OB/GYN

MEDICINE
KING SAUD UNIVERSITY

Puberty Disorder

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References: 437 Lectures And Notes , 436 teamwork

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Objectives:

1. Describe the endocrinological-Hypothalamus-Pituitary- gonadal axis and target organ in normal Puberty.
2. Describe the different stages of somatic and psychological changes of puberty.
3. Define puberty abnormalities (Precocious and delayed puberty).
4. List types of female precocious puberty.
5. Mention the investigations used to evaluate precocious and delayed puberty.
6. List treatment options of precocious and delayed puberty

Normal Puberty

What is puberty?

-It is the transitional period between childhood & adulthood
-The physiological changes leading to the development of adult reproductive capacity
-The period of attainment of adult sexual & reproductive characteristic
-It is the transitional period of development during which an individual mature from childhood to sexual & reproductive maturity

WHAT ARE THE MAJOR CHARACTERISTICS OF THIS PERIOD?

1. Maturation of the 1ry sexual characters regulated by Hypothalamic Pituitary Ovarian Axis.internal changes
2. **Development of 2ry sexual characters**:external changes
   a) Sexual hair. b) Breasts. c) Genitalia
3. Dramatic growth spurt.increase in height
4. Physiological changes such as: mental & emotional maturity.

Normal pubertal development

What is the age of onset of puberty?

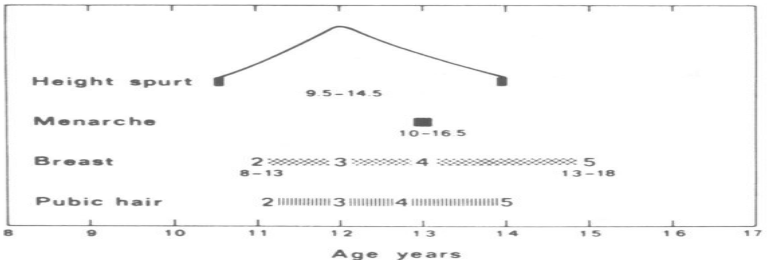
- females 8-13
- Males 9-14

What is the usual sequence of somatic changes of puberty?

1. Breast development (mean age is 10.6 Y)start before the hair,but always there is variation
2. Pubic & axillary hair (11.2 Y)
3. Maximal growth velocity (12 Y), onset of growth spurt is (9.6 Y)be careful between *maximal* and *onset*
4. Menarche (12.7 Y)

The average age of menarche has decreased over the last 3-4 decades (secular trend) attributed to improved nutrition, general health & lifestyle.

Ages of girls at various stages of pubertal development



What is the interval between onset of breast development & menarche?

2.3 +/- 1 year.

Does Menarche mark the attainment of reproductive maturity?

- No, the reproductive system continues to mature for around 3-4 years
- No. of ovulatory cycles increases from 10% to 90%
- Duration of menstrual cycle decreases

The first few years the girl will have anovulatory cycles that occur every 2-3 months, until the maturation of the HPO axis then the cycle will become regular.

Do Girls stop growing after Menarche ?

No Growth continues at a decelerating rate for a No. of years

What is the time from onset to completion of puberty?

- Average 4.2 Y
- range 1.5-6 Y

Etiology of Puberty

Hypothalamus

- GnRH secretion by the arcuate nucleus is modulated by two inhibitory mechanisms :
  1. Intrinsic CNS inhibitory mech
  2. Neg feedback of circulating sex steroid

DEVELOPMENT OF THE HPO AXIS

- At fifth month gestation, the ovaries become responsive to gonadotropin follicular growth to early antral stage (1-2 mm, followed by atresia) → estrogen production → neg feedback
- A functional HPO axis exists in utero
- In utero the fetoplacental unit is the 1ry source of estrogen production → increase estrogens → decrease FSH & LH levels

MATURATION OF THE HPO AXIS

After birth estrogen decreases dramatically therefore, increases FSH & LH which leads to an increase in ovarian estrogen production in early infancy

