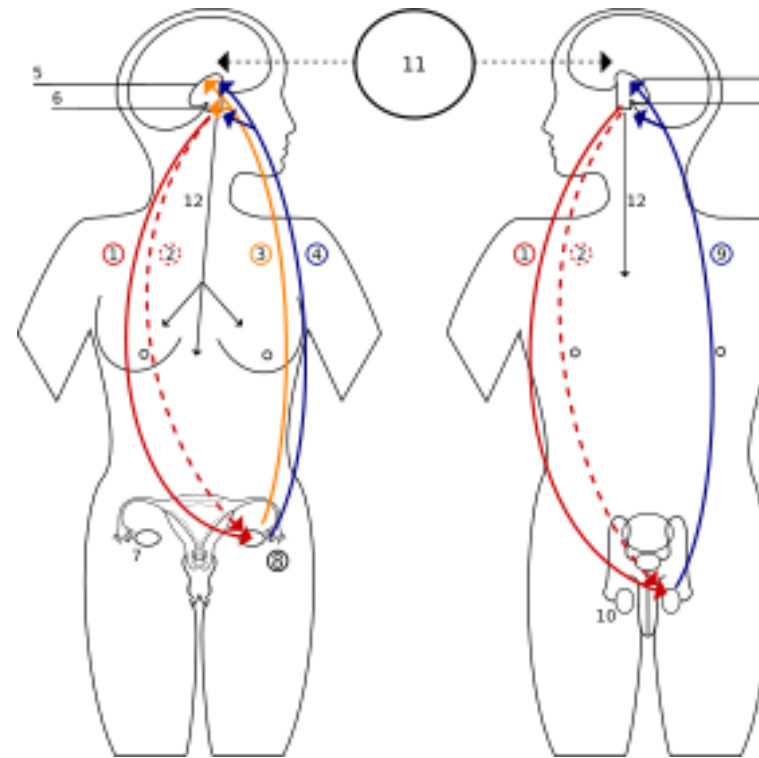


Normal & Precocious Puberty

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Objectives

- Describe the normal progression through puberty and normal changes.
- Define precocious puberty (PP).
- Identify and describe the causes and clinical findings of PP (central vs. peripheral).
- Develop an approach to a child with PP via history, clinical examination (Tanner staging), investigations (hormonal and bone age), and treatment.

Puberty

- The stage between the onset of secondary sexual characteristics & completion of physical maturity.
- The period in which reproductive capability is attained, manifested by spermatogenesis in males & ovulation in females.

Occurs between 8 - 13 yrs in girls.

Occurs between 9 - 14yrs in boys.

Puberty

BRAIN



INHIBITORY
NEUROTRANSMITTERS



HYPOTHALAMUS

GnRH



PITUITARY GLAND

LH / FSH

GONADS



TESTOSTERONE / E2
ACTIVIN
INHIBIN

Normal secondary sexual stages of Puberty

- **In girls (stages by following sequences):**
 - Thelarche = breast development (usually appeared in one side followed by the other side, painful when it appears).
 - Adrenarche = axillary, pubic hair appearances, acne, oily skin and hair.
 - Growth spurt usually happens just before menarche (with first menarche, 95% of height has achieved).
 - Menarche = first period which is usually by age 11-13 years (usually 2-3 years from breast development).
- **In boys (stages by following sequences):**
 - Testicular enlargement > 4ml volume measured by orchidometer).
 - Adrenarche = axillary, pubic hair appearances, acne, oily skin and hair.
 - spermatogenesis usually by age 15 years.
 - Growth spurt happened prior and continue after spermatogenesis.

Normal Puberty influencing factors

- Genetics: 50-80% of variation in pubertal timing.
- Environmental factors including:
 - Nutritional status (over nutrition enhances puberty & vice versa).
 - Exercise (athletes tend to have late puberty).
 - Weather (hot weather tend to accelerate age of puberty).
 - Exogenous hormonal disruptors (e.g. usage of plastics, nylon or food products “meat and plants” rich with oestrogen).
 - Obesity as adipose tissues produces Leptin peptide which has stimulating effects on the hypothalamus with earlier onset of puberty.

