Normal & Precocious Puberty

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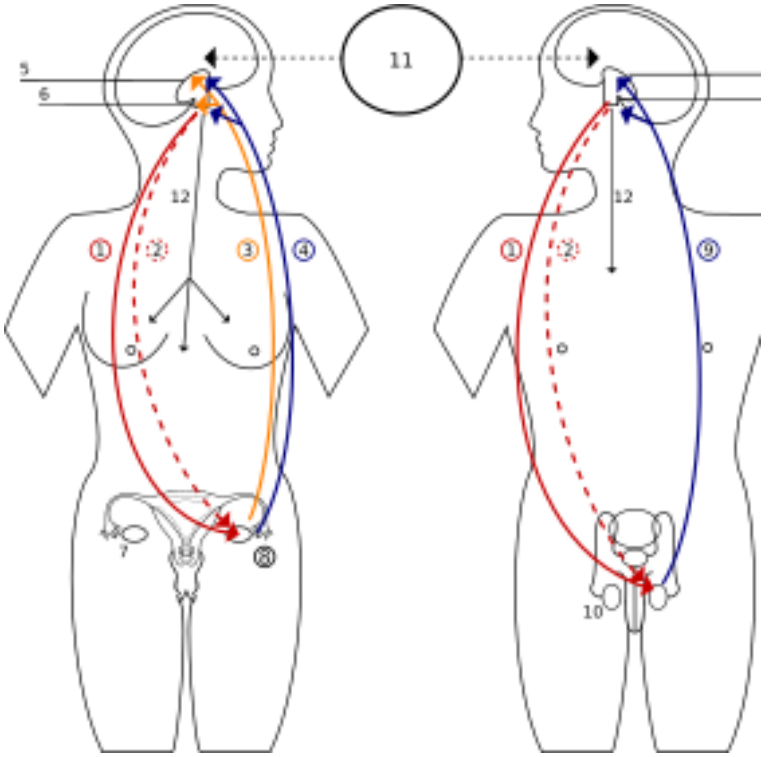


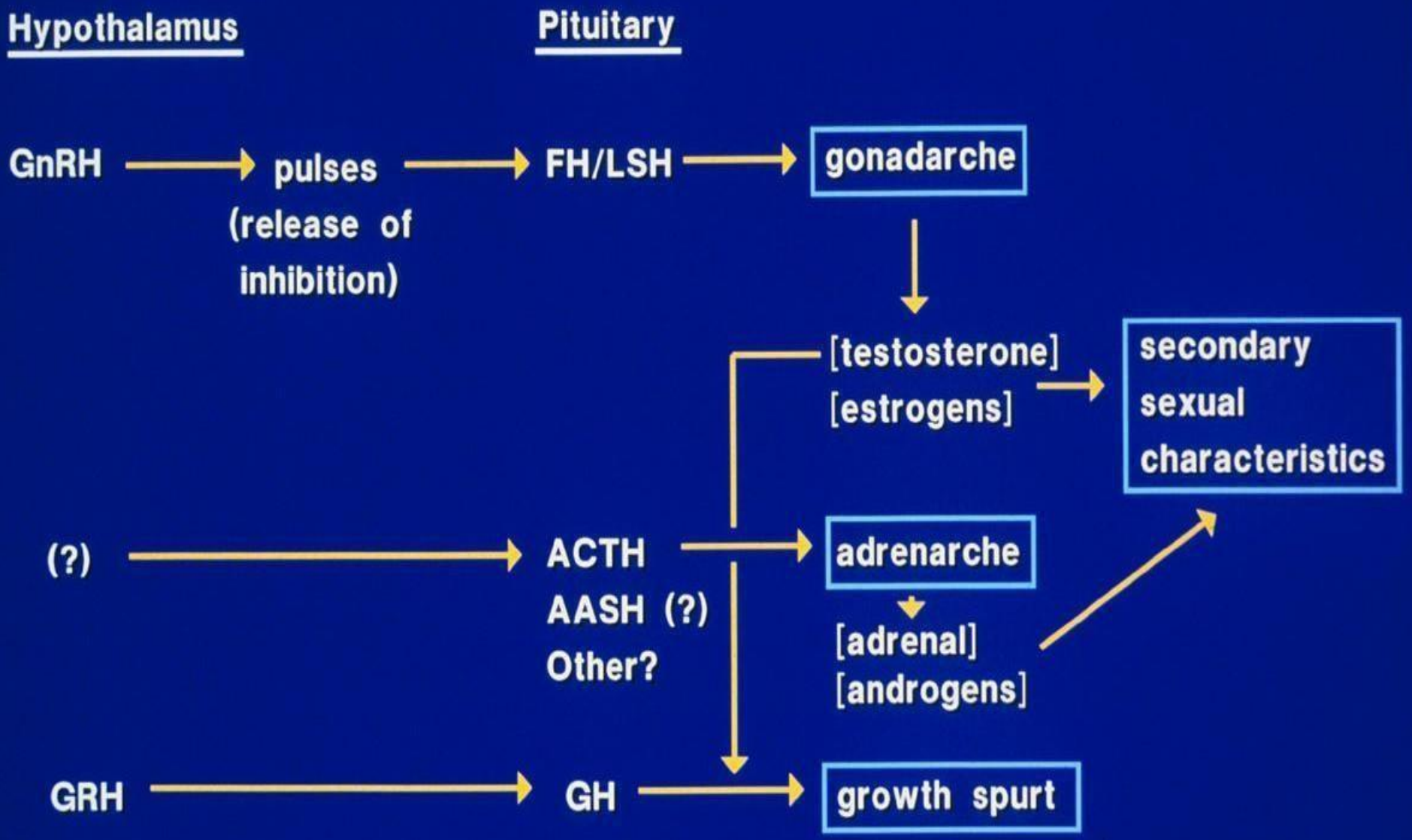
Puberty

- 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.

