Precocious

Precocious got started in Latin when the prefix *prae-,* meaning "ahead of," was combined with the verb *coquere,* meaning "to cook" or "to ripen," to form the adjective "praecox," which means "early ripening" or "premature." By 1650, English speakers had turned "praecox" into "precocious" and were using it especially of plants that produced blossoms before their leaves came out. By the 1670s, "precocious" was also being used to describe humans who developed skills or talents before others typically did.

Puberty

n. the period or age at which a persons is first capable of sexual reproduction of offspring, in common law, presumed to be 14 years in males and 12 years in females

n. "the time of life which the two sexes begin first to be acquainted" [Johnson] late 14c. From Old French puberte' and directly from Latin pubertatum (nominative pubertas), "age of maturity, manhood," from pubes (genitive pubertis) "adult, full-grown, manly." Related: puberal; pubertal

Puberty – Brief review of normal & abnormal

Bruce Tjaden, DO
Reproductive Endocrinology and Infertility

Puberty

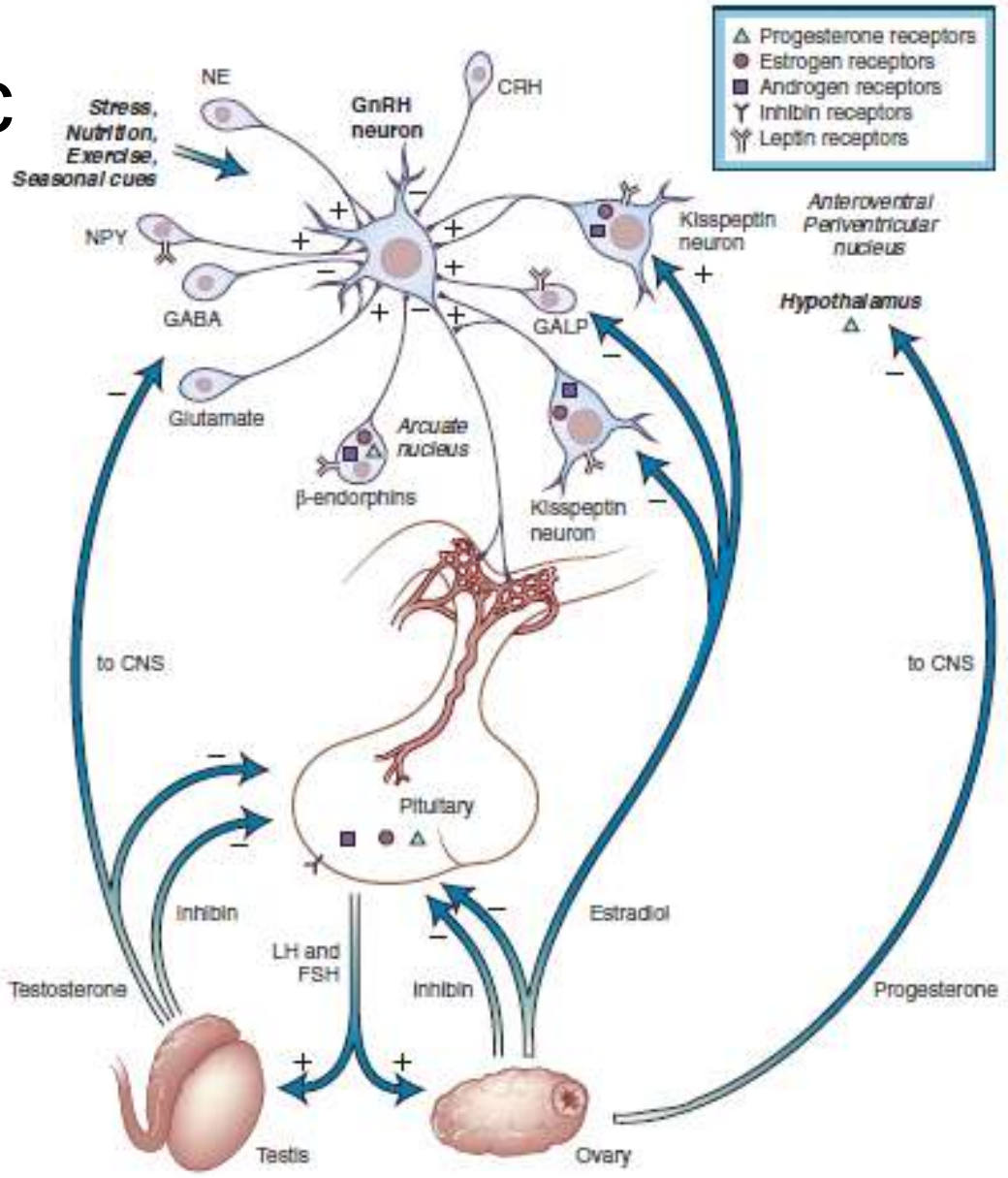
- Pubertal disorders are one of most common referrals to pediatric endocrine clinics
- Precocious puberty affects up to 29 per 100 000 girls per year.
- As always careful history and examination are very important
- Puberty is a highly sensitivity issue for adolescents AND parents
- Chaperone during pubertal examination

Puberty

- Physical and physiological transition from childhood to reproductive maturity
- Associated with:
  - Linear growth
  - Appearance and developments of secondary sexual characteristics

- Occurs between 8 and 14 yrs of age in girls
- Occurs between 9 and 14 yrs of age in boys

Hypothalamic Pituitary Gonadal Axis (HPG) (HPO)