Pubertal changes (girls):

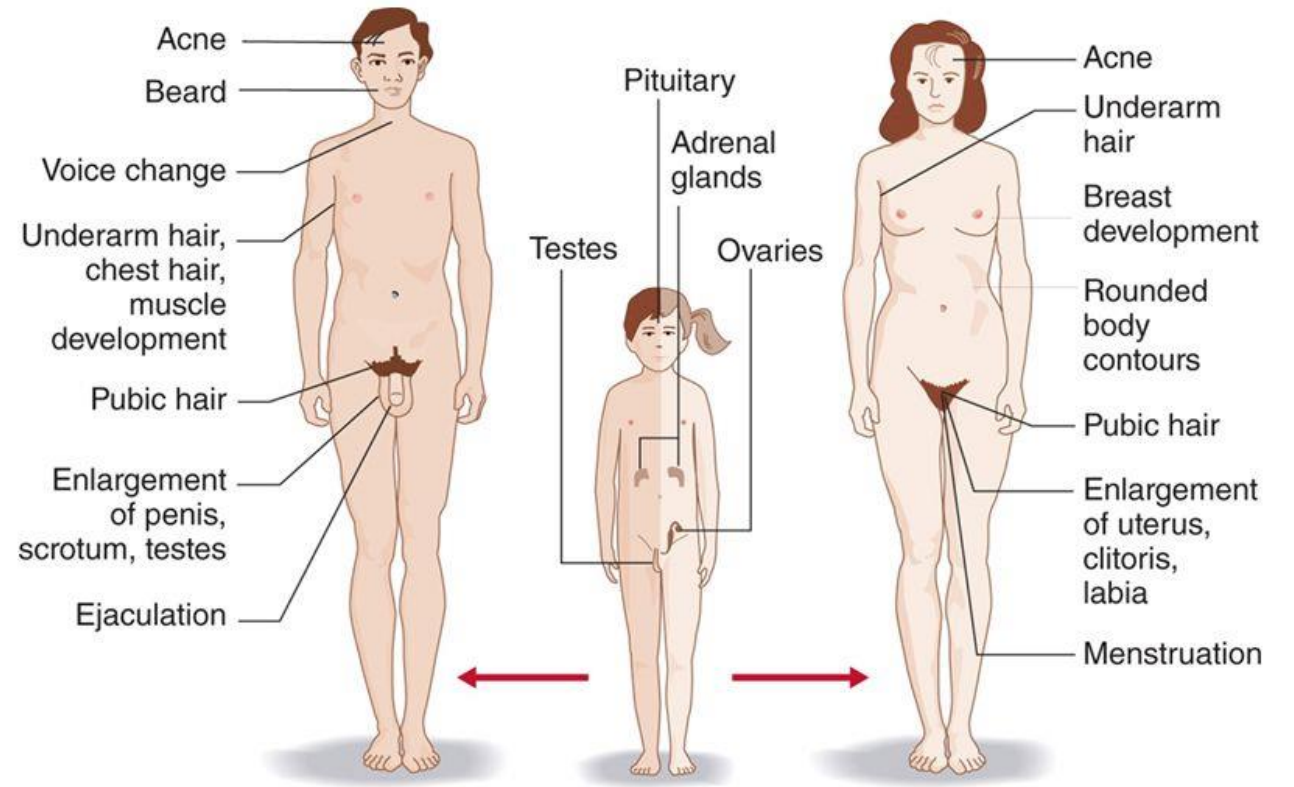
- Breast enlargement is the first sign.
- Secondary sexual characteristics appearances.
- perspiration and characteristic body odour (release of volatile acids= glutaric acid).
- Increased adipose tissue in feminine regions (breast, buttocks & upper thighs).
- Widening of the pelvic bone (gynecoid pelvis).
- Increase carrying angles of the arms.
- Growth spurts (happened just before the first period).
- Menarche (average age of 11-13 years)
- Bone density is increasing rapidly.
- Behavioral changes e.g. shy, isolated, very sensitive, easy tearing.