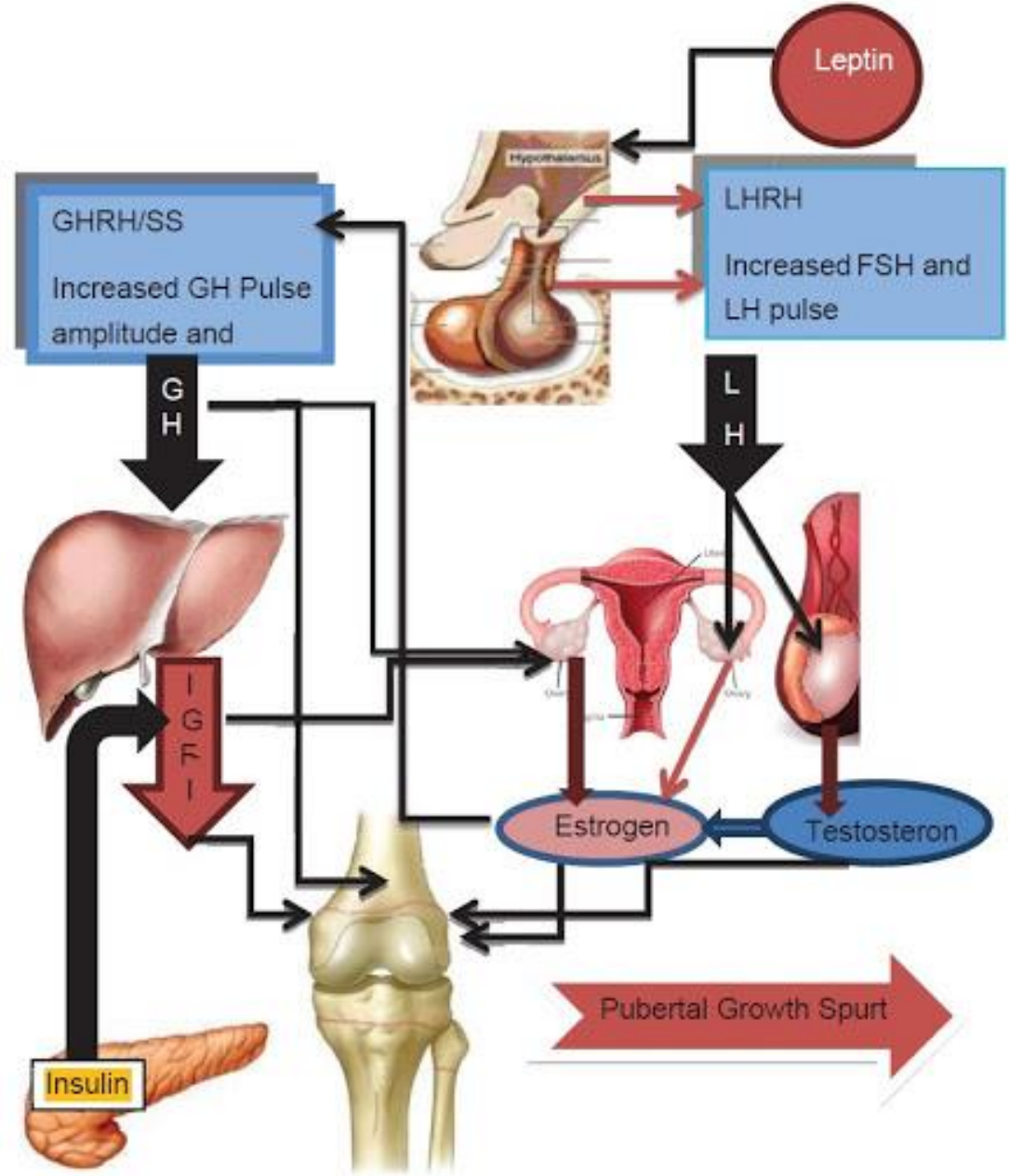
Puberty


Hypothalamus
Pituitary
GnRH
pulses
(release of
inhibition)
FH/LSH
gonadarche
[testosterone]
[estrogens]
secondary
sexual
characteristics
(?)
ACTH
AASH (?)
Other?
adrenarche
[adrenal]
[androgens]
GRH
GH
growth spurt

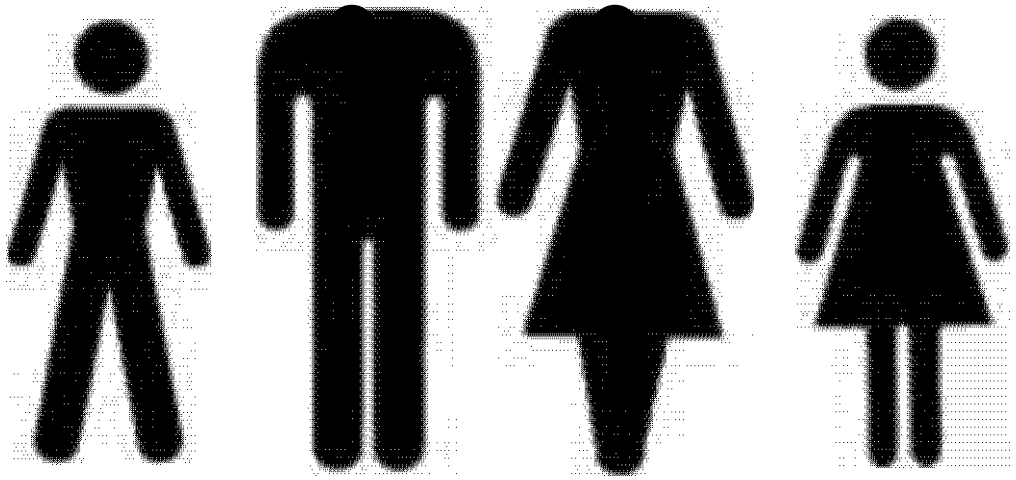
Puberty: Influencing factors

- Genetics: 50-80% of variation in pubertal timing.
- Environmental factors: nutritional status, environmental hormonal disruptors e.g. usage of plastics, nylon or food products rich with estrogen.
- Obesity: as obese children tend to have earlier puberty as their adipose tissues produces Leptin peptide which has stimulating effects on the hypothalamus.