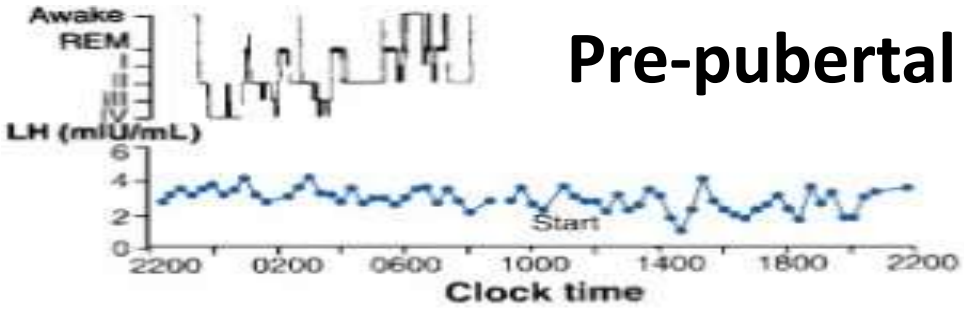


Timeline of Events

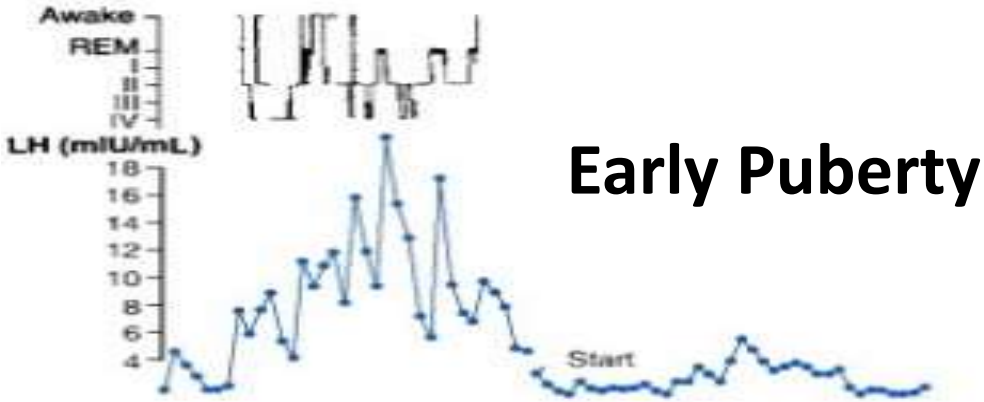
- 4 weeks – 4 months
  - HPG axis is active
    - Gonadotropins (FSH & LH) are measurable
    - Testosterone/estradiol levels ~ pubertal levels
    - “Mini-puberty of infancy”
- 4 months – 7 years
  - HPG axis is dormant
    - Gonadotropins are low;
    - Testosterone and estradiol are “absent”
    - “Quiescence of childhood”

Timeline of Events

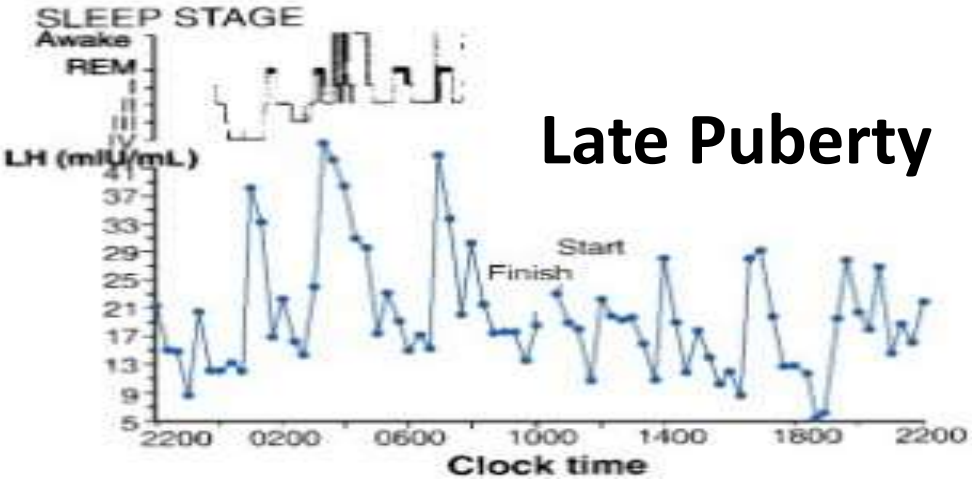
- 8 years – adolescence
  - A “triggering event” initiates the pubertal process.
  - Hypothalamic GnRH is secreted in a pulsatile fashion
  - Nocturnal pulses of LH are demonstrable
  - LH pulses increases in amplitude and, to a lesser extent, frequency
  - There is enlargement and maturation of the gonads and sex hormones are measurable.
  - True, or central pubertal development, begins.



Pre-pubertal



Early Puberty



Late Puberty

Neuroendocrine changes of puberty

- In the prepubertal child, GnRH is released in low amplitude pulses at a relatively low frequency.
- **The earliest identified neuroendocrine manifestation of puberty is the production of kisspeptin from hypothalamic neurons.**
- Kisspeptin alters release of GnRH from the hypothalamus.
- In the early stages of puberty, GnRH pulse amplitude increases and pulse frequency increases to every 1–2 hours, primarily at night
- As maturation progresses, these changes extend into the daytime hours.
- In response to GnRH secretion, LH and FSH production also increase, initially during the night and then during the day in later pubertal stages.

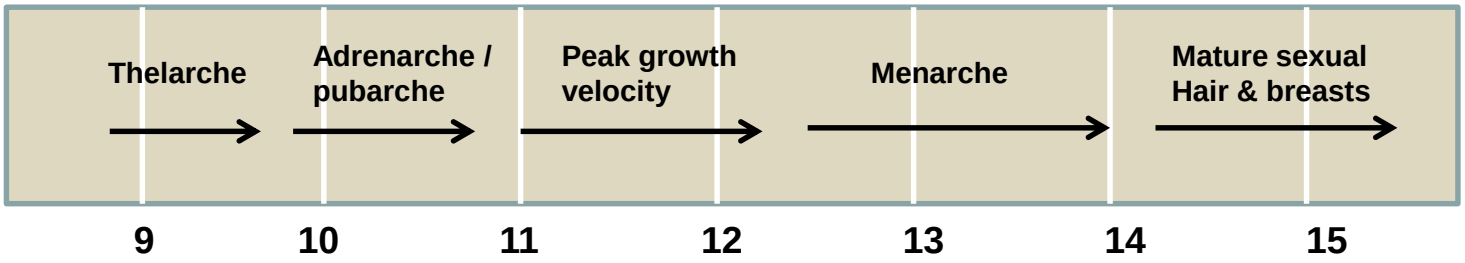
Factors influencing the onset of puberty

- “Gonadostat”
- Nutrition / nutritional status
- Leptin
- Genetics: 50-80% of variation in pubertal timing
- Parental status (??)