Pubertal changes (Boys):

- Enlarged testes (> 4ml) is the first sign.
- Secondary sexual characteristics appearances.
- perspiration and characteristic body odour (release of volatile acids= glutaric acid).
- Increase muscle mass & decreased adipose tissue.
- Widening of the shoulders.
- Gynecomastia in 60 % which disappears within 2 years.
- Growth spurts (around age of 13.5 years)
- Sperm production (average age of 14- 15 years)
- Bone density is increasing rapidly.
- Behavioral changes e.g. aggressiveness, hard-minded, self dependent, loves fighting.

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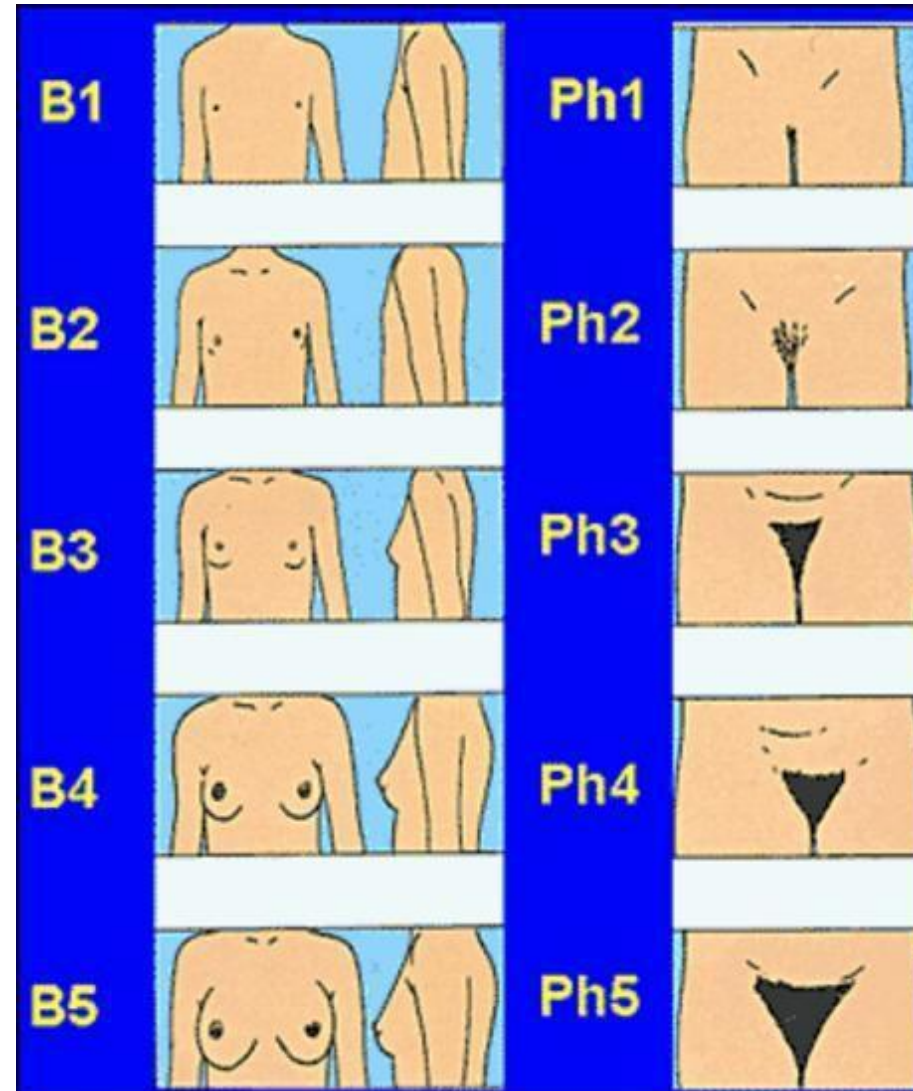
Puberty