1-THE MAIN MECHANISM CONTROLLING FSH & LH SECRETION IN INFANTS IS THE LEVEL OF SEX STEROIDS

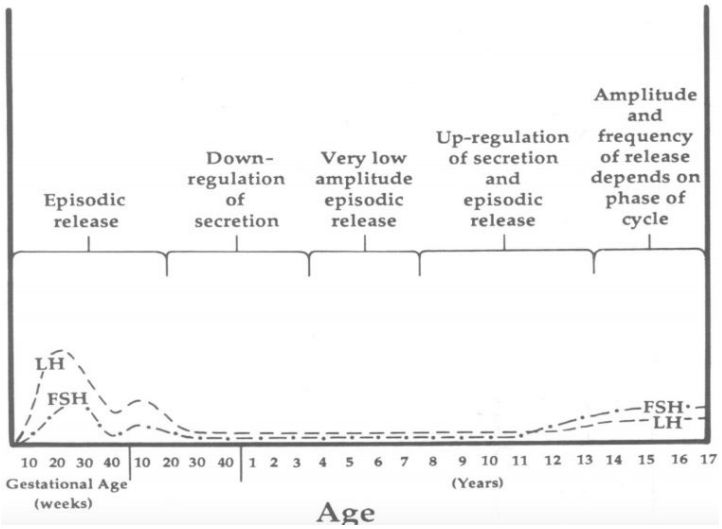
▲Peak FSH & LH in 1-2 years

2- THE INTRINSIC CNS INHIBITORY MECHANISM

▲Gradually develops with continued growth & maturation of the CNS leads to Minimum FSH & LH level for 6-8 years

▲The principal CNS inhibitor of GnRH is GABA

LEVELS OF LH & FSH DURING FETAL LIFE, INFANCY CHILDHOOD & PUBERTY



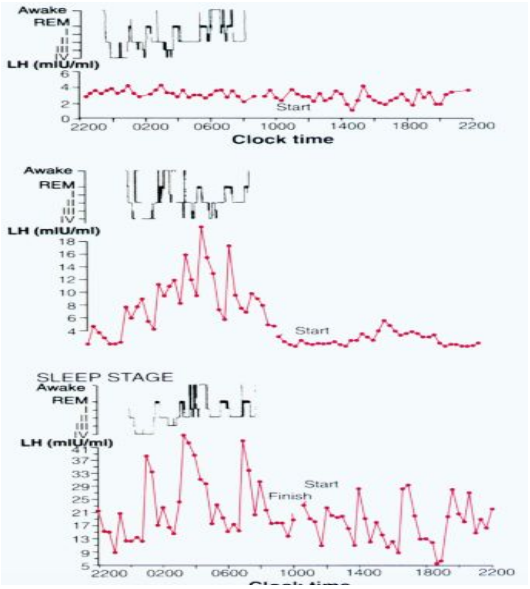
After delivery there will be maternal estrogen withdrawal and as a result some newborn will have vaginal bleeding which is physiologically normal, during childhood LH,FSH level is low then will increase when we reach puberty age.

Maturation Of The HPO Axis

THE SEQUENCE OF MATURATION:

- At the onset of puberty GnRH pulses occur during sleep LH pulses
- The frequency of LH pulses increases with further maturation
- LH pulses appear during day time & increases in amplitude
- As menarche approaches , the pulses are detected all the time (no diurnal variation)
- Similar changes occur in FSH pulses
- LH/FSH ratio increases

PLASMA LH CONC MEASURED EVERY 20 MIN FOR 24 HRS



1- LH,FSH secretion prepubertal very low.

2- Early pubertal we start to get it during sleep

3- Late pubertal will increase during sleep and day(all time)

Initiation of puberty

Factors responsible for initiation of puberty?

Unknown

*FRISCH THEORY

- A critical body fat & body wt are required for the initiation of menarche
- Supported by :

1. Highly competitive athletic training causes delayed puberty
2. Delayed menarche in malnutrition
3. Overweight girls have early menarche
4. Pt with anorexia nervosa revert to prepubertal pattern of gonadotropin secretion as body wt decreases

Against the Theory

Changes in body composition occurs simultaneously with gonadotropin increase & does not precede it

Leptin

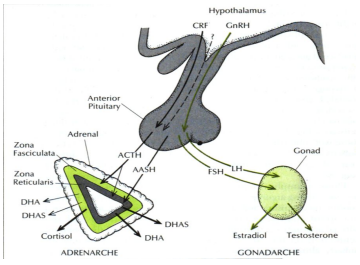
An adipose derived protein may play a role in the initiation of puberty

Mechanism:

- Gonadostat begins to lose its sensitivity to the –ve feedback by estrogen causes reactivation of GnRH pulsatility which leads to puberty
- In late childhood CNS inhibitory influence on the hypothalamus wane causes increase GnRH then increase of FSH & LH then increase estrogen (gonadarche)
- increase sensitivity of the pituitary to GnRH
- increase sensitivity of the ovary to LH & FSH causes increase in estrogen secretion

ADRENARCHE & GONADARCHE CONTROLLED BY DIFFERENT MECHANISMS

Adrenarche	Gonadarche	Menarche

• The maturational increase in adrenal androgen secretion (DHEA , DHEAS, AND)
  ○ development of pubic & axillary hair
  ○ adult type body odor
  ○ acne
  ○ oily skin & hair
• Adrenal androgens ⟶ increase bone age & linear growth.so it have a role in growth spurt
• Premature adrenarche ⟶ decrease adult height. early closure of epiphysis.
• The mechanism of initiation is unknown
• Adrenarche & gonadarche are not associated
	• The onset of pubertal gonadal activity due to reactivation of HPO axis ⟶ high estrogen
	• Reactivation of HPO axis causes an increase gonadotropin pulses ⟶ sustained follicular development to antral stage ⟶ significant estrogen production
	• The process of ovarian follicular growth & atresia is initiated in utero & continues from birth to puberty It is independent of gonadotropin secretion & results in only minimal estrogen secretion
	• High estrogen cause development of breast, genitalia and secondary sex characteristic
	• There is direct relationship between follicular size & estrogen secretion
		When there is sufficient gonado-tropin stimulation of the ovaries causes increase follicular growth (~16mm)
		then increase estrogen which causes proliferation of the endometrium until it outgrows the estrogen capacity to maintain it then the follicle undergo atresia which causes a decrease in estrogen then ,as a result, menstruation happens (MENARCHE)
		• Anovulatory cycles occur during the first 6-18M-4Y. may goes up to (3-4)years and this due to HPO axis still not mature
		"endometrium is not exposed to progesterone" ⟶ irregular
		 
		
		unpredictable menstrual flow.

OVULATORY MENSTRUAL CYCLES

- Early ovulatory cycles have short or inadequate luteal phase HPO axis has not achieved full maturity Ovulatory menstrual cycles:
- Requires further maturation of the HPO axis ⟶ development of the +ve feedback mechanism.

Physical events of puberty:

PREPUBERTAL	PUBERTAL ---ADULT
1-UTERUS -Ratio of corpus : cx 1:2 -Tubular shape -Length --- 2-3 cm -Volume ----- 0.4-1.6 -Endometrium=single layer of cuboidal cells	**1-UTERUS** -Ratio of corpus :cx 2:1 -Pear shape -Length ----5-8 -Volume ----- 3-15 --- -Endometrium increases thickness
2-OVARIES -Volume -----0.2-1.6 ml -Non functional	**2-OVARIES** -Volume ------2.8-15 ml -Multicystic
3-VAGINA -Reddish in color -Thin atrophic columnar epithelium -PH ---neutral -Length—2.5-3.5	**3-VAGINA** -Thickening of the epithelium Cornification of the superficial layer to stratified squamous Epithelium -Dulling of the reddish color -PH ----acidic 3.8-4.2 -Secretion of clear whitish discharge in the months before menarche -Length ---7.5 cm

EXTERNAL GENITALIA

Under the effect of estrogens:

1. Labia majora & minora increase in size & thickness
2. Rugation & change in color of the labia majora
3. The hymen thickens
4. Clitoris enlarge
5. Vestibular glands begin secretion

Under the effect of adrenal androgens & ovarian androgens causes growth of pubic & axillary hair

Summary:-

1. Maturation of the genital organs: Uterus, Ovaries increase in size, Vagina become more thick and External genitalia
2. Breast development (THELARCHE)