In Females		Age Range of Appearance
Breast development	thelarche	8-13
Pubic hair development	pubarche adrenarche	8-14
Growth spurt	peak growth velocity	9.5-14.5
First menses	menarche	10-16.5
Underarm hair		Approximately 2 years after the appearance of pubic hair
Increased oil- and sweat-gland output		Simultaneous w/ underarm hair

Sequence of puberty

1. **Thelarche**
2. **Adrenarche →Pubarche**
3. **(Time of highest growth velocity)**
4. **Menarche**



Acronym / mnemonic

TAPuP Me

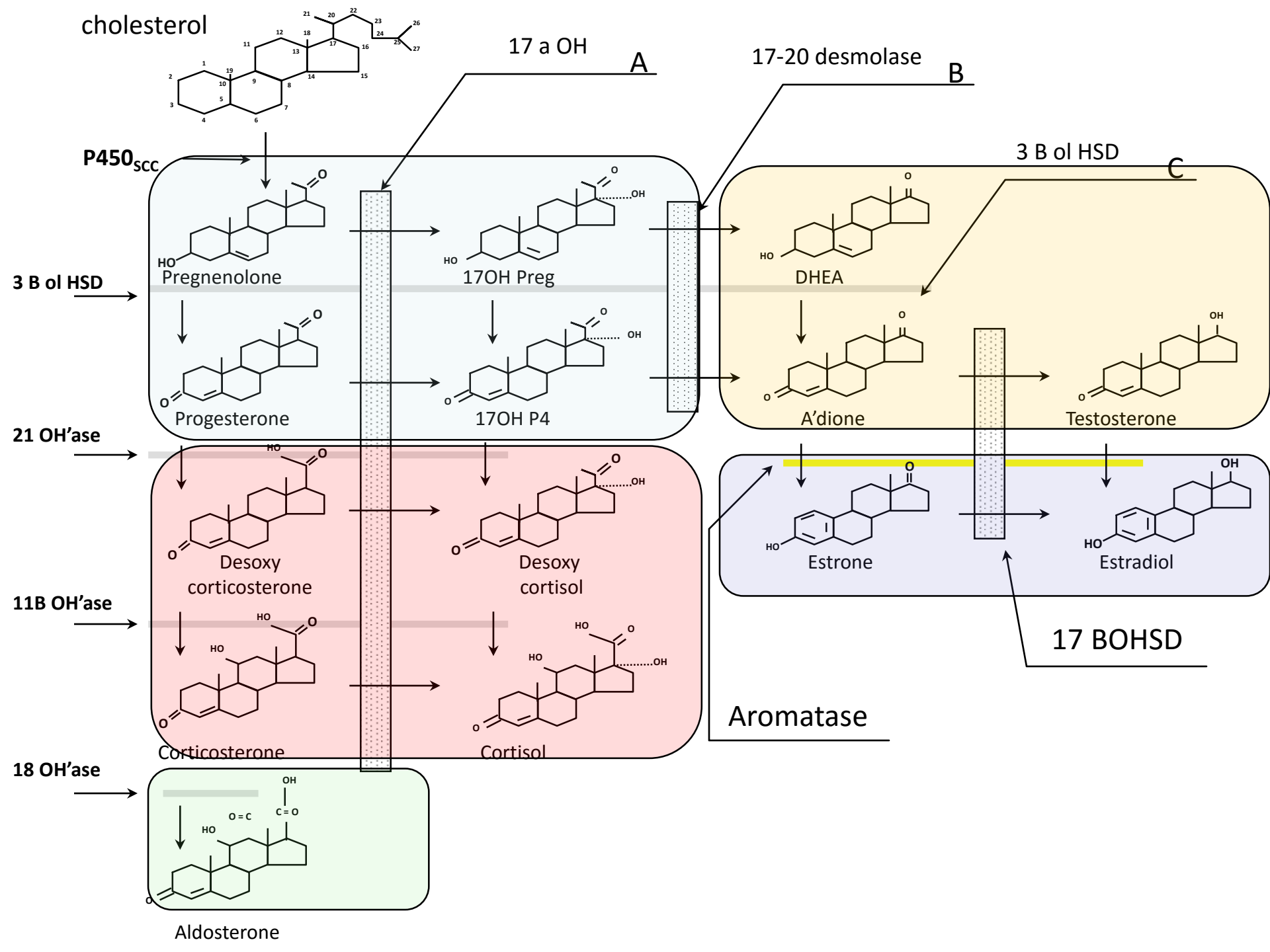
Thelarche, **A**drenarche, **Pu**barche, **P**eak growth velocity, **M**enarche

TPAM

Thelarche, **P**ubarche, **A**drenarche, **M**enarche

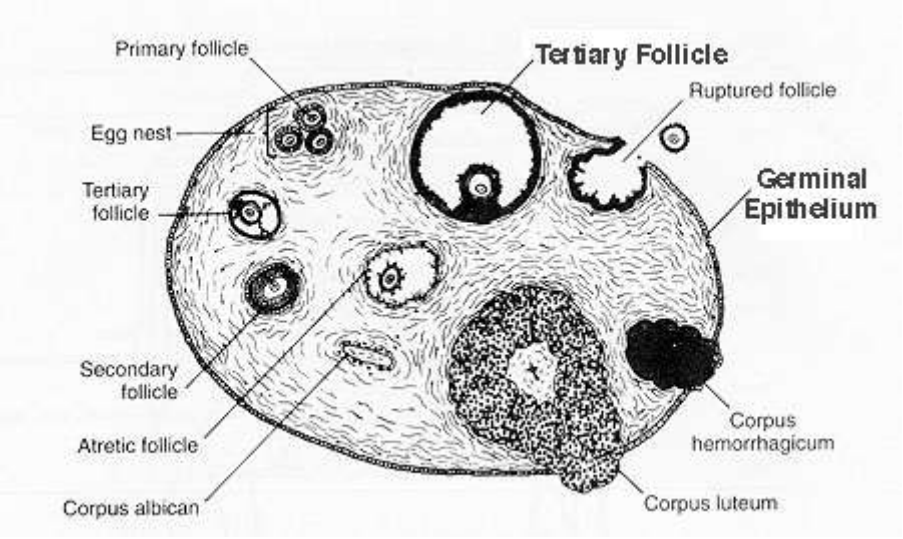
TAG Me **T**helarche **A**drenarche (pubarche) **G**rowth **Me**narche