Obesity & Puberty

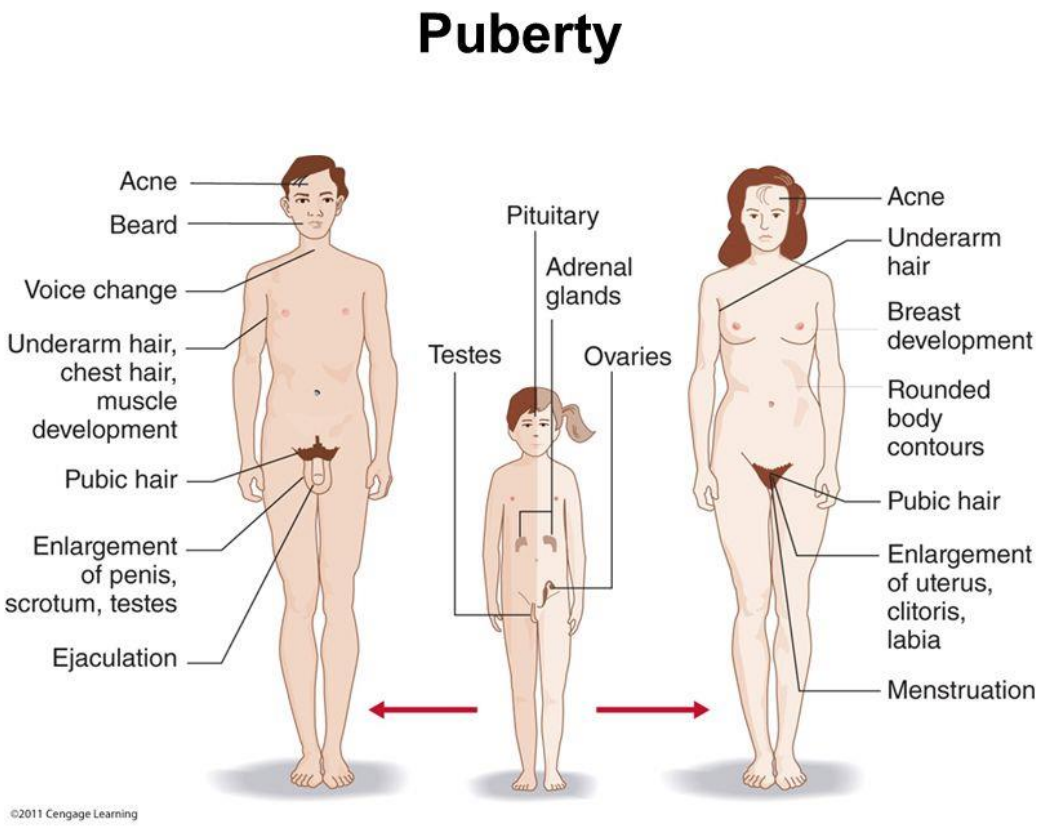


Exogenous sources of estrogens



Changes during puberty

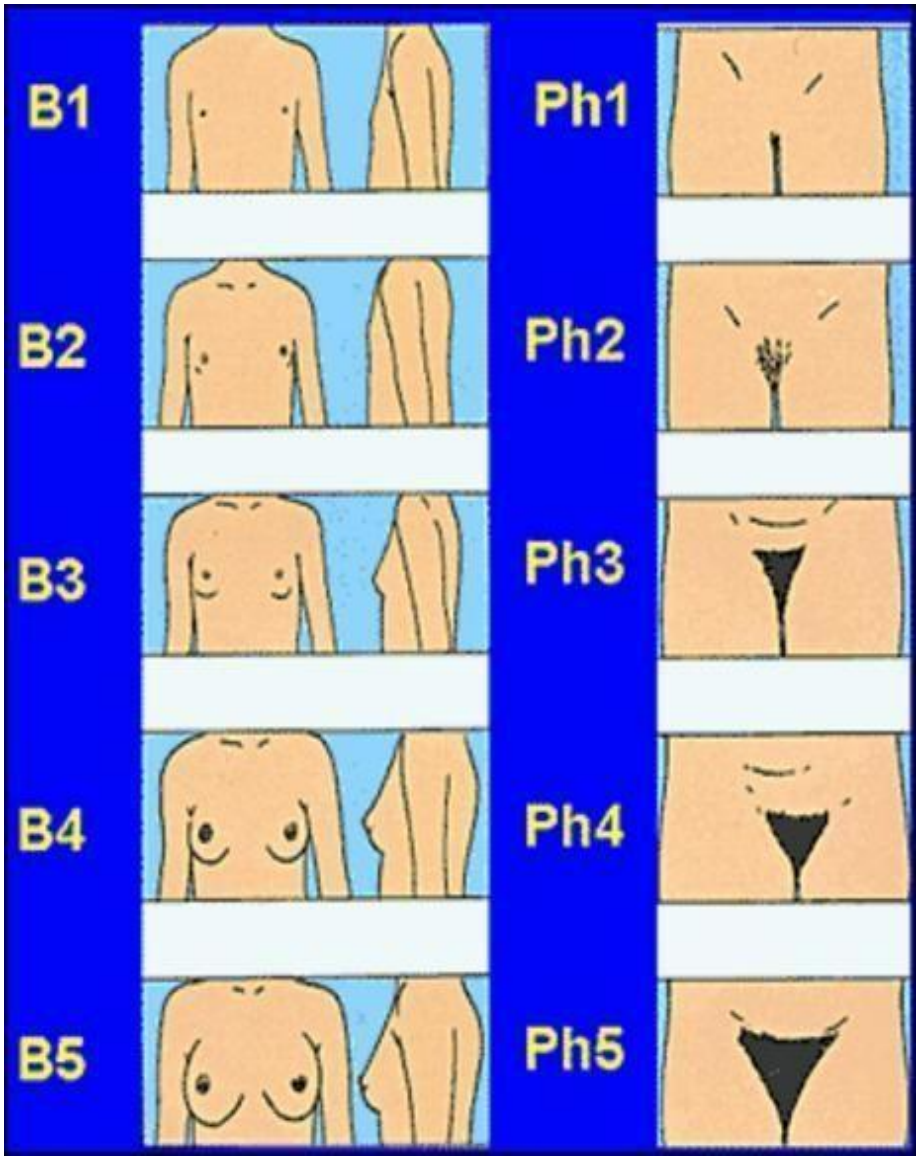
قال تعالى (فَلَمَّا وَضَعَتْهَا قَالَتْ رَبِّ إِنِّي وَضَعْتُهَا أُنْثَى وَاللَّهُ أَعْلَمُ بِمَا وَضَعَتْ **وَلَيْسَ الذَّكَرُ كَالأُنْثَى**



Secondary sexual Changes

- Five stages from childhood to full maturity described by Dr. Tanner (British citizen).
- Stage 1 is prepubertal, while stage 5 is full adult.
- In females; 5 stages for breast development and another 5 stages for pubic hair.
- In males; 5 stages for genital development and another 5 stages for pubic hair.
- Secondary sexual characteristics appearances:
  - starting age 8– 13 yrs in girls
  - starting age 9 – 14yrs in boys

Tanner stages females



Puberty: Girls

- Breast enlargement (Thelarche) usually first sign.
- Often begins unilateral then become in both sides.
- Usually starts as firm, painful small mass behind the nipples.
- Second stage is (Adrenarche): pubic & axillary hair development, oily skin & hair with acne.
- Adrenarche is common stage between males and females.
- Menarche usually 2-3 yrs after breast development.
- Growth spurt peaks just before menarche.

Pelvic U/S changes

Ovary volume

prepuberty < 1.5 ml

postpuberty > 3-4 ml

Follicle size

prepuberty < 6mm

postpuberty > 6mm

Uterus to cervix ratio

prepuberty $\leq$ 1 postpuberty >1

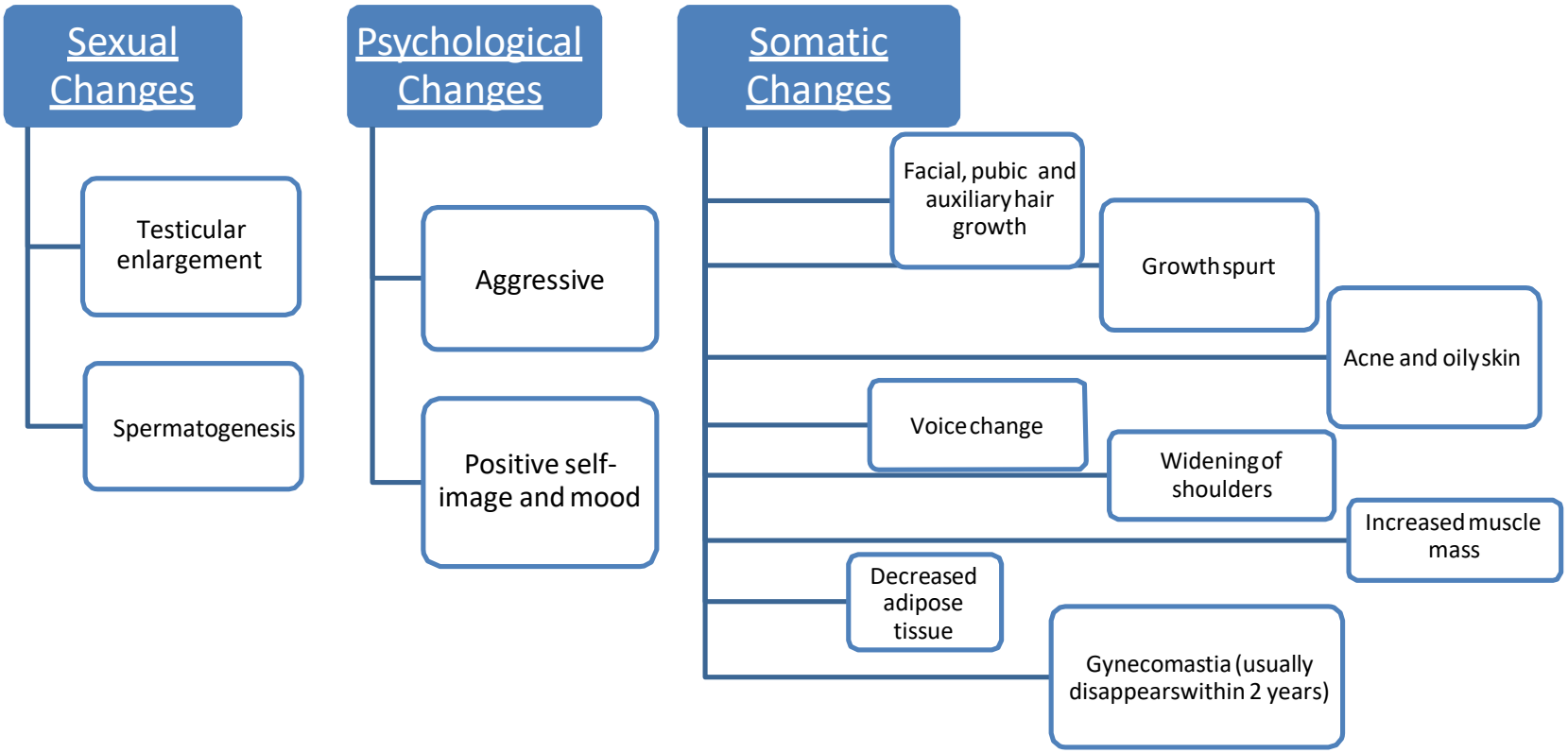
Endometrial echo

prepuberty = None postpuberty=present

Somatic changes: Girls

- Widening of the pelvis & carrying angle.
- Major increase in bone mineral density.
- Increased adipose tissue in female distribution (buttocks, upper thighs & breast tissues).
- 95% of growth happened just before menarche.
- Increase of only 5% of final height after menarche.
- Menarche usually by age 13 years.
- Increased in muscle bulk but not to same extent as males.