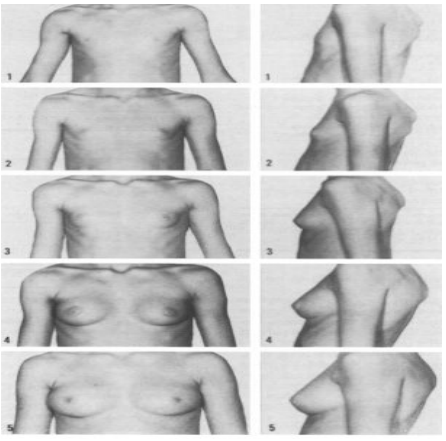
3. Pubic hair development
4. Growth spurt dependent mainly on estrogen & growth hormone
    - The onset of growth spurt antedates thelarche & pubarche
    - ↑ Ht → onset of growth spurt → cessation of growth = 25 cm As we said it start early even before breast development and reach maximum at 12 (it just mean early onset of growth spurt lead to early cessation of growth)
    - Girls who start the growth spurt early will have a shorter adult height.
    - Peak Height Velocity 8.1 cm/year (pre- puberty 3-6 cm/y)

- Estrogen has:
    - Direct anabolic effect.
    - Increase growth hormone.
    - Increase insulin like growth factors.

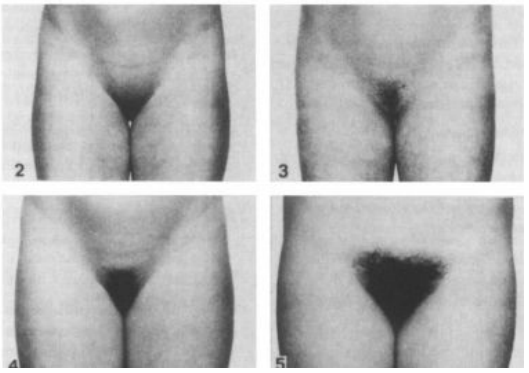
BREAST DEVELOPMENT (THELARCHE)

- The first visible change of puberty
- Thelarche is induced by estrogen
- Starts at 10.6 completed in ~ 3 years
- Effects of estrogen on the breast:
    1. Ductal proliferation
    2. Site specific adipose deposition
    3. Enlargement of the areola & nipple
- Breast development may be unilateral for several months
- Other hormones that play a role in breast development : prolactin, glucocorticoids & insulin
- In normal girls the stage of breast development is consonant with the stage of pubic hair development

Tanner staging (very important)

Breast development (THELARCHE)		
Stage 1	Prepubertal. No glandular tissue; areola follows the skin contours of the chest.	
Stage 2	Breast bud forms with small area of surrounding glandular tissue; areola begins to widen	
Stage 3	Enlargement of breast and areola. The breast extends beyond the borders of the areola	
Stage 4	Areola and nipple (papilla) form a mound atop breast tissue, areola more prominent	
Stage 5	Adult configuration areola & breast having smooth contour with a projecting central papilla	

Pubic hair development	
Stage 1	No pubic hair.(prepubertal state)
Stage 2	Sparse downy hair on the medial aspect of the labia majora with slight pigmentation of labia majora
Stage 3	Darkening, coarsening & curling of hair which extends upwards & laterally.
Stage 4	Hair of adult consistency limited to the mons. Extends across the pubis but sparing medial thighs
Stage 5	Hair spreads to medial aspect of thighs.



Usually both breast and pubic hair staging go together>if breast stage 2 in the same time pubic hair will be stage 2

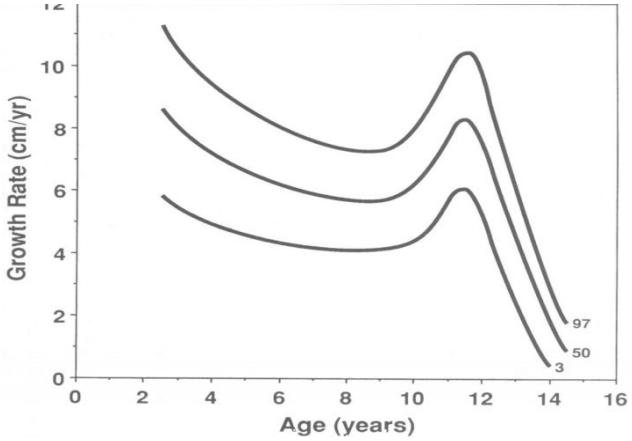
Growth Spurt

A global process involving:

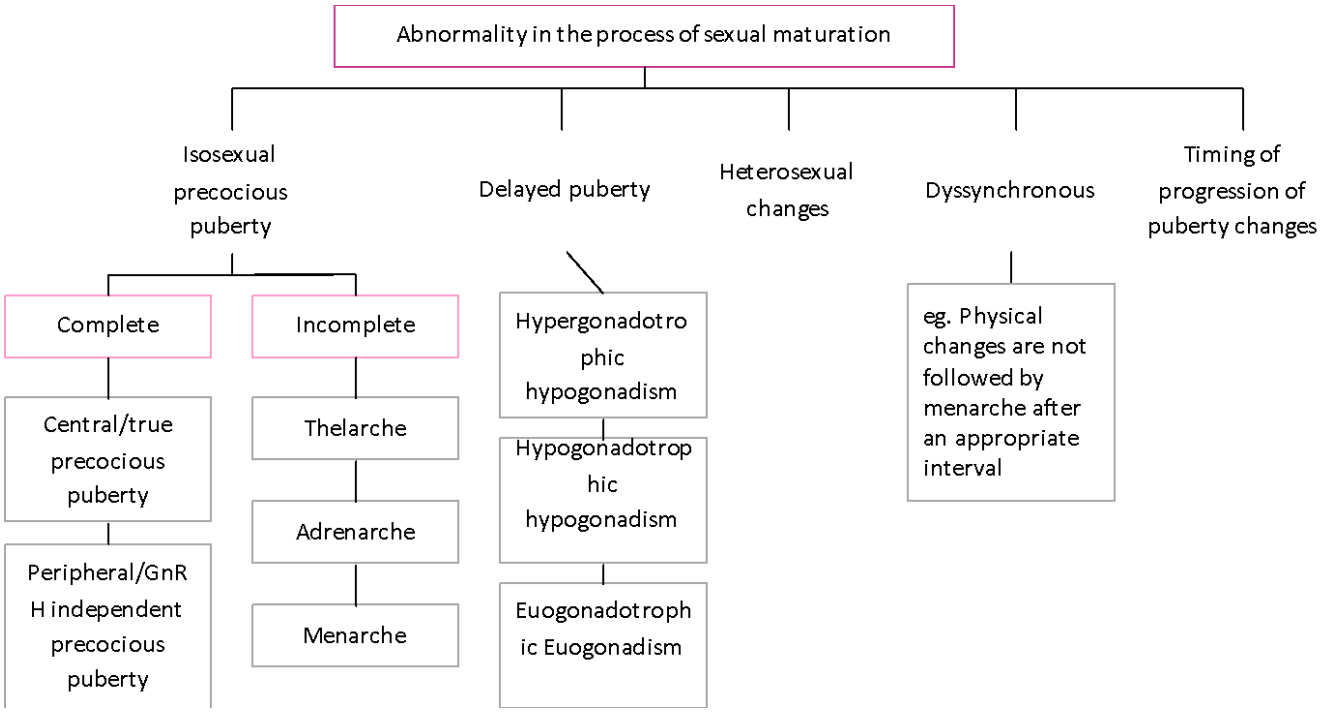
1. increase skeletal growth rate
2. increase muscle mass
3. growth of all internal organs

- Dependent on mainly on estrogen & growth hormone however adrenal androgens also play a role
- Estrogen has :
    1. direct anabolic effect
    2. increase growth hormone
    3. increase insulin like growth factors
- The onset of growth spurt antedates thelarche & pubarche
- Coincident with increase shoe size

GROWTH RATE VERSUS AGE IN GIRLS



Abnormalities of Puberty



Precocious Puberty

What is precocious puberty? Early onset of puberty before 8 years of age in girls and 9 years in boys [1]

- Difficult to ascertain the early age limit because:
    A. 15% of black girls, 5% of white girls have Breast development at 7 Y of age without associated early menarche
    B. 17.7% of black girls, 2.8 % of white girls have Pubic hair development at 7 Y of age. but in general since it under 8 we need to investigate
- Most cases (75%) of PP are 2ry to idiopathic premature maturation of the HPO axis with GnRH release.