(for boys it's TAG S)


cholesterol
17 a OH
A
17-20 desmolase
B
P450scc
3 B ol HSD
C
3 B ol HSD
Pregnenolone
17OH Preg
DHEA
Progesterone
17OH P4
A'dione
Testosterone
21 OH'ase
Desoxy corticosterone
Desoxy cortisol
Estrone
Estradiol
11B OH'ase
17 BOHSD
Aromatase
Corticosterone
Cortisol
18 OH'ase
Aldosterone

Ovarian development

- Prepuberty volume – 0.3 – 0.9cm^3
- > 1.0cm^3 indicates puberty has begun
- During puberty – rapid increase in size
- Mean post pubertal volume 4cm^3



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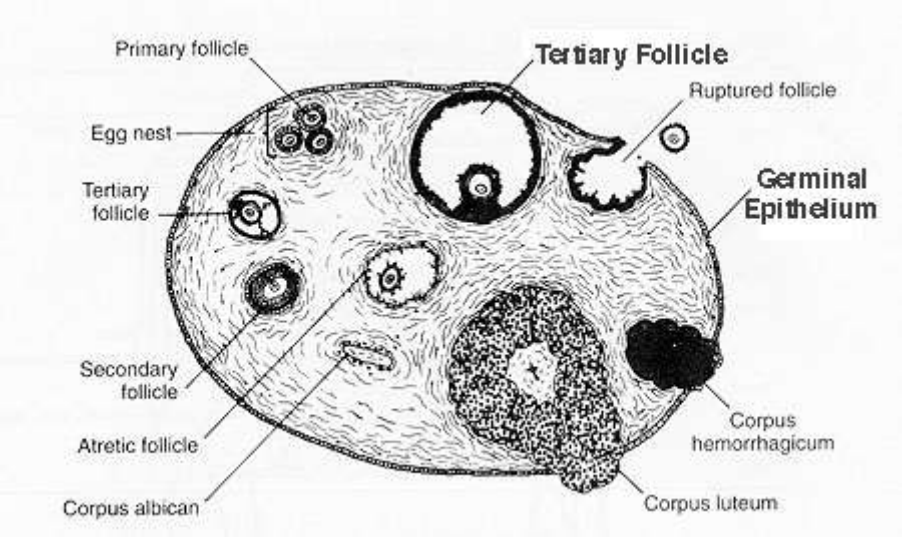


Rising levels of plasma gonadotropins
Stimulate ovary to produce increasing amounts of estradiol
Resulting in secondary sexual characteristics
Breast growth and development
Reproductive organ growth and development
Fat redistribution (hips, breasts)
Bone Maturation

Development of Uterus

- Prepubertal
    - “small” size
    - tear-drop shaped
    - cervix & isthmus account for up to 66% of uterine volume
- Post pubertal
    - “normal” size
    - Pear shaped
    - Uterine body increases in length (max 6 – 8cm) and thickness (3-4 cm)
    - Proportionally, more growth in the body of the uterus than the cervix

Menarche

- During puberty estradiol levels fluctuate widely (reflecting successive waves of follicular development that fail to reach ovulatory stage)
- Endometrium affected by estradiol. Undergoes cycles of proliferation and regression until point where withdrawal of estrogen results in the first menstrual bleed (menarche)
- **Increase of only 4% of final height after menarche**

Pubertal abnormalities

- Delayed
- Early (precocious)

Pubertal abnormalities

- Delayed
    - Hypogonadotropic
    - Hypergonadotropic
- Early (or precocious)
    - Gonadotropin dependent
    - Gonadotropin independent

Pubertal abnormalities

- Delayed
  - Hypogonadotropic **(low to low normal gonadotropins)**
    - Constitutional
    - Genetic causes
    - Medical diseases
    - Neoplastic processes
  - Hypergonadotropic **(elevated gonadotropins)**
    - Congenital
    - Acquired

Delayed Puberty: Hypogonadotrophic

- Constitutional (familial, sporadic)
- Chronic illness (CF, Crohn's Disease, Renal failure)
- Malnutrition (Anorexia, CF, coeliac disease)
- Exercise
- PCOS ?
- Tumors of pituitary/hypothalamus (craniopharyngioma)
- Hypothalamic syndromes (PWS, Laurence-Moon-Biedl)
- Hypothyroidism
- Suppression 2^{o} to hyperthyroidism, hyperprolactinemia, Cushing Syndrome, CAH
- Panhypopituitarism

Delayed Puberty: Hypergonadotropic

- Congenital
  - Gonadal dysgenesis (eg, Turner Syndrome 45 XO)
  - Klinefelter Syndrome (XXY)
- Acquired
  - Irradiation / Chemotherapy
  - Surgery
  - Ovarian torsion
  - Infection
  - Autoimmunity

What is Precocious Puberty?

- Definition - Onset of pubertal development at an earlier age than is expected based upon established normative standards.
  - There is variation in the age of onset of puberty in normal children, particularly in different cultures / racial / ethnic groups
  - In US:
    - < 8 years of age in girls
    - < 9 years of age in boys

In approximately 90% of girls who experience precocious puberty, no underlying cause can be identified—although heredity and being overweight may contribute in some cases. When a cause cannot be identified, the condition is called **idiopathic precocious puberty**. In boys with precocious puberty, approximately 50% of cases are idiopathic.