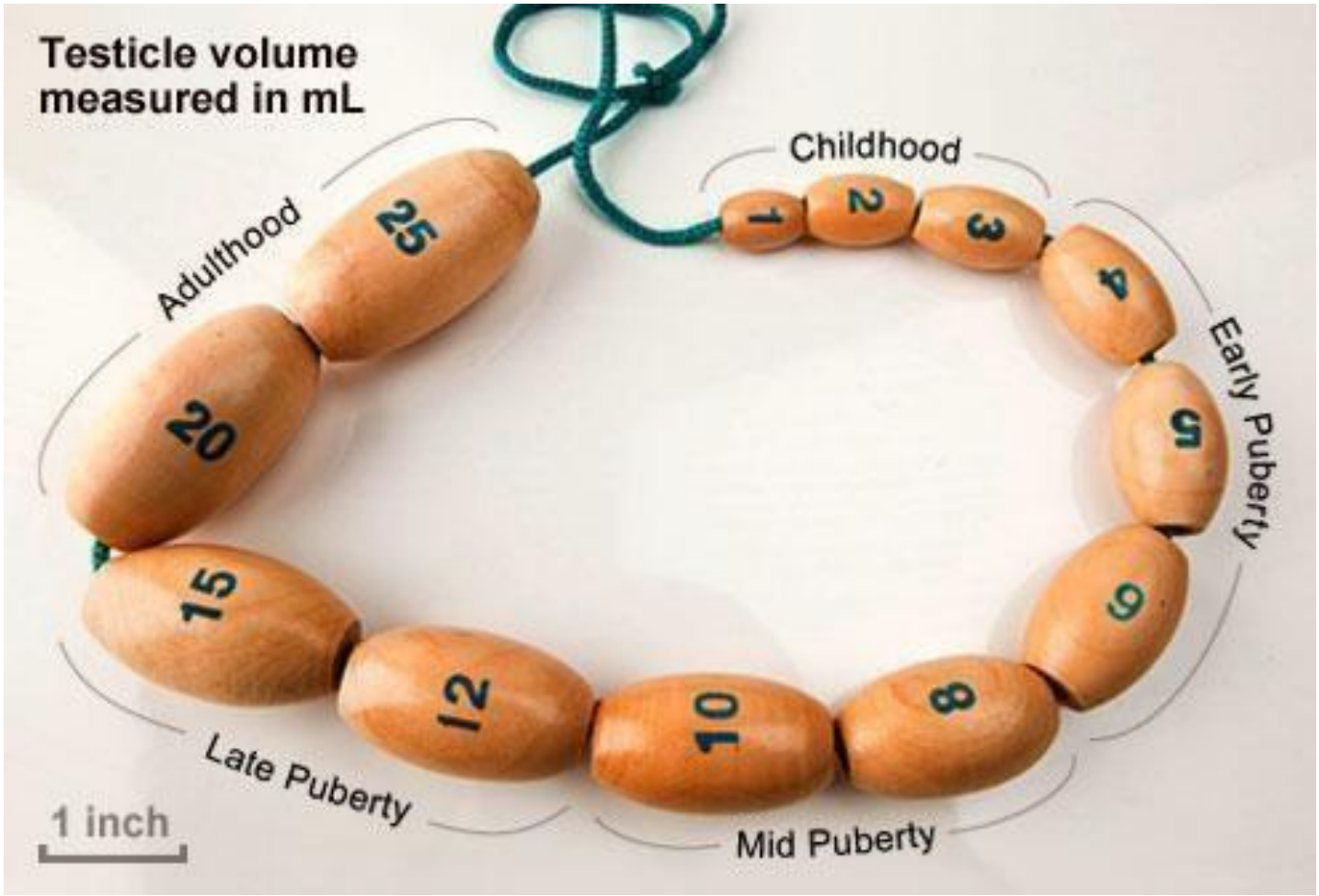
Puberty in boys



Puberty in boys

- First sign is testicular enlargement, followed by pubic hair development and genital enlargement.
- Puberty starts when the testes are 4 ml in size (measured by Orchidometer).
- Adult testes are 20-25 ml in size.