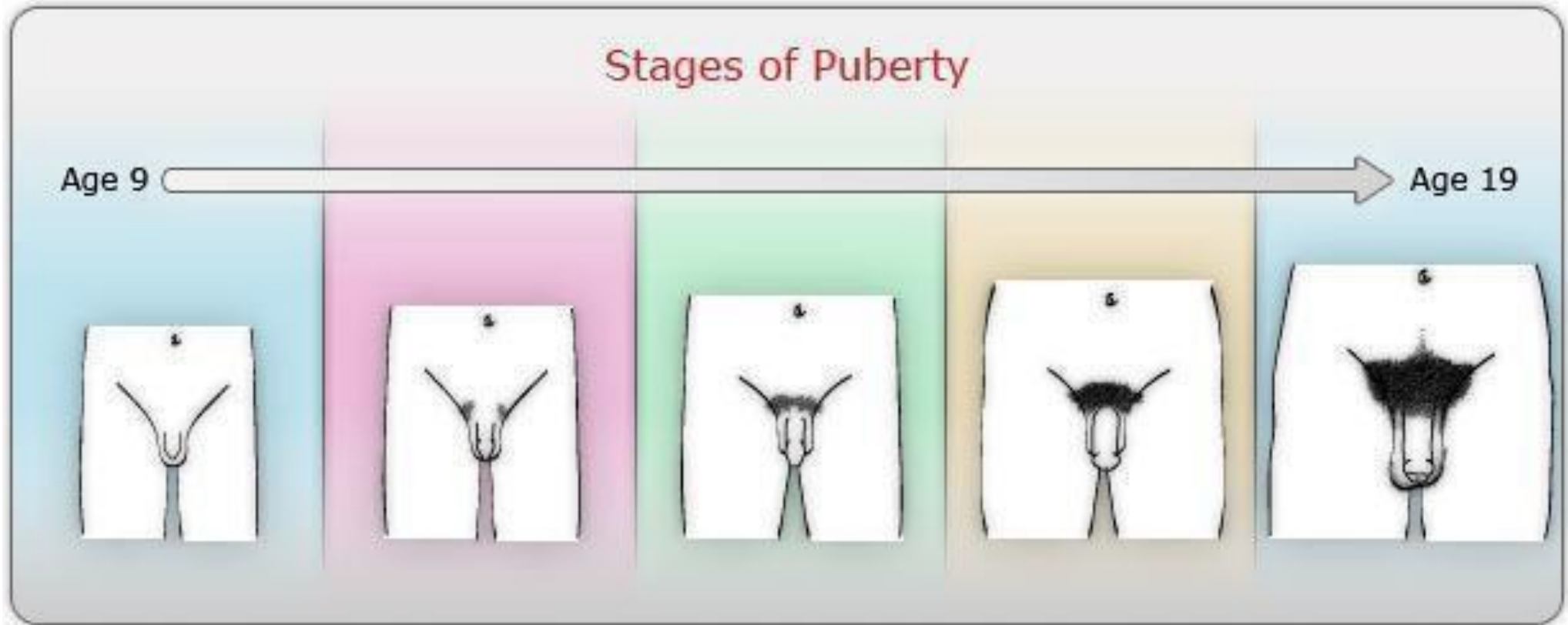
Tanner staging of Puberty

- Dr. Tanner (British citizen) has described five stages of puberty in both sexes.
- Stage 1 is prepubertal, while stage 5 is full adult.
 - In females: 5 stages for breast development & another 5 stages for Pubic hair development.
 - In males: 5 stages for genital development & another 5 stages for Pubic hair.