So what's the problem with Precocious Puberty

- Organic disease
- Genetic disease
- Early sexual maturation
- Shortened adult height *

*30% of girls and nearly half of boys the PP will be <5th percentile for height when they are adults

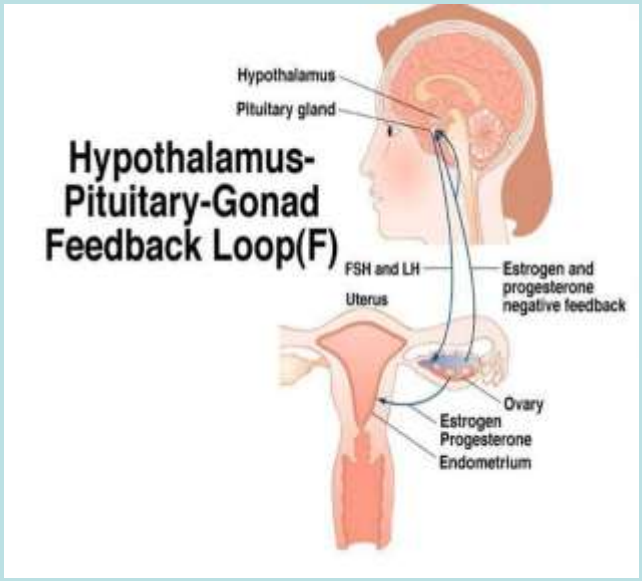
- Isosexual – secondary sexual characteristics c/w the genetic sex of the individual

- Contrasexual (heterosexual) – secondary sexual characteristics NOT c/w with genetic sex of the individual

    Feminization in males

    Masculinization in females

Precocious Puberty



Precocious Puberty

- Onset of secondary sexual characteristics
    - < 8yrs in girls
    - < 9yrs in boys
- 5-6 times more common in girls
- Central (True) PP is **USUALLY** a benign central process – **IN GIRLS**
- Central (True) PP is indicative of **significant pathology in ~ 50% (60%) in boys**

INCOMPLETE PRECOCITY

- Partial (often transient) pubertal development in the absence of other stigmata of puberty
- Slow progression, with little to no change or there is waning of the physical findings
    - Premature thelarche
    - Premature pubarche
    - Premature adrenarche
    - Premature menarche

PREMATURE THELARCHE

- Premature beast development in the absence of other signs of sexual maturation
- Estradiol level ↑↑
- Unilateral or bilateral, without areolar development
- Frequently < 2 Y of age & non progressive
- Follow up should distinguish cases of slow progressing CPP
- Treatment is NOT indicated & subsequent normal puberty occur

PREMATURE PUBARCHE

- THE APPEARANCE OF PUBIC HAIR BEFORE 8 Y OF AGE IN GIRLS
- Early maturation of the normal pubertal adrenal androgen production "Adrenarche"
- It is evidence of premature adrenarche without activation of the HPO axis
- Breast development is absent
- Slightly accelerated growth velocity & advanced skeletal maturation
- Puberty occur normally at the appropriate age
- Diagnosis by exclusion of CAH, androgen secreting tumors & CPP
- 50% of pt. with premature pubarche progress to PCOS
- Late onset CAH may have a similar presentation

PREMATURE ADRENARCHE

- Adrenal tumors
    - RARE
    - Function autonomously
    - ↑ DHEA , DHEAS, testosterone
    - ↑ Cortisol
    - Benign or malignant with poor prognosis

- OVARIAN TUMORS
    - Arrhenoblastoma, lipoid cell tumors
    - ↑ Testosterone
    - Normal DHEA, DHEAS

PREMATURE MENARCHE

- Uncommon
- Rule out serious cause of bleeding
    a. Neonatal period

        Due to withdrawal of estrogen produced by the feto-placental unit

    b. Spontaneous regression of ovarian cysts
    c. Hypothyroidism
    d. McCune Albright Syndrome
- Differential diagnosis
    - Vulvo-vaginitis
    - Foreign body in the vagina
    - Trauma
    - Sexual abuse
    - Vaginal tumors

Adrenarche and Adrenal Androgens

- Besides hypothalamic-pituitary-gonadal axis, adrenal hormones (DHEA, DHEAS) also play important role in puberty
- Levels of DHEA/DHEAS start to increase at 6-8 years
  - Before LH rise or any sex hormone changes
  - Consequence of adrenal maturation and development in process known as ADRENARCHE
  - Precedes onset of puberty by 1-2 years
- Normally leads to appearance of pubic and axillary hair at the onset of puberty.

Adrenarche and Adrenal Androgens

- Do adrenal androgens contribute to maturation of HPG axis and initiation of puberty? → **NO**
- How do we know? 2 clinical reasons
  - Patients with PREMATURE ADRENARCHE (increased adrenal androgens) enter puberty and undergo menarche at normal age.
  - Patients with adrenal insufficiency /Addison's disease (no adrenal androgens) undergo normal puberty when given adequate glucocorticoid and mineralocorticoid.
- Current thinking is that adrenarche and puberty are two distinct and independent processes.

Growth and Puberty

- Growth hormone-releasing factor (GRF) levels and GH secretion increase considerably during puberty, mainly at night
- Amplitude of GH peaks increases in early puberty – growth spurt
- IGF-1 ►important modulator of growth during childhood and adolescence
- Adrenal androgens have little physiological role in normal growth

Growth and Puberty

- GH plays role in pubertal development
- Amplifies ovarian response to gonadotrophins
- IGF-1 enhances gonadotrophin effect on granulosa cells
- Isolated GH deficiency associated with pubertal delay, diminished Leydig cell function and decreased response to chorionic gonadotrophins
- GH administration can restore testicular responsiveness to LH and Leydig Cell steroidogenesis

Precocious Puberty: Gonadotropin dependant

- Idiopathic (sporadic / familial)
- Congenital (Hydrocephalus)
- Acquired (irradiation/surgery/infection)
  - Hypothalamic Hamartoma (most common)
  - Brain Tumors
    - Astrocytomas, ependymomas, optic tract tumors
    - Germinomas (via hCG)
- Hypothyroidism
- Rare / unusual causes (eg, Russell Silver Syndrome -- methylation abnormalities 7 & 11 ??)