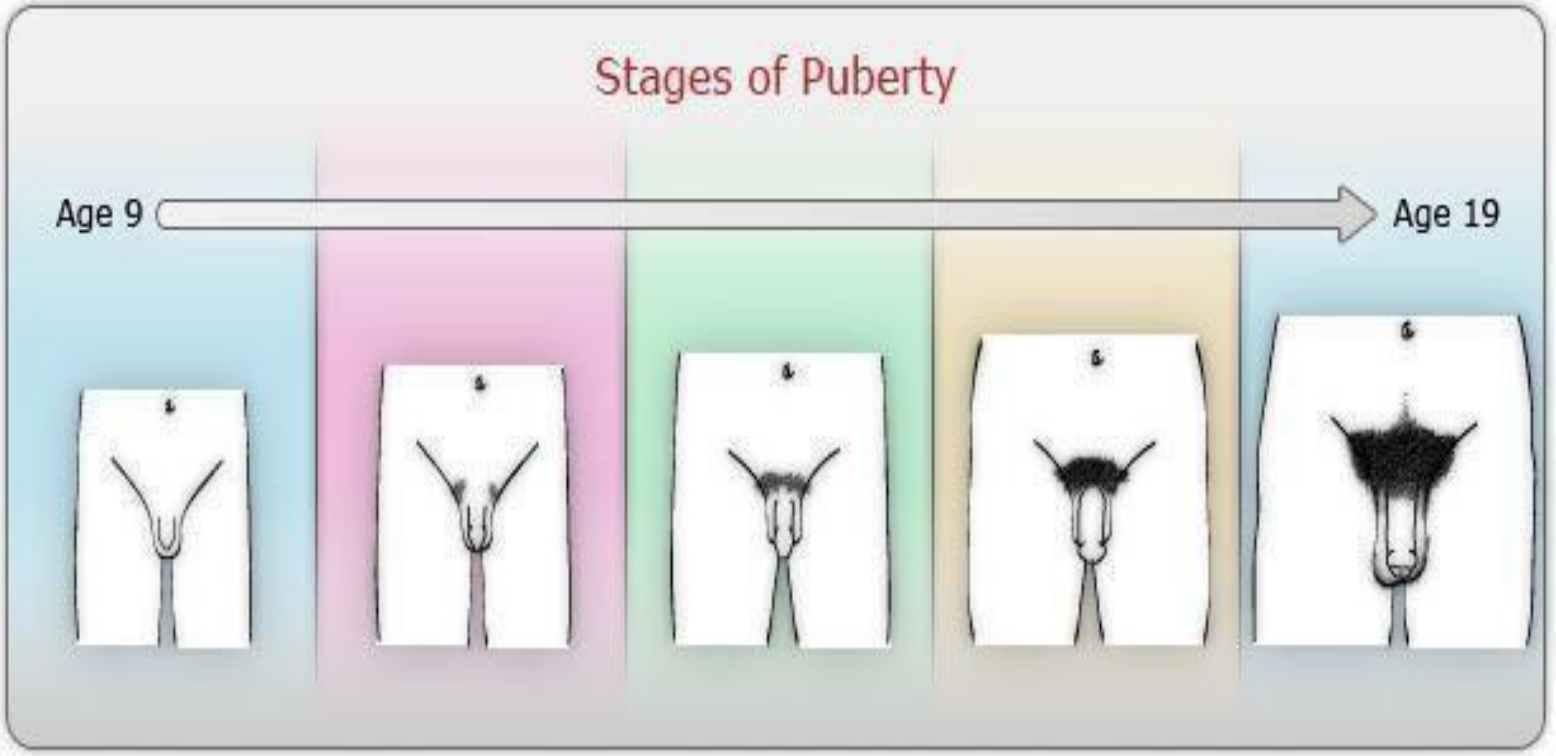
Orchidometer



Puberty: Boys

- First sign is testicular enlargement (often go unnoticed).
- Pre-pubertal testicular volume is (1-3 ml).
- Puberty begins when testicular volume is 4ml and above.
- Penile & scrotal enlargement occur approx 1 year after testicular enlargement.
- Pubic hair appears at same time.

Tanner Stages: Males

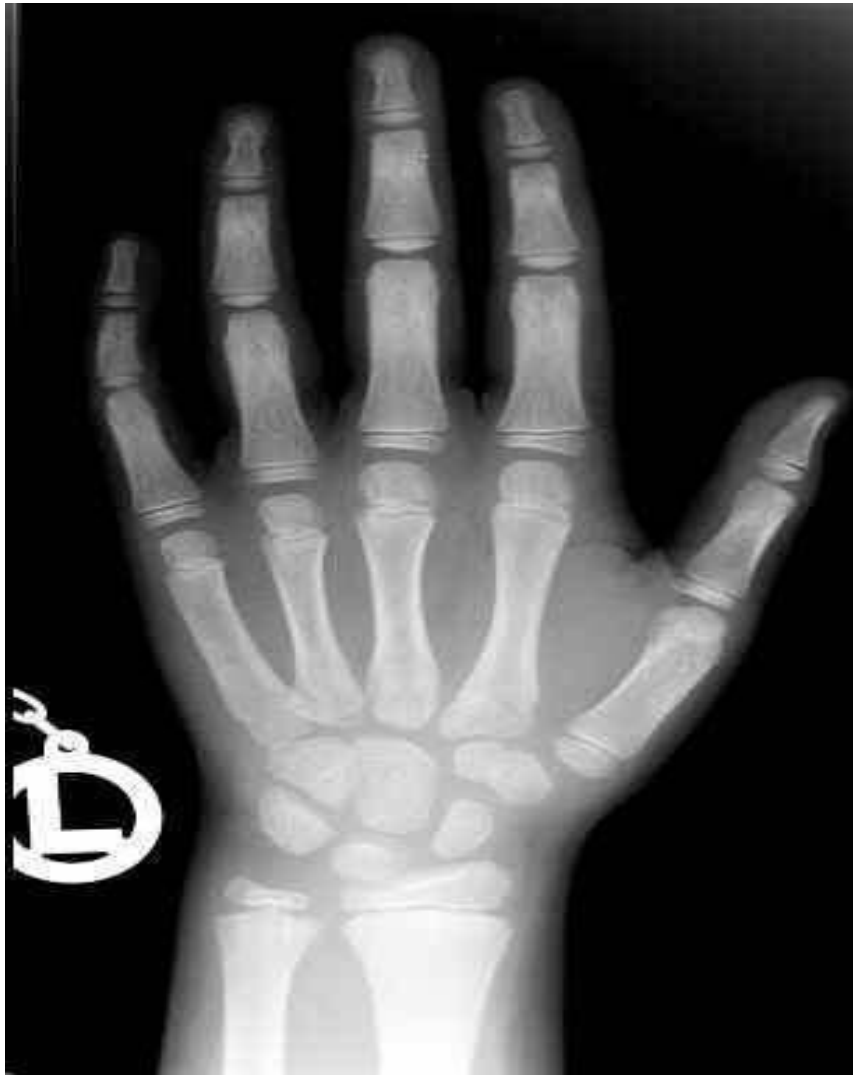


Pubertal Growth Spurt: Boys

- Occurs later than in females by average 2 years.
- Testosterone less stimulus to GH responsiveness than estradiol.
- Testosterone required in larger concentrations to produce same anabolic effect.
- Greater and later growth spurt in boys.

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.



Somatic changes in boys

- Growth spurt is later than girls by 2 year
- Increased muscle mass.
- Decreased adipose tissue.
- Skeletal changes (increased BMD).
- 60% have transient gynecomastia.
- Spermatogenesis by 15 year.

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.

Central Precocious Puberty

- Result from premature activation of Hypothalamus-Pituitary-Gonadal axis.
- The pulsatile GnRH secretion leads to pulsatile secretions of LH & FSH with subsequent release of sex steroids.
- Similar to normal mechanism but happened earlier than expected age.

Central “true Precocious puberty

- Idiopathic (most girls in 90 % of cases)
- Secondary to CNS pathology (most boys 70-80%)

Secondary CNS causes

- Hypothalamic Hamartoma.
- Astrocytoma, craniopharyngioma, ependymoma, germinoma, glioma…..etc.
- CNS radiotherapy.
- Post pituitary surgery or head trauma.
- Inflammation (meningitis, encephalitis, Brain abscesses).
- Neurological & mental retardation.
- Hydrocephalus.
- Prolonged primary hypothyroidism (α-TSH stimulates FSH, LH, Prl).

Peripheral “Pseudo precocious puberty

- Suppression of central axis (Hypothalamic-Pituitary-gonadal axis).
- LH & FSH levels are low (basal & stimulated).
- Sex hormones are high.
- Gonads are small in size (unless tumor is present).

Pseudo precocious puberty

- Gonadal: McCune-Albright, tumour, cyst
- Adrenal: CAH, tumours
- Ectopic: hCG secreting tumours
- Exogenous source of hormone
- Familial male dependent (Testotoxicosis)
- Chronic primary hypothyroidism (α-TSH works on α subunits of LH &FSH)

Autonomous gonadal steroid production

McCune Albright syndrome

Familial gonadotrophin-independent

Familial male-dependent precocious puberty (Testotoxicosis)

- Autosomal dominant.
- Male – limited.
- Mutation in LH receptors.
- autonomous Leydig cell activity & testicular enlargement.
- Prepubertal levels of LH, FSH with pubertal testosterone level.
- Females not affected (FSH is needed).

McCune - Albright syndrome (MAS)

- First described by McCune & Albright (1937).
- Affects both sexes.
- Activating mutation of Gs α gene GNAS 1 on 20q13.2.
- Results in increased activity of the Gsα protein and cAMP in the affected endocrine tissue.
- Gonadal autonomy.
- Happen more commonly in girls.
- Menses usually happen < 2-3 years of age.

In girls, the presenting feature is often menses with / without thelarche.

Abnormalities in McCune-Albright syndrome

Endocrine

• Precocious Puberty	++++
• Goitre / Hyperthyroidism	+++
• Acromegaly/ Gigantism	++
• Cushing's syndrome	+
• Hyperprolactinemia	+
• Hypophosphatemic rickets	+

Abnormalities in McCune-Albright syndrome

Non-endocrine

- Cafe-au-lait spot ++++
- Fibrous dysplasia of bone ++++
- Facial asymmetry ++
- Elevated hepatic transaminases ++
- G.I polyposis +
- Cardiomyopathy +
- Arrhythmias +

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.
- Prepubertal pelvic U/S findings.
- Onset between 6m to 4 y of age.
- Increased sensitivity of the breast tissue to low level of estradiol.
- Benign nature.
- Need no therapy.