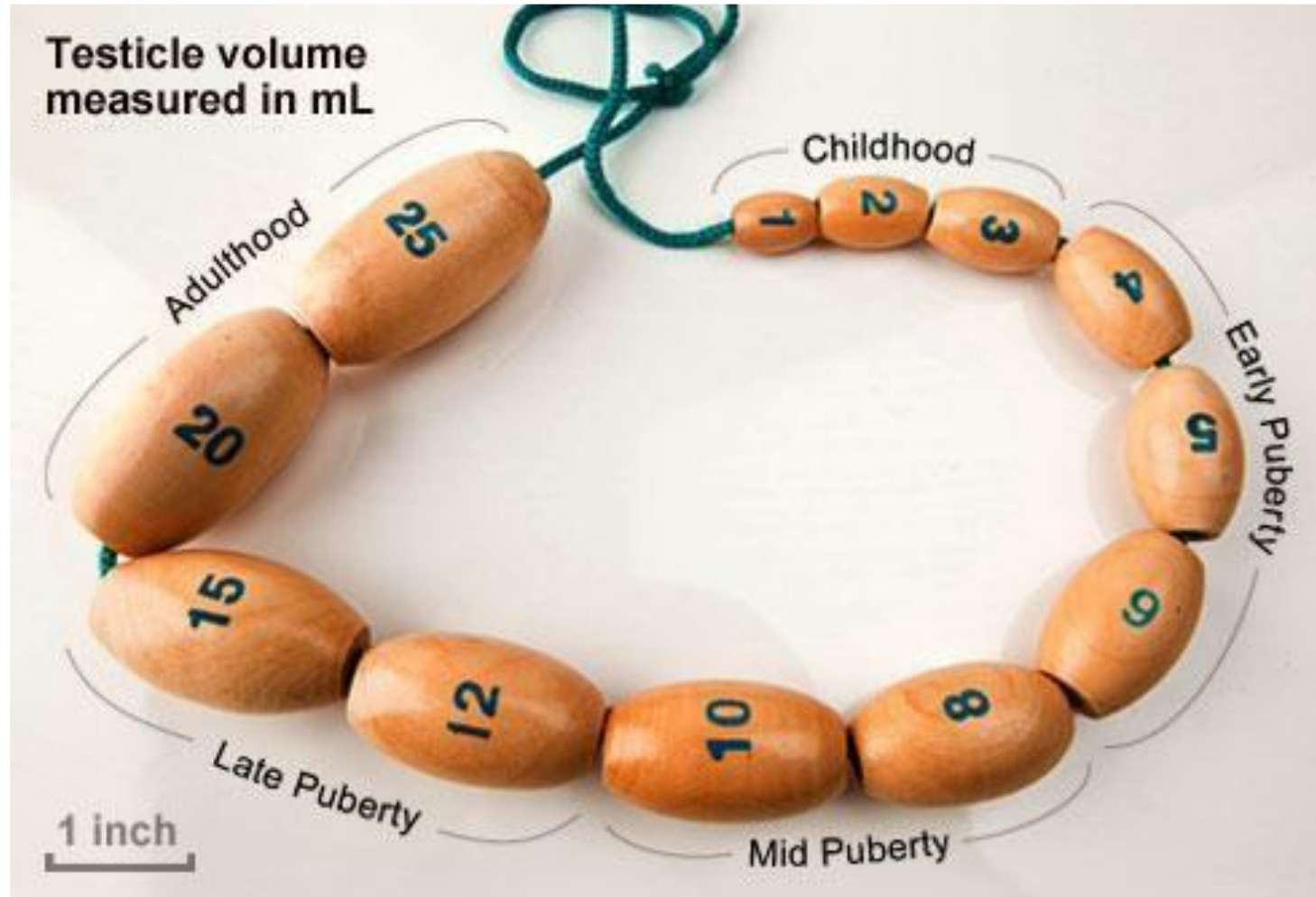
Tanner stages in Females



Tanner stages in Males



Orchidometer to measure testicular volume



Precocious puberty

- In girls, defined as onset of puberty "breast enlargement" before age of 8 years.
- In boys, defined as onset of puberty "testicular enlargement" before age of 9 years.
- 5 times more common in girls than boys.

Types

- Central, True, GnRH dependent
 - 85-90% of cases (major type)
- Peripheral, Pseudo, GnRH Independent
 - 10 - 15 % of cases (not major type)
- Isolated Forms (Benign in nature)
 - Thelarche
 - Adrenarche / Pubarche

Central Vs Peripheral Precocious Puberty

- Central “True, GnRH-dependent” results from premature activation of Hypothalamus-Pituitary-Gonadal axis like the true mechanism of puberty but the axis was activated prematurely.
- Peripheral “Pseudo, GnRH-independent” , Hypothalamus-Pituitary-Gonadal axis was not activated, rather sex hormones were released from peripheral tissues (Adrenal gland, gonads or ectopic tissues) outside the central nervous system.
- Central precocious puberty usually the pathology is idiopathic or CNS cause, while the peripheral type always there is pathology outside CNS causing sex hormone secretion.
- Central precocious puberty all pubertal axis hormones (LH, FSH and sex hormones will be in pubertal range), while in peripheral type (LH & FSH values will be low “prepubertal” and only sex hormones will be high levels).