Precocious Puberty Gonadotrophin Independent

- Normal pattern (ie, the sequence) of puberty is absent
    - Virilization of female (CAH)
    - Adrenal Tumor
    - Ovarian Tumor
    - McCune Albright Syndrome
    - Exposure to exogenous gonadal steriods

Approach to the patient (& parents)

- Full history of previous growth and development
- Record timing and sequence of physical milestones and behavioral changes of puberty
- Full medical and surgical history; including full nutritional history
- Family hx of early or delayed puberty
- Family hx of any genetic disease

Approach to the patient (& parents)

- Plot height, weight, BMI and growth velocity
- Compare with old measurements if available
- Examine all systems: endocrine / neurology
- Optic fundi, visual fields, sense of smell
- Genitalia, body habitus, stage of puberty

Examination

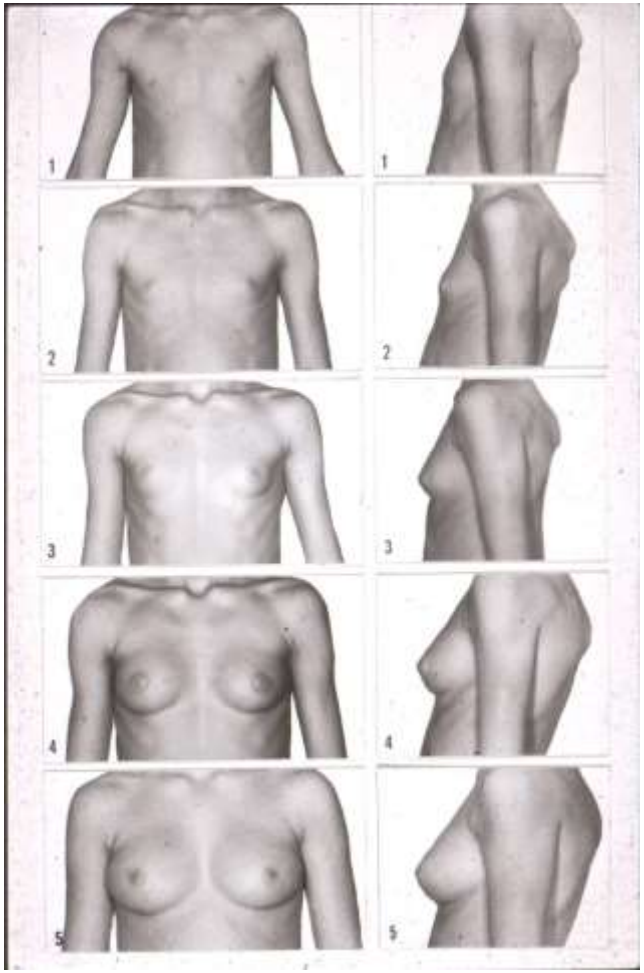
- Examine in supine position. Helps differentiate between true breast enlargement vs adiposity
- Genital exam (visual observation): pubic hair, changes in vaginal mucosa.
- Clitoromegally suggests androgen excess and virilization
- Acne
    - “mild” – probably normal
    - Rapid onset / “severe” - may suggest androgen excess
- Limited vaginal examination – in the office
- Rectal exam – not necessary

Physical Changes

- Marshall and Tanner described five stages of pubertal development
- Reflect progression in changes of the external genitalia and of sexual hair
- Secondary sexual characteristics
  - Mean age 10.5yrs in girls
  - Mean age 11.5 – 12yrs in boys

Pubertal Stages (Tanner) Female

Stage	Physical finding
Tanner 1	Prepubertal
Tanner 2	Early development of subareolar breast bud +/- small amounts of pubic and axillary hair
Tanner 3	Increase in size of palpable breast tissue and areolae, increased dark curled pubic/axillary hair
Tanner 4	Breast tissue and areolae protrude above breast level. Adult pubic hair but no spread to medial thighs.
Tanner 5	Mature adult breast. Pubic hair extends to upper thigh



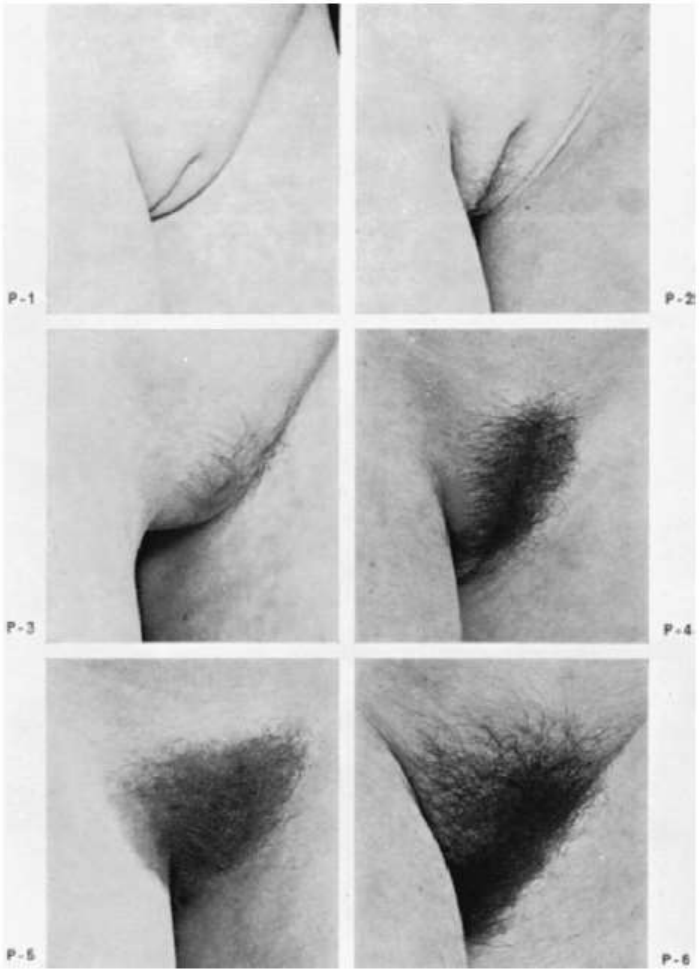
Tanner I – Preadolescent stage
No breast buds; elevation of papillae only