Isolated Benign Adrenarche

- Occurs when the adrenal androgens are turned on prematurely in the absence of gonadal activation.
- Premature appearance of pubic & axillary hair, acne, body odor & oily skin.
- Idiopathic &Benign in nature.
- No treatment.
- Only observation for progression to precocious puberty.

Isolated Benign Adrenarche

- Elevated adrenal androgens
- Normal LH / FSH & gonadal steroids
  - Need to exclude late-onset CAH
  - Need to exclude adrenal tumours
  - Need to exclude PCOS

Evaluation of Precocious Puberty

- History & physical examination.
- Current height percentile.
- Calculation of target height.
- Bone Age assessment.
- Predicted adult height (PAH).
- Crucial Investigations should include initially:
  - Basal LH, FSH and sex steroids
  - GnRH stimulation test

Other investigations !!

- hCG : hepatoblastoma, germ – cell tumor.
- Inhibin : ovarian granulosa cell tumor.
- 17 OHP : non - classical CAH.
- Radiological investigations depending on type of precocious puberty.
  - MRI Brain: hypothalamic Hamartoma, optic glioma, other CNS tumores.
  - U/S Testes
  - Pelvic & Adrenal U/S

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.

GnRH agonists

- First reported in 1981.
- The treatment of choice of central type.
- Alteration of peptide sequence of native GnRH with more potency, affinity to the receptors.
- Acts continuously with down regulation of GnRH receptors.
- Depot. “slow release preparations.
- Various brands available:
  - Leuprorelin acetate (Lucrin): 0.3 mg / kg
  - Tryptorelin (Decapeptyl) 50-100 mcg/kg
  - Goserelin (Zoladex)

Treatment of peripheral type

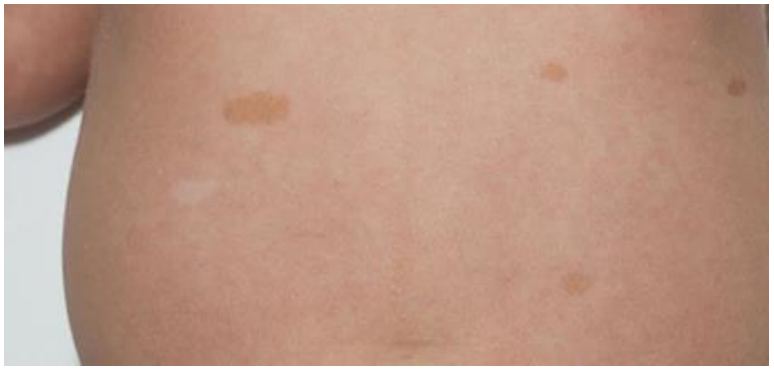
- Medroxyprogestrone acetate (Provera)
- Ketoconazole
- Aromatase enzyme inhibitors:
  - Testolctone (1st. Generation).
  - There are three aromatase inhibitors (3rd. Generation):
    Arimidex (anastrozole)
    Aromasin (exemestane)
    Femara (letrozole)
- Androgen antagonists.
- Selective estrogen receptor modulators “SERMs “for short, block the effects of estrogen in the breast tissue.

Puberty cases

- Six- year - old girl, not known to have any medical illness, came with history of vaginal bleeding for 2 days, was admitted to the hospital because of sexual precocity.
- The history started 3 weeks prior to presentation, where the parents noticed bilateral breast enlargement.
- Two days prior to presentation, there was vaginal bleeding, associated with abdominal pain and distention.

What other important history is needed?

- On examination, she was alert and active.
- her height was 105 cm (below 3rd percentile), her weight was 18.5 kg (10th percentile), and her head circumference was 56 cm (above 97th percentile).
- Vital signs were normal.
- Skin examination (photo).



- Abdomen was distended with a palpable hard mass measuring 7x 6 cm located in the right lower quadrant.
- There was no pubic or axillary hair (tanner stage 1).
- Bilateral breast enlargement (Tanner stage 3).

What other examination you are interested to do?

Investigations

- A complete blood count and differential, electrolytes, calcium and phosphorous, liver function test, CRP, ESR, Coagulation profile were normal.
- The Free T4 Hormone (FT4) and the thyroid stimulating hormone (TSH) were normal.
- The Luteinizing Hormone (LH) was low 0.04 mIU/L, and Follicle Stimulating Hormone (FSH) was 2.17 IU/L.
- Serum Estradiol was high 152.72 Pmol/L (26-125 Pmol/L).
- Bone age assessment of left hand using Greulich and Pyle method show advanced bone age (8 years and 4 months).
- Abdomen ultrasound shoed right adnexal mass.

What other diagnostic laboratory & radiological examination you are going to order?

What is your differential diagnosis?

Investigations

- CT Abdomen & Pelvis with contrast show a well defined Heterogenous solid right ovarian/adnexal mass measuring 7.8*7.4*6.2 cm associated with stretching of the uterus superiorly with thickened endometrium.
- Skeletal survey was normal.
- Beta Human Chorionic Gonadotropin was <0.1 mIUI/mL,

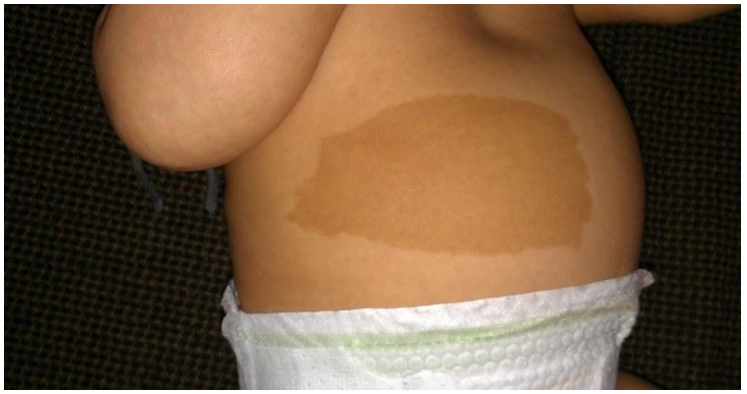
- Inhibin B was >1300 pg/ml (<18 pg/ml).
- Alpha Fetoprotein (AFP) was 0.57 ng/ml (0-8.7 ng/ml),
- CEA (Carcinoembryonic Ag) was 0.95 ng/ml (0-5 ng/ml)

- What is the final diagnosis??