Central Vs Peripheral Precocious Puberty

	Central type	Peripheral type
H-P-G axis	Activated axis	suppressed
LH & FSH	Adult values	Pre-pubertal
Sex steroids	High	High
Gonads	Pubertal size	Small in size (unless tumor)

Central, True, GnRH dependent

Etiology

- Idiopathic
 - most girls (90 %).
- Secondary
 - most boys (70-80%).

Pathological causes of central precocious puberty

CNS disorders

- Hypothalamic Hamartoma.
- Glioma (NF-1).
- Astrocytoma.
- Craniopharyngioma.
- Ependymoma, germinoma.
- CNS radiation therapy.
- Post trauma (surgery).

Pathological causes of central precocious puberty

- CNS infections (meningitis, encephalitis & brain abscesses).
- Mental retardation.
- Hydrocephalus.
- Prolonged sex steroid exposure associated with peripheral puberty.

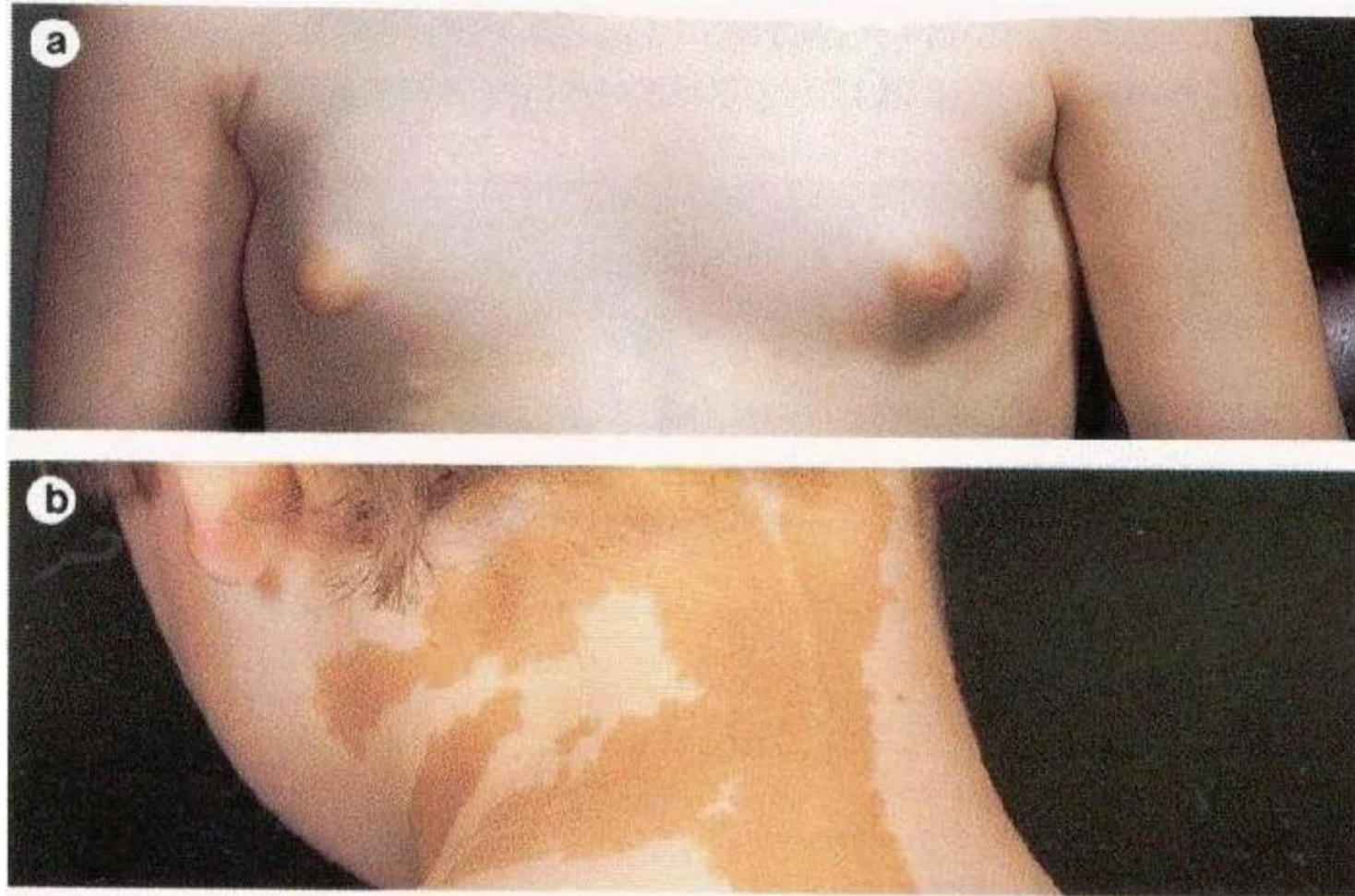
Pathological causes of Peripheral precocious puberty