Tanner II – Breast bud stage; 1st sign of puberty
Breast and papilla raised as a small mound

Tanner III – Further enlargement of breast/areola
with no separation of their contours

Tanner IV – Areola and papilla project to form a
secondary mound above the breast level

Tanner V – Mature stage; projection of papilla only



Tanner I – Preadolescent stage
No pubic hair

Tanner II – Sparse, long, downy, slightly-pigmented straight hairs appearing chiefly along labia

Tanner III – Pubic hair is longer, darker, and curlier. Hair spreads sparsely over the pubic region.

Tanner IV – Hair is adult in type but covered area is less than in adults. No spread to medial thigh.

Tanner V – Mature stage; hair is adult in size and type. Distributed in classic inverted triangular pattern with spread to the medial thigh.

Investigations

- Laboratory tests
  - LFT's
  - TFT's
  - gonadotropins
  - Estradiol
  - Testosterone
  - 17 OHP / 11 DOC
  - Adrenal androgens
  - Prolactin
  - GnRH assay
  - Beta –HCG
  - Karyotype if indicated

Diagnostic Imaging

- Pelvic USS (ovarian tumors / cysts)
- Testicular USS (tumor)
- Adrenal USS (MRI / CT better if tumor considered)
- Bone Age
- Brain MRI in all males and patients with neurological signs or symptoms

Management

- Treat systemic disease
- Psychological support
- Promote puberty / growth if necessary
  - Low dose testosterone
  - Ethinyloestradiol

Issues

- Treatment of the cause e.g. cranial neoplasm
- Behavioral difficulties – psychology
- Reduce rate of skeletal maturation (early growth spurt may result in early epiphyseal closure and reduced final adult height)
  - Halt or slow puberty (GnRH analogue)
  - Inhibit action of excess sex steroids

Central Precocious Puberty

- Alternatively, a GnRH stimulation test or GnRH agonist (leuprolide) stimulation test can be used to aid diagnosis
  - Boys: Brisk LH response (LH peak>5-10 IU/L) with predominance of LH over FSH an hour after administration
  - Girls: “Pubertal” estradiol level 20-24 hours after stimulation with leuprolide is diagnostic of CPP
- Bone age is variably advanced (usually >2-3 SD above mean)
- Pelvic ultrasound shows enlarged ovaries (with or without follicles) and uterus that approaches pubertal size
- Brain MRI may show physiologic enlargement or CNS pathology

Peripheral Precocious Puberty (Girls)

- Isosexual (Feminizing) Conditions
  - McCune Albright Syndrome
  - Autonomous ovarian cysts
  - Ovarian tumors/Granulosa-theca cell tumors/Teratoma
  - Feminizing adrenocortical tumor
  - Exogenous estrogens
- Heterosexual (Masculinizing) Conditions
  - Congenital Adrenal Hyperplasia
  - Adrenal tumors/Ovarian tumors
  - Exogenous androgens

Central Precocious Puberty (Treatment)

- Candidates for treatment
  - All boys and girls with rapidly progressive CPP
  - Those born SGA and CPP (usually in conjunction with GH)
  - Patients with early menarche (for psychological/social reasons)
- Patients with slowly progressive CPP can be monitored
- Treatment is based on observation that gonadotropin release from pituitary requires a pulsatile stimulation of GnRH
  - GnRH agonists – more potent and longer duration of action
  - It desensitizes pituitary to endogenous GnRH and halts puberty

