glandular breast tissue
II	Sparse, pigmented, long straight hair on labia majora Breast bud (small glandular tissue, wider areola)
III	Darker, coarser, curlier hair Elevated breast (beyond borders of areola), areola darker
IV	Adult hair with less distribution Secondary breast mound
V	Hair spread to medial thighs Final adult size, protruding nipples, no edge between areola/breast

PUBERTAL ONSET

DRIVEN BY THE: HYPOTHALAMIC-PITUITARY-GONADAL (HPG) AXIS

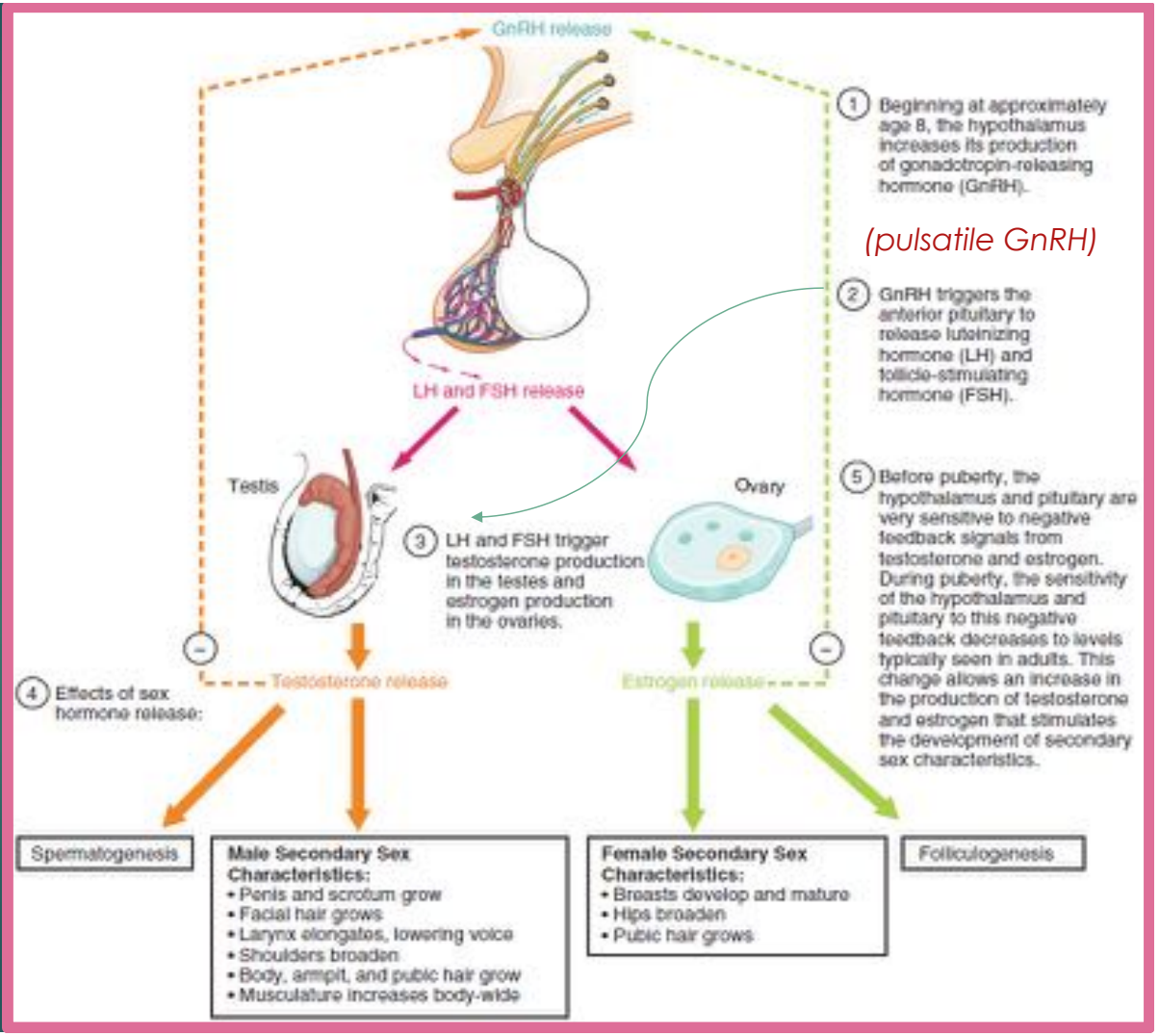


Illustration free-to-use from Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/ , June 19, 2013.