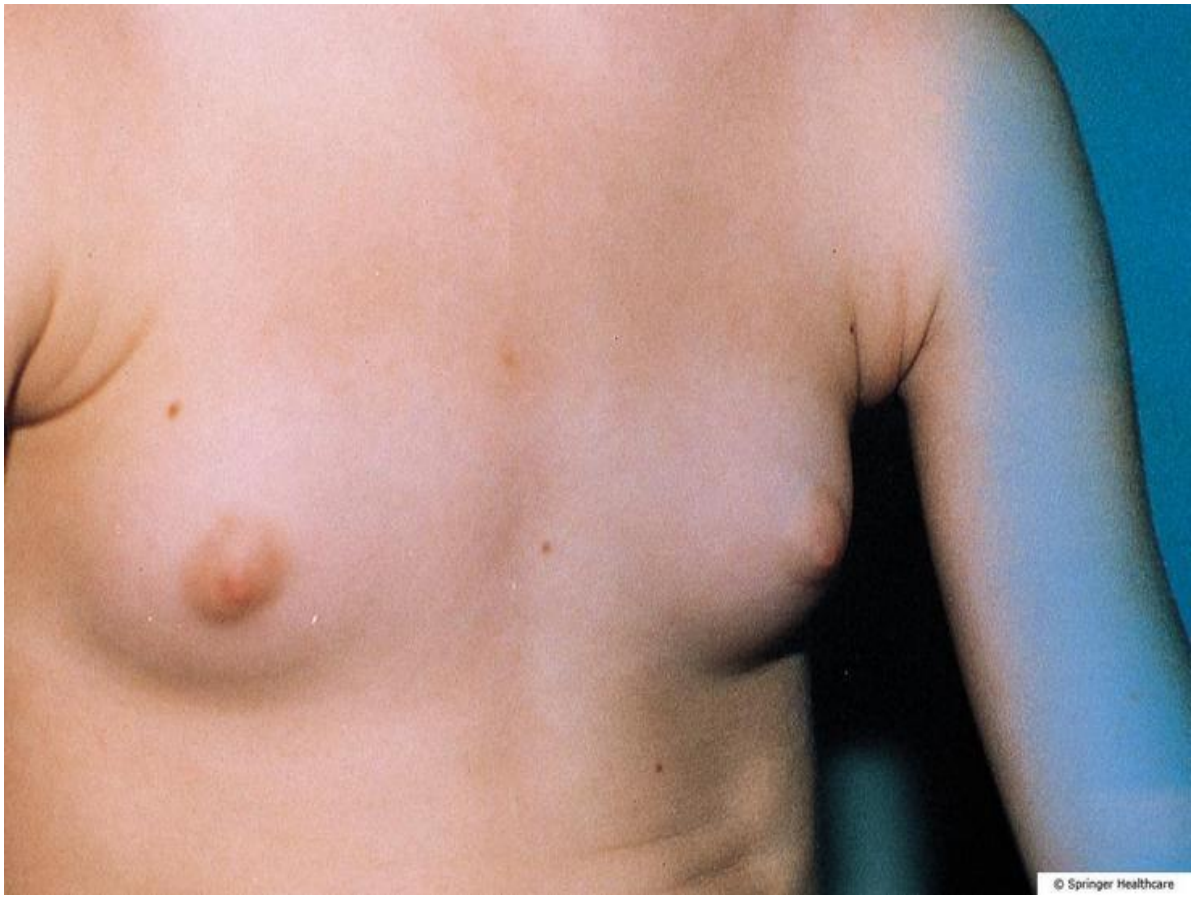
- An 18-month-old female infant was brought to the pediatric endocrine clinic because of vaginal bleeding for the first time with all the characteristics of menstruation.
- The bleeding was moderate with a bright brown color and clots.
- There was no bleeding from any other orifices and no history of trauma or child abuse.
- There was no history of hormonal exposure as well.
- The mother noticed multiple skin pigmentations on her daughter's body, and she was growing faster than the other siblings.

What other important history information you are going to ask?

- A physical examination revealed that her height (80 cm) and weight (10 kg) were at the 50th percentiles.
- The patient had a normal vaginal orifice with an intact hymen and no evidence of bruises or lacerations.
- Bilateral enlargement of the breasts was also noted (stage B3 according to Tanner score) with no pubic hair.
- Skin examination (Figure).



What other examination you are interested to do?
How to investigate her?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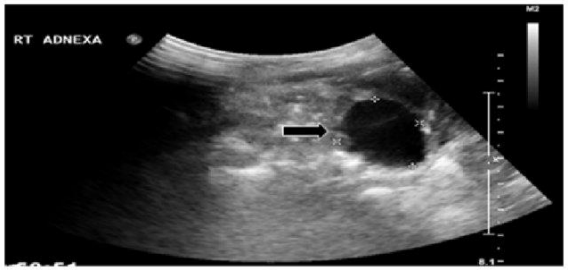
Investigations

Laboratory tests	Results	Normal value
Luteinizing Hormone (LH)	0.2	0-0.9 mIU/l
Estradiol Hormone	595	26-125 Pmol/l
Follicle Stimulating Hormone (FSH)	0.2	0.2-3.8 IU/l
Prolactin	439	83-539 mIU/l
Random cortisol hormone	117.1	138-636 nmol/l
Progesterone hormone (PRGE)	2.52	< 3.18 nmol/l
Thyroid stimulating hormone (TSH)	3.21	0.27-5 uIU/l
Free T3 hormone (FT3)	5.8	2.8-7 Pmol/l
Free T4 hormone (FT4)	18.1	12-22 Pmol/l
Growth hormone (GH)	2.16	1-10 ng/ml
Insulin like growth factor binding protein 3 (IGFBP-3)	4920	800-3900 ng/ml
Insulin like growth factor 1 (IGF-1)	209	108-350 ng/ml
Total protein (TP)	60	64-82 g/l
Albumin (Alb)	32	40.2-47.6 g/l
Alkaline phosphatase (ALP)	328	156-369 U/l
Aspartate amino transferase (AST)	54	15-37 U/l
Alanine amino transferase (ALT)	41	12-78 U/l
Gamma-glutamyl transferase (GGT)	103	5-85 U/l
Serum calcium	2.35	2.12-2.52 mmol/l
Serum phosphate	0.76	0.81-1.58 mmol/l

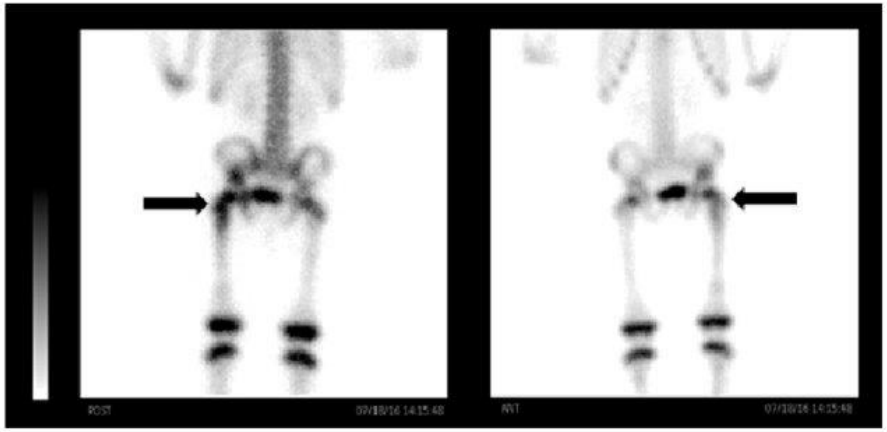
What is your differential diagnosis?

What next you are going to do?

Radiological Investigations



A pelvic ultrasound of the patient showing an ovarian cyst of the right ovary (arrow).



Bone scan shows abnormal uptake at left proximal femur and acetabulum.

Final diagnosis:
McCune-Albright syndrome

- A 5-year-old boy was brought to the pediatric endocrinology clinic with a five-month history of pubic hair appearance associated with aggressiveness, increased penile length, and change in body odor.
- He was a product of full-term, normal vaginal delivery, with uneventful medical and surgical histories.

What other history information you are interested to ask

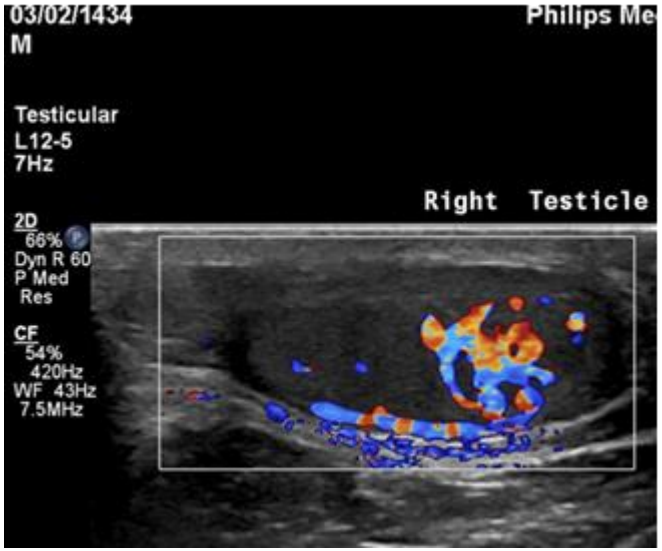
- On examination, his vitals were unremarkable.
- His height percentile was on 90th. Percentile.
- Pubic hair and genitalia were Tanner stage II and the volume of each testis was 3 ml (Figure).
- Bone age advanced by 2 years.