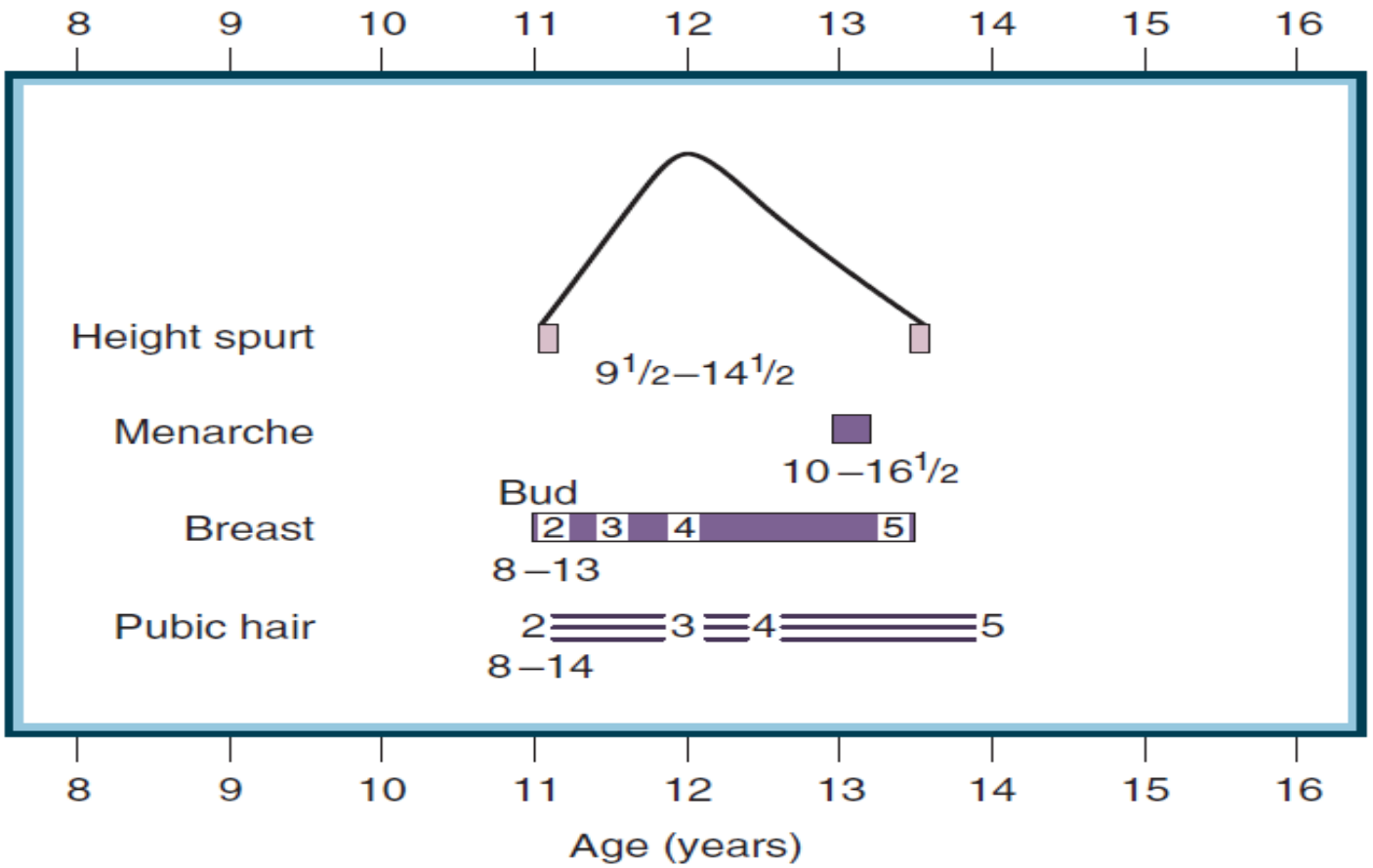
Lupron Therapy for CPP

- Most common formulation is Lupron Depot Ped at 0.25-0.3mg/kg (7.5mg or 11.25mg) dose given every 4 weeks
  - There is also a 3-month formulation and 1-year subcutaneous implantable (histrelin) form as well.
- Benefits of Lupron therapy:
  - Causes cessation of pubertal advancement and deceleration of growth (to age-appropriate rate)
  - Menses, if present, ceases; pubic hair remains stable.
  - Pelvic ultrasound shows decrease in ovarian and uterine size.
  - Serum LH levels are suppressed.
  - Estradiol and testosterone levels return to prepubertal range.

Lupron Therapy for CPP

- There are no adverse effects reported with Lupron use.
  - Puberty returns promptly after cessation of therapy.
- Menarche occurs usually by 18 months after discontinuation of treatment
- Aside from setting of SGA, the use of GH in patients with CPP is controversial.
  - No clear benefit has been demonstrated.

Pubertal Development by Age



Breast development – Avg 8.9 to 10.0 years
PH development – Avg 8.8 to 10.5 years
Height acceleration – starts inT2; peaks T3
It starts earlier but shorter than in males
Menarche – Avg 12.2 to 12.9 years

How Would You Evaluate?

- Girls with premature pubic hair w/o breast development?
  - Labs: DHEAS, 17OHP, free testosterone,
  - Imaging: Bone age, pelvic US, adrenal ultrasound/CT/MRI
  - Differential Dx: CAH, adrenal tumor, premature adrenarche
- Girls with premature pubic hair AND breast development?
  - Recognize that this is precocious puberty
  - Labs: FSH, LH, estradiol,
  - Imaging: Bone age, pelvic US, Brain MRI

TREATMENT OF CPP

- Purpose of treatment
- To gain normal adult height
- (Pt with CPP will have an ultimately shortened adult height)
- Amelioration of the psychosocial consequences of ↑ size ⇨ unrealistic adult expectations

- Who should be treated?
- Pt. with early puberty (<6Y) , accelerated growth & advanced skeletal age should be treated, (bone age >2Y>chronologic age).
- Menarche <8Y
- Pt. with early onset but without indication that puberty is advancing should be followed up

Premature thelarche / pubarche

- Thelarche – beginning of breast development
- Pubarche – first appearance of pubic hair
  - (more common in certain populations e.g asian / afro-caribbean)
- More common than true precocious puberty
- Benign variants
  - breast development in girls < 3yrs with spontaneous regression
  - Pubic hair in boys and girls < 7yrs due to adrenal androgen secretion in middle childhood

Precocious Puberty

- Precocious puberty is classically defined by onset of secondary sexual characteristics
  - Breasts before age 8 in girls and
  - Testicular development before age 9 in boys
  - In African-American and Hispanic girls, age cutoff is before 7 years of age
- It is categorized based on etiology
  - Central precocious puberty (CPP)
  - Peripheral precocious puberty (PPP)

Categories of Precocious Puberty

- Central PP – activation of the hypothalamic-pituitary-gonadal (HPG) axis
    - Always isosexual
- Peripheral PP – appearance of secondary sex characteristics without HPG axis activation
    - Can be isosexual or contrasexual
- Be aware though that Peripheral PP can induce activation of HPG axis and trigger onset of central PP (i.e. treated CAH)

Central (GnRH Dependent) Precocious Puberty

- Idiopathic
- Organic Brain Lesion
  - Hypothalamic Hamartoma (most common)
  - Brain Tumors
    - Astrocytomas, ependymomas, optic tract tumors
    - Germinomas (via HCG)
  - Hydrocephalus
  - Severe Head Trauma
  - Myelomeningocoele
- Prolonged and untreated hypothyroidism

Combined Peripheral and Central Precocious Puberty

- Treated Congenital Adrenal Hyperplasia
  - Excess of testosterone bone age advancement CPP
- McCune Albright Syndrome (late)
  - Mutation in a subunit of Gs protein found in FSH, LH receptors
  - Constitutive activation of FSH, LH receptors in ovary/testis
  - Estradiol/testosterone advances bone age and can cause CPP
- Familial male precocious puberty
  - Mutation in LH receptor
  - Constitutive production of testosterone in absence of seminiferous tubule development
  - Testosterone can be in pubertal range and result in bone age advancement and CPP