[1] PP is more common in girls than boys

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1- Central precocious puberty

Facts

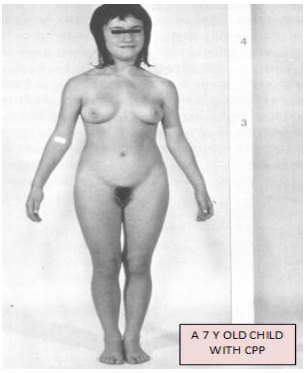
- CPP is physiologically normal pubertal development that occur at an early age.
- GnRH dependent: ↑ GnRH pulses → ↑ gonadotropins (high FSH levels) → ↑ ↑ ovarian estrogen production & eventual ovulation.
- It follows the pattern of pubertal changes that occur in normal puberty
- More common in girls than boys

Causes

I. Idiopathic (80-90% of precocious puberty) agonist.

II. CNS tumors e.g. **Hypothalamic hamartomas:**
   - A congenital malformation
   - The most common type of CNS tumor that cause CPP
   - Size & shape do not change significantly over time
   - May be associated with seizures (the intrahypothalamic type).
   - Rapidly progressing CPP in a child < 2 Y suggest this Dx, we can roll it out by MRI brain
   - GnRH Rx is satisfactory & safe

Other examples of CNS tumors: Optic gliomas, Craniopharyngioma, Dysgerminoma, Ependymoma, Ganglioneuroma



III. CNS dysfunction:
   A. Space occupying lesion e.g. Arachnoid cyst
   B. Hydrocephalus
   C. Irradiation
   D. Trauma
   E. Infection
   F. Septo-optic dysplasia (congenital)
   G. Excessive exposure to sex steroids (congenital adrenal hyperplasia)

Treatment

Purpose of treatment:

1. To gain normal adult height (Pt with CPP will have an ultimately shortened adult height[2])
2. Amelioration of the psychosocial consequences of increased size > unrealistic adult expectations

Who should be treated?

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

Medications

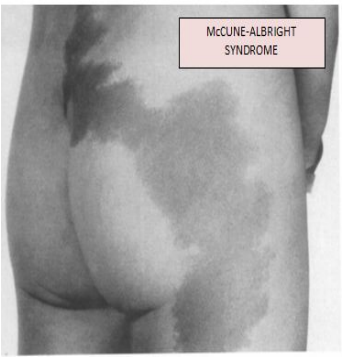
A. The treatment of choice is A GnRH Analogue best treatment available, because it stop the whole process

[2] due to the premature fusion of the long bone epiphyses.
[4] it will be in steady level which suppress LH+FSH and estrogen, normal GnRH release in plusital pattern

	• GnRH agonists[4] (zoladex) bind to GnRH receptors (competitive inhibition) → down regulation of receptor function → decreased gonadotropin secretion → inhibition of the HPO axis → decreased estrogen secretion → regression of the manifestation of puberty ○ The goal of therapy is complete suppression of gonadotropin secretion → prepubertal GnRH stimulation test result. ○ Adult height of treated pt. is higher than untreated, and is related to skeletal age at the onset of treatment (the sooner the better), but still less than the target / predicted height for the normal. ○ Rx is continued until the progress of puberty is age appropriate ○ Best statural outcome when pt. treated until bone age 12 -12.5 years ○ Growth hormone may be added to Rx ○ After discontinuation of Rx, resumption of puberty occurs & precedes at a normal pace ○ **Side effects:** local injection reaction & sterile abscess B. Medroxyprogesterone acetate: Used in the past, suppress the progression of puberty & menses and has no effect on skeletal maturation & adult height.
2-Peripheral precocious puberty/ Pseudo PP (PPP)	
Facts	• GnRH independent, it due to peripheral estrogen not to hypothalamic development • Due to inappropriate sex hormone secretion or exposure to exogenous sex steroids. • LH & FSH levels are prepubertal (low), while estrogen levels are elevated. • May present with some or all of the physical changes of puberty
Causes	1. **Exogenous sex steroids or gonadotropins** 2. **Abnormal secretion of gonadotropins** (rare) e.g. Tumors secreting hCG (teratoma) 3. **Functioning ovarian tumors** (uncommon): • Functional ovarian tumors present with rapid progression of breast development, vaginal bleeding & abdominal pain, palpable mass & dulling of vaginal mucosa[3] • Estradiol level excessively elevated. • U/S, CT, MRI, are helpful in confirming the Dx • Rx: Excision → regression of 2ry sexual characteristics. A. **Granulosa cell and Granulosa-theca cell tumors**: 70% present with PP ○ Malignant ovarian tumors are responsible for 2-3% of all cases of precocious pseudopuberty (PPP) in girls. The most common are the granulosa cell tumors. A pelvic mass will be identified on examination of pelvic imaging B. **Mixed germ cell**: usually benign. C. **Cystadenoma, Gonadoblastoma, Lipoid**: May produce estrogen or androgen or both (rare). 4. **Functioning ovarian cysts** ○ Secrete estrogen → breast development → cyst rupture or resolution → decreased estrogen → vaginal bleeding ○ Surgery should be avoided! 5. **Adrenal tumors** (RARE) 6. **Congenital adrenal hyperplasia**