PUBERTAL ONSET
HORMONAL ACTORS

Testosterone Source	Testosterone Function	Estradiol Source	Estradiol Function	Progesterone Source	Progesterone Function
50% from ovary 50% from conversion of adrenal DHEA In early puberty, before HPG axis activation, almost all androgens come from the adrenal gland	↑ linear growth Growth of pubic and axillary hair ↑ libido ↑ acne	90% secreted by the ovary 10% from peripheral conversion of testosterone & androstane-dione Normal level 110-410 pg/mL	Stimulates growth of breasts, uterus, labia, vagina Stimulates endometrial proliferation Triggers LH surge Increase fat mass *Low levels* - ↑ growth *High levels* - fuse epiphyses	Ovary after ovulation (from the corpus luteum) Adrenal (minor) Placenta	Stimulates secretory endometrium Maintains pregnancy Relaxes uterine smooth muscle

PRECOCIOUS PUBERTY
CLINICAL FINDINGS

- EARLY pubic hair, axillary hair, acne, axillary odor, and/or breast development
- Patients initially experience ACCELERATED GROWTH and are taller than peers, but **usually do not achieve full height** due to premature closure of epiphyseal plates by estrogen
- Higher proportion of negative psychosocial outcomes, such as behavioral problems or increased libido, as compared to age-matched peers
- As with normal puberty, precocious puberty will occur one year earlier on average in African-American than in Caucasian and Hispanic girls

PRECOCIOUS PUBERTY CLASSIFICATIONS

- Central Precocious Puberty (CPP)
  - Also known as gonadotropin-dependent or true precocious puberty
  - From early maturation of the HPG axis
  - Estimated to affect 1 in 5,000-10,000 girls
- Peripheral Precocious Puberty (PPP)
  - Also known as gonadotropin-independent or precocious pseudopuberty
  - From excess, ectopic, or exogenous secretion of sex hormones
- Benign Pubertal Variants
  - Premature, isolated thelarche or adrenarche

CENTRAL PRECOCIOUS PUBERTY

- Patients show the full spectrum of pubertal physical and hormonal changes – pattern and timing of progression are maintained
  - High-amplitude pulses of GnRH from hypothalamus → **increased LH and FSH levels** → increased androgens and estrogen
- Causes
  - Idiopathic (80-90% of girls)
  - CNS Abnormalities
    - Hypothalamic hamartoma (most common cause)
    - Tumors including astrocytoma, glioma, germ cell tumor secreting HCG
    - Acquired injury including CNS radiation, surgery, or trauma
    - Congenital anomalies including hydrocephalus or arachnoid cyst
  - Genetic: loss of function mutation of MKRN3 gene → lose GnRH suppression

NIH – NICHD: "Puberty and Precocious Puberty". 2017.
GHR: "Central precocious puberty". 2017.

PERIPHERAL PRECOCIOUS PUBERTY

- Patients have EXCESS sex hormones from the gonads or ectopic or exogenous sources
  - Estrogen and androgens are high, but typically **FSH and LH are low** due to negative feedback
- Causes
  - Gonadal: ovarian cyst or tumor (i.e. granulosa cell tumor secretes estrogen)
  - Genetic syndromes: CAH, McCune-Albright
  - Exogenous sources: OCPs, estrogen creams, steroids, possibly food sources (phytoestrogens in soy)

BENIGN PUBERTAL VARIANTS

- These variants are defined as early pubertal development that is not pathologic
- Premature Thelarche
  - Early isolated breast development
  - Normal hormones, growth velocity, and bone age
  - <3 years old is usually self-limited and isolated
  - May be related to a small ovarian cyst that is independent of the HPO axis
  - Can be asymmetric
  - Usually can just be observed