Test	Date and time		Result
Follicular stimulating hormone	14/02/2018		0.2
	14/02/2018	0 min	0.2
		15 min	1.8
		30 min	2.5
		45 min	3.1
		60 min	4
		90 min	4.6
		120 min	5.1
Luteinizing hormone	14/02/2018		0.2
	14/02/2018	0 min	0.2
		15 min	0.5
		30 min	0.7
		45 min	0.8
		60 min	0.9
		90 min	1
		120 min	1
Testosterone	14/2/2018		7.7
			7.6

The gonadotropin-releasing hormone (GnRH) stimulation test showed a high testosterone level but no luteinizing hormone (LH) peak response.

Investigations

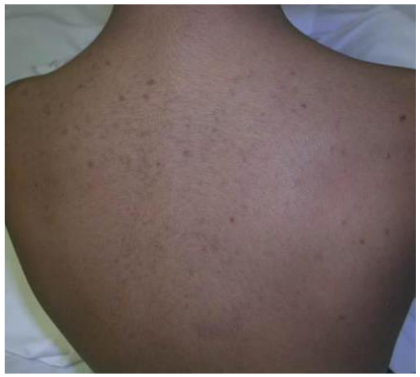
Hormone	0 min	30 min	60 min
17 OH progesterone	2.9 ng/ml	3.6 ng/ml	3.9 ng/ml
cortisol	348.6 nmol/l	734nmol/l	859.4 nmol/l
DHEA-S	0.54 umol/l	-	-
ACTH	2.12 pmol/l	-	-

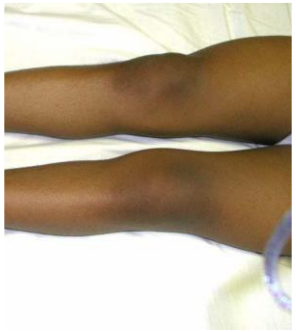


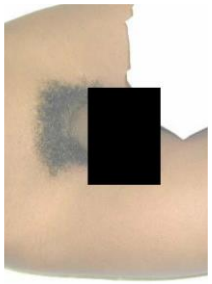
Testicular ultrasound shows right testicular mass

Five -year-old boy previously well, started to develop pubic hair, which has been increasing steadily, adult type body odor, and acne on his back (photos). On examination, pubic hair and penis Tanner stage 2, testicular volumes of 3 ml bilaterally. Which one of the following is most likely diagnosis?

a) Non – classical CAH
b) Premature Adrenarche.
c) Hypothalamic hamartoma.
d) Idiopathic precocious puberty.



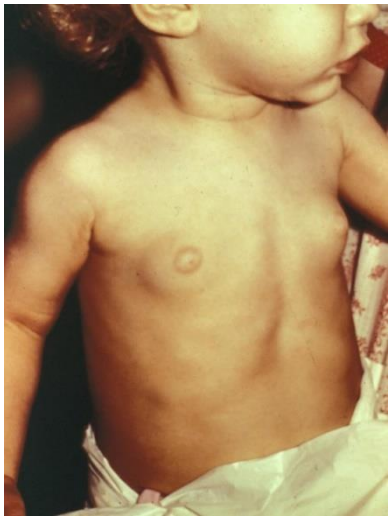




"Non classic" / late-onset CAH

- It does not manifest with neonatal genital ambiguity; rather, it presents later in life with signs of androgen excess.
- Clinical features in late childhood include premature pubarche, acne, and accelerated bone age.
- In adolescent girls and adult women, non classic CYP21A2 deficiency is characterized by acne, hirsutism, and menstrual irregularity (oligoovulation) that are indistinguishable from the polycystic ovary syndrome.
- Never presents with adrenal crisis.

Two- year old girl with bilateral breast development with no growth acceleration, no bone age advancement & normal estradiol, LH or FSH. What is the most likely diagnosis ?



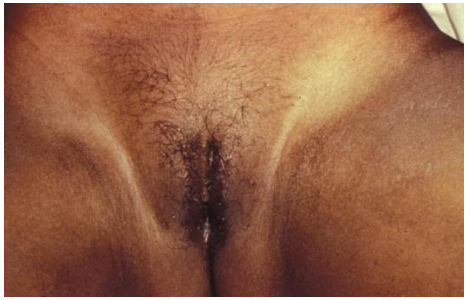
a) Ingestion of her mother's OCPs.
b) Precocious puberty.
c) Benign isolated premature thelarche.
d) McCune Albright Syndrome.

Benign Premature Thelarche

- Isolated breast development
  - 80% before age 2 years.
  - Rarely after age 4 years.
- Not associated with other signs of puberty. (growth acceleration, advancement of bone age)
- Children go on to normal timing of puberty and normal fertility.
- It may be associated with functional follicular cysts that spontaneously regress and perhaps with especially responsive breast tissue
- Benign process.
- Routine follow-up.

Six- year old girl, with 6 months history of pubic hair growth associated with fine axillary hair as well as adult odor to sweat. No breast development with no acceleration of growth. Otherwise normal history and examinations.

What is the most likely diagnosis?

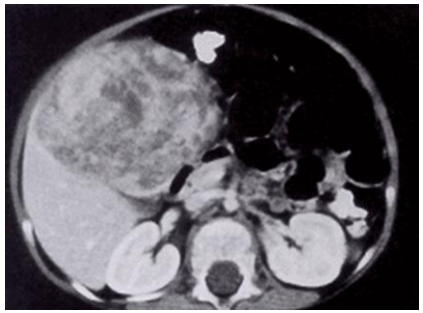


a) Precocious puberty.
b) Benign premature Adrenarche.
c) Non-classical congenital adrenal hyperplasia.
d) Adrenal tumor.

Benign premature adrenarche

- Production of adrenal androgens before true pubertal development begins.
- Presents as isolated pubic hair in mid childhood
  - No growth acceleration.
  - No testicular enlargement in boys.
- If normal growth rate, routine follow-up.
- If accelerated growth and/or bone age advancement, screen for:
  - CAH
  - Virilizing tumor (adrenal/gonadal)

Two - year old girl, presented with abdominal distension, there was three months history of bilateral breast enlargement, pubic hair appearances & rapid growth. Her abdominal CT scan (photo).



Which one of the following is most likely diagnosis?

a) β-HCG secreting hepatoblastoma
b) McCune Albright syndrome.
c) Benign premature Adrenarche.
d) Ovarian cyst.

Gonadotropin independent precocious puberty secondary to β-HCG secreting hepatoblastoma

Hepatoblastoma

- Is the most common primary hepatic malignancy in early childhood.
- The majority of cases occur in the first two years of life and rarely in children older than five years.
- Syndromes with an increased incidence of hepatoblastoma include:
  - Beckwith Wiedemann syndrome.
  - trisomy 18 & trisomy 21 .
  - Aicardi syndrome.
  - Li-Fraumeni syndrome.
  - Goldenhar syndrome.
  - type 1a glycogen storage disease.
  - familial adenomatous polyposis.
- Serum alpha-fetoprotein (AFP) levels are markedly elevated.
- Sexual precocity may be present due to the synthesis of ectopic gonadotropin (HCG).


Thanks