[3] The normal vagina is glistening and glossy, here there is a change in color from bright to dull

7. **Chronic 1ry hypothyroidism** May also cause delayed puberty (primary amenorrhea in females):
   high TRH > high TSH and prolactin.
   - TSH acts on FSH receptors → PPP.TSH have a lot similarity with FSH and can work on FSH receptor
   - RX: thyroxine → resolution of the PPP.
8. **McCune-Albright syndrome** (it is congenital disease)
   - Also known as Polyostotic fibrous dysplasia
   - Autonomous functioning ovaries with 1 or 2 ovarian cysts → increased estradiol. Autonomous means independent from FSH and LH effect on the ovaries
   - Café-au-lait spots and multiple cystic bone lesions
   - GnRH independent PP
   - Endocrine disorder (hyperthyroidism, hyperparathyroidism, Cushing syndrome).
   - Rx: Testolactone inhibit aromatase activity → decreased estrogen synthesis.



Treatment

1. Treat the cause (if possible) e.g. if tumor remove it
2. Drugs:
   - Testolactone: aromatase inhibitor, inhibit conversion of testosterone to estrogen, 35 mg/kg/D , 3 divided doses.
   - Ketoconazole: inhibit steroid biosynthesis (200mg tds.)
   - Cyproterone acetate: Potent progestin & antiandrogen (inhibit androgens at the receptor level) > suppress gonadal & adrenal steroidogenesis (antigonadotropic),100 mg/m2, 2 divided doses.
   - Spironolactone: inhibit androgens at the receptor level > decrease ovarian androgen production (antimineralocorticoid) 50-100mg bd
   - Medroxyprogesterone acetate

Girls with prolonged PPP → prolonged exposure of the CNS to estrogen > central precocious puberty, that why it important to treat PPP early

3- Incomplete precocious puberty

- Partial (often transient) pubertal development in the absence of other stigmata of puberty.
- Slow progression, no change or waning of the physical finding may occur.

Premature Thelarche	Premature pubarche "Adrenarche"	Premature menarche
• Premature breast development in the absence of other signs of sexual maturation. • Estradiol level is high • Unilateral or	• The appearance of pubic hair before 8 yof 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.	• Uncommon • We should rule out serious causes of bleeding. 1. Neonatal period: Due to withdrawal of estrogen produced by the fetoplacental unit.

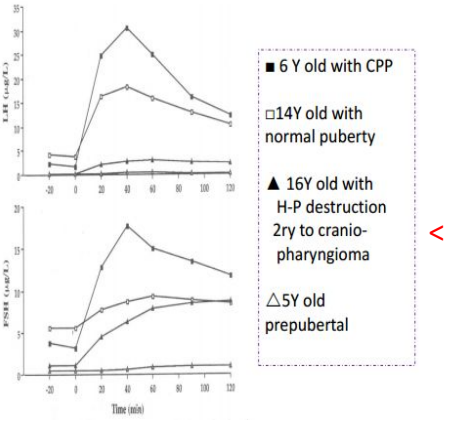
bilateral, without areolar development
• 2 years of age & non progressive.
• Follow up should distinguish cases of slow progressing CPP need to roll it out
• No Rx is indicated & subsequent normal puberty occur.
	• Slightly accelerated growth velocity & advanced skeletal maturation.ended with short adult hight
	• Puberty occur normally at the appropriate age
	• **Investigation**
	  ○ ACTH stimulation test ⟶ marked of increased 17-OH progesterone.
	  ○ plasma level of 17-OH progesterone, AND, DHEA
	• Dx: by exclusion of CAH, androgen secreting tumors & CPP
	• **Complications**
	  ○ CPP can occur 2ry to late Dx or inadequate Rx of CAH.
	  ○ 50% of pt. with premature pubarche progress to PCO
	  ○ Hyperandrogenism & insulin resistance are characteristic of PCO
	  ○ Late onset CAH may have a similar presentation
	  ○ Rx: glucocorticoids
		physiological
		2. Spontaneous regression of ovarian cysts
		3. Hypothyroidism
		4. McCune Albright Syndrome.
		• DDx
		  ○ Vulvovaginitis
		  ○ Foreign body in the vagina
		  ○ Trauma
		  ○ Sexual abuse
		  ○ Vaginal tumors