- Gonadal: McCune-Albright syndrome, ovarian / testicular tumor, ovarian cyst.
- Adrenal: Non classical CAH, tumors.
- Ectopic: hCG secreting tumors
 - Germinoma, Hepatoblastoma.
- Exogenous source of hormone.
- Familial male dependent (Testotoxicosis).

Exogenous source of estrogens



McCune Albright Syndrome



Variants of normal puberty

- Isolated benign Thelarche
- Isolated benign Adrenarche (Pubarche)

Isolated Benign Thelarche

- Premature breast enlargement with absence of growth spurt.
- Bone age is not accelerated.
- Pre-pubertal levels of LH, FSH & estradiol.
- Pre pubertal pelvic US findings.
- Onset between 6m to 4 years of age.
- Increased sensitivity of the breast tissue to low levels of sex steroids.
- Benign nature and need no therapy.

Isolated benign Adrenarche

- Occurs when the adrenal androgen production is turned on prematurely in the absence of Gonadal activation.
- Premature appearance of pubic & axillary hair, acne, body odor & oily skin & hair.
- Idiopathic.
- Benign nature with no treatment.
- We need to exclude other causes of hyperandrogenism especially non classical CAH.

Evaluation of Precocious Puberty

- History.
- Physical examination.
- Growth percentiles.
- Calculation of target height
- Bone Age assessment.
- Basal LH, FSH and sex steroids.
- GnRH stimulation test.

History

- Age when secondary sexual development were noted?
- Any family history of early puberty?
- Age of parent's puberty?
- Any recent acceleration of height (growth spurt).
- Symptoms of increased intracranial pressure (headache, dizziness, nausea, vomiting, blurred visionetc.)
- Order of appearances of secondary features?
- Virilization symptoms?
- Isolated pubic/ axillary hair appearance?
- Body odor?
- Breast enlargement?
- Vaginal discharges & menarche?
- Cyclical mood changes?
- Medications (any sex hormone containing medication)?

Examination

- Tanner staging.
- Vital signs including blood pressure.
- Assessment of growth percentile & height velocity.
- Degree of virilization (if present).
- Testicular volume measurement (orchidometer).
- Looking for hyperpigmentation (non classical CAH).
- Clitoromegaly in girls indicate abnormal androgen.
- Visual field assessment & fundoscopy.
- Abdominal examination looking for any mass.
- Skin (café-au-lait patches in McCune –Albright syndrome, NF-1)