BENIGN PUBERTAL VARIANTS

- Premature Adrenarche
  - Early appearance of pubic or axillary hair, axillary odor
  - Elevated DHEAS (adrenal)
  - Rule out androgen-secreting tumors & CAH
  - No treatment needed, but higher risk of PCOS
- Benign Prepubertal Vaginal Bleeding
  - Uncommon transient, self-resolving bleeding due to sensitive endometrium
  - Rule out tumors & foreign body
- Non-Progressive/Intermittent Precocious Puberty
  - Clinical signs of CPP but does not progress
  - Normal hormones, bone age

OVERVIEW

PRECOCIOUS PUBERTY

GONADOTROPIN INDEPENDENT (PPP)

ENDOGENOUS
- *Gonadal*
  - Ovarian Cysts
  - Ovarian Tumors (e.g. Granulosa Cell)
  - Adrenal Tumors
- *Genetic*
  - Congenital Adrenal Hyperplasia
  - McCune-Albright Syndrome (MRKH)
- *Endocrine*
  - Severe Hypothyroidism

EXOGENOUS
- OCPs
- Estrogen creams
- Steroids
- Phytoestrogens

GONADOTROPIN DEPENDENT (CPP)

IDIOPATHIC (90%)

ORGANIC
- *Brain Tumor*
  - Hypothalamic Hamartoma
  - Glioma
- *Congenital Anomaly*
  - Hydrocephalus
  - Arachnoid Cyst
  - Cerebral Dysgenesis
- *CNS Insult*
  - Infection
  - Head Trauma
  - Neurosurgery
  - Radiation Exposure
- *Genetic*
  - MKRN3 Mutation

EVALUATION OF PRECOCIOUS PUBERTY

- History
  - Personal onset and sequence
  - Exposures, traumas, CNS disease
  - Family history
  - Psychosocial history
  - ROS including linear growth, headaches, vision changes, pelvic pain
- Physical
  - Tanner Staging
  - Height, weight, and height velocity (plot on growth chart)
  - Visual field assessment and full neurological exam
  - Examination for skin changes, abdominal or pelvic masses
  - External genitalia exam

EVALUATION OF PRECOCIOUS PUBERTY

- Labs
  - LH (more useful than FSH)
    - Random LH >0.3 U/L suspect CPP
  - Estradiol
    - >20 pm/mL consistent with precocious puberty
  - Prolactin
    - Tumors → stalk compression
  - Thyroid testing
  - *Note: limited utility to measuring GnRH
- Imaging
  - Pelvic ultrasound for suspected pelvic cyst/tumor
  - MRI for suspected brain lesions
  - Left wrist/hand X-ray for bone age

TREATMENT: CPP

- Goals:
  - Slow skeletal maturation to improve final height
  - Halt or regress secondary sexual characteristics & prevent menarche
  - Avoid psychosocial sequelae
- Treatment is aimed at gonadotropin suppression with the goal of decreasing sex steroid hormone production
  - Continuous GnRH agonist (e.g. leuprolide) causes suppression of the HPG axis and desensitization of gonadotrophs → suppressed gonadotropin production → decreased sex steroid production
- Patients with earlier age of onset (<6 yrs) and more rapid pubertal progression have a better response to therapy

TREATMENT: PPP

- Treatment is aimed at blocking the production of or response to excess sex steroid hormone levels
  - Remove tumor or functional ovarian cyst (latter may also resolve spontaneously)
  - Remove source of exogenous sex steroids
  - Give glucocorticoids if defect in adrenal steroidogenesis
  - Aromatase inhibitors (e.g. letrozole) or SERMs (e.g. tamoxifen) for girls with McCune-Albright Syndrome
    - Prevent premature epiphyseal plate fusion and recurrent vaginal bleeding
- *Note: GnRH agonist therapy is ineffective for these patients

REFERENCES

- UpToDate: Definition, etiology, and evaluation of precocious puberty
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- Tirumuru SS, Arya P, Latthe P. Understanding precocious puberty in girls. *The Obstetrician & Gynaecologist* 2012;14:121–129.