4- Adrenal Tumors (RARE)	5- Ovarian Tumors
• Function autonomously • Elevated DHEA , DHEAS, testosterone • Elevated Cortisol • Could be benign or malignant with poor prognosis	• Most commonly Arrhenoblastoma then lipoid cell tumors • Elevated Testosterone & AND • DHEA, DHEAS are NORMAL

Evaluation of patients with sexual precocity

We have to differentiate between CPP & PPP

History	• Onset & progression of symptoms (Normal tempo ⟶ CPP, Abrupt & rapid ⟶ estrogen sec Tr) • Hx of CNS trauma or infection. • Symptoms associated with neurological / endocrine dysfunction. • Exposure to exogenous steroids. • Hx of abdominal pain or swelling. • Family Hx ⟶ early puberty, short stature.
Physical examination	• Tall stature for age / changes in Hight velocity • 2ry sexual characteristics (Tanner staging) ⟶ synchronous ⟶ CPP • Neurological examination • Fundoscopy & gross visual field evaluation • Virilization • Evidence of hypothyroidism or hyperadrenalism • Examine the skin for acne, odor, café-au-lait spots, hirsutism

	• Abdomen: masses & PR.
Investigations	**1. Lab studies** • Elevated DHEA, DHEAS ⟶ adrenarche, adrenal origin of PPP. • TSH, T4, hCG • LH, FSH, Estradiol ○ Decreases LH: LH/FSH ratio < 1 ⟶ Prepubertal gonadotropin secretion ○ Increased LH: LH/FSH ratio > 1 ⟶ Pubertal gonadotropin response CPP • GnRH stimulation test (100 ugm of GnRH IV, Check FSH & LH at baseline, 20,40,60 min): ○ Prepubertal(PPP): FSH > LH, LH rise is minimal 10 IU/ml. ○ Pubertal(CPP): high LH > FSH, LH peak above upper limit for prepubertal.  **2. Bone age radiography** ○ Advanced in both CPP & PPP ○ Premature adrenarche ⟶ slightly increased ○ Premature thelarche > Normal **3. CT / MRI OF THE HYPOTHALAMIC PITUITARY REGION** ○ Important in all Pt. with suspected CPP or Pt. with neurological symptoms & signs **4. U/S:** usually done for all pt because it easy ○ Adrenal ○ Ovaries to rule out ovarian cysts or tumors & to assess size ○ Uterus to assess size **5. Vaginal smear for pyknotic index:** invasive we don't do it usually ○ A simple method of assessing the level of estrogen stimulation ○ Result is expressed in the form of % of basal, parabasal & superficial cells. ○ The greater the % of superficial cells the greater the estrogen effect.

Psychosocial consequences of precocity

1. Children with PP are taller & appear older than their peers' unrealistic expectations from parents, teachers & others child will be under stress
2. They perceive themselves as different however this does not have any long term effect & they do well psychologically
3. Sexual maturity at an immature age make them vulnerable to be victims of sexual abuse

MCQs

1- Which one of the following is NOT under the effect of Dehydroepiandrosterone, Dehydroepiandrosterone Sulfate or Androstenedione?

A- development of pubic & axillary hair

B- Breast Development

C- acne, oily skin & hair

D- adult type body odor

2- Which one of the following is the most common cause of central precocious puberty?

A- Constitutional (idiopathic)

B- Hypothalamic hamartoma

C- Congenital Adrenal Hyperplasia

D- Ovarian Tumor

3- A 6 years old girl presented to the clinic with sign and symptoms of precocious puberty. GnRh stimulation test was done, the result showed FSH levels were higher than LH levels. Which one of the following is the type of precocious puberty?

A- (True) Central precocious puberty

B- (Pseudo) Peripheral precocious puberty

4- A 7 years old girl presented to the clinic with sign and symptoms of precocious puberty, Café-au-lait spots, hyperthyroidism, history of easily fractured bones and signs of cushing disease. Which one of the following is the diagnosis?

A- Peutz-Jeghers Syndrome

B- Kallmann Syndrome

C- Swyer Syndrome

D- McCune-Albright Syndrome

Answers: 1-B. 2-A. 3- B. 4- D.