Investigations

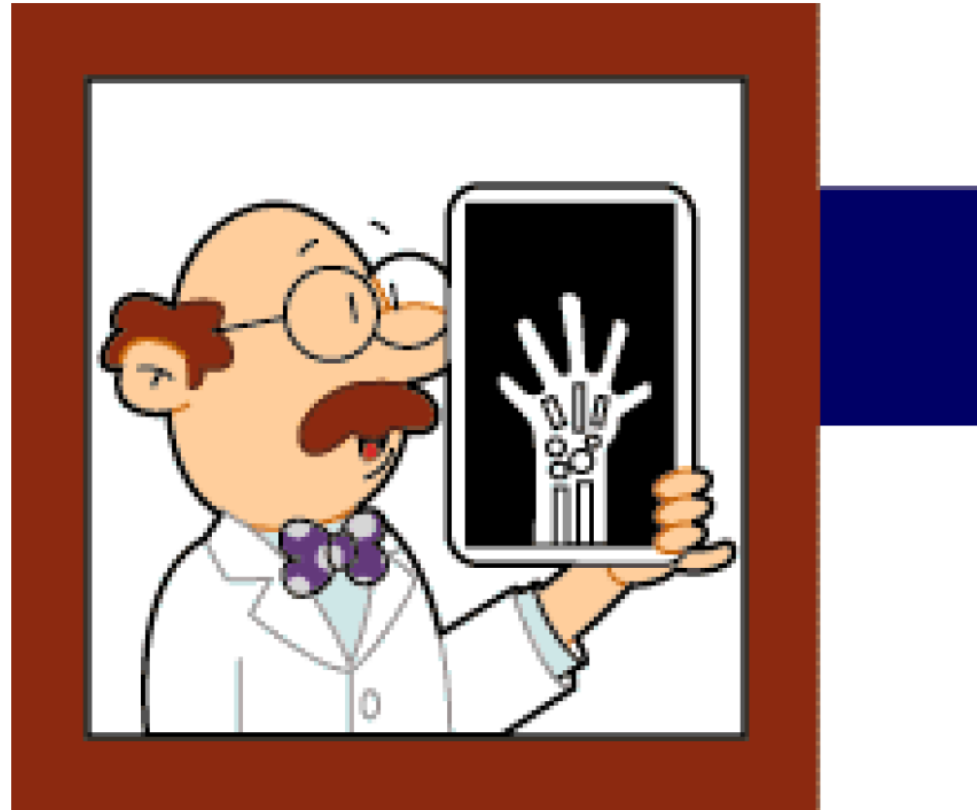
- Crucial Investigations should include initially to differentiate between central and peripheral types:
 - Basal LH, FSH and sex steroids
 - GnRH stimulation test
- In central type, LH& FSH levels are pubertal level, while in peripheral both LH & FSH is prepubertal level.
- hCG : Hepatoblastoma, germ cell tumor.
- Inhibin : Ovarian granulosa cell tumor.
- 17 OHP : Non - classical CAH.
- Adrenal Androgens (androstenedione, DHEA, DHEAS & testosterone)

Investigations

- Radiological investigations depending on type of precocious puberty.
 - Bone age (advanced bone age in both types).
 - MRI Brain: CNS tumors especially for hypothalamic hamartoma.
 - U/S Testes (testicular tumors, familial testotoxicosis).
 - Pelvic U/S (ovarian cyst or tumors).
 - Adrenal ultrasound (non classical CAH, Adrenal tumor).
 - Abdominal ultrasound (ectopic sex hormone producing tumor).

Bone Age

A radiograph of the hand and wrist to determine bone age is a quick and useful means to estimate the likelihood of precocious puberty and its speed of progression



Final adult height

- Puberty usually completed within 3 - 4 years of onset.
- Left wrist x-ray to assess bone age.
- Final adult height. results from complete fusion of epiphyses.
- Occurs approx. 1 yr. after menarche.



Treatment of central Precocious Puberty

- How early is the onset of puberty?
- How much advancement of the bone maturation?
- What is the predicted adult height (PAH)?
- Comparison of PAH to MPH ?
- How fast the progression of physical changes?
- Familial / social issues.

GnRH agonist

Treatment of underlying pathology

Goals of treatment

- Decrease the progression of pubertal changes.
- Decrease bone maturation.
- Increase the predicted final adult height.
- Psychosocial and behavioral therapy.

Treatment could be with GnRH agonist alone or with combined GnRH agonist and GH depending on predicted adult height calculation and how advanced bone age.

Treatment of CPP

- GnRH agonist
- Treatment of underlying pathology.

Treatment of peripheral type

- Medroxyprogesterone acetate (Provera).
- Ketoconazole (rarely to be used).
- Aromatase enzyme inhibitors.
- Androgen antagonists.

