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Puberty disorders

Objectives:

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

Note: delayed puberty will be discussed in details in Amenorrhea lecture

We advise you to study this lecture with embryology and after that amenorrhea it will be much easier

References: 435 lecture and notes, Kaplan and Hackers & Moore, team 433

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PART 1: Normal pubertal development

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**.

What are the major characteristics of this period?

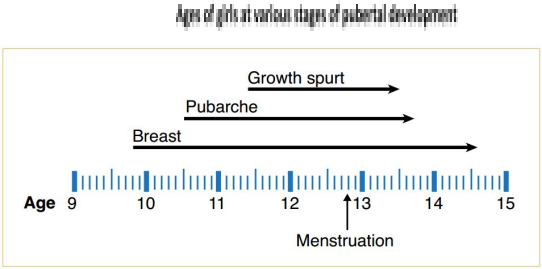
1-Maturation of the 1ry sexual characteristics: The gonads are regulated by *Hypothalamic Pituitary Ovarian Axis*
2-Development of 2ry sexual characteristics: Sexual hair, breasts and genitalia.
3-Dramatic growth spurt.
4-Psychological changes: mental & emotional maturity.

What is the age of onset of puberty[1]?

- Females: **8-13**
- Males: 9-14

What is the usual sequence of somatic changes of puberty?

1. Onset of growth spurt (at 9.6 years)
2. Beast development (mean 10.6 years)
   Note that the growth spurt starts before the breast budding but you cannot notice because it just started at 9.6 years but the maximal is reached at 12
3. Pubic & axillary hair (11.2 years)
4. Maximal growth velocity (12 years)
5. Menarche (12.7 years)



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

Physical events of puberty (KAPLAN):

- Thelarche (breast development): 9-10 yrs -most common initial change-
- Adrenarche (pubic and axillary hair development): 10-11 yrs
- Maximal growth (growth spurt): 11-12 yrs (mainly the effect of **estrogen** that induces secretion of **growth hormone** and **insulin-like growth factor**)
- Menarche (onset of first menses): 12-13 yrs

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

2.3 ± 1 years

Does menarche mark the attainment of reproductive maturity?

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

Do girls stop growing after menarche?

No, growth continues at a **decelerating rate** for a number of years.

What is the time from onset to completion of puberty?

Average 4.2 Y / Range 1.5-6 Y.

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[1] The onset of pubertal changes is determined primarily by genetic factors, and environmental factors "geographic location, nutritional status, physical activity, and psychological factors"

- **Etiology of puberty:**

  Hypothalamus: GnRH secretion by the arcuate nucleus is modulated by two inhibitory mechanisms:

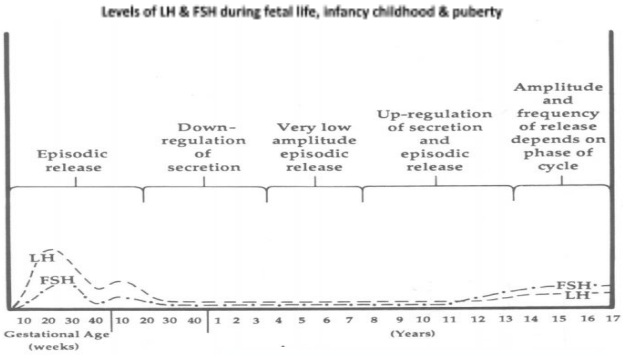
  1-Intrinsic CNS inhibitory mechanism.

  2-Negative feedback of circulating sex steroid.

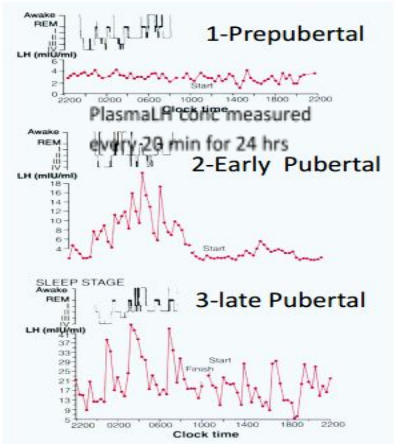
Development and maturation of the HPO AXIS (Hypothalamic-Pituitary-Ovarian axis):

- **In utero:**
  - At fifth month gestation[2], the ovaries become responsive to gonadotropin > follicular growth to early antral stage (1-2 mm, followed by atresia) > estrogen production > negative feedback.
  - A functional HPO axis exists in utero
  - the **fetoplacental unit** is the 1ry source of estrogen production[3] > Increased estrogens > decreased FSH & LH levels.

- **After birth:**
  - ➢ **The main mechanism controlling FSH & LH secretion in infants is the level of sex steroids:**
    - ➔ Peak FSH & LH at 1-2 years after birth (because estrogen levels decrease dramatically > FSH & LH levels increase > increased ovarian estrogen production in early infancy).
  - ➢ **The intrinsic CNC inhibitory mechanism:**
    - ➔ Gradually develops with continued growth & maturation of the CNS > Minimum FSH & LH level at 6-8 years.
    - ➔ The principal CNS inhibitor of GnRH is **GABA**.



- **At the onset of puberty (THE SEQUENCE OF MATURATION):**
  1) **At the onset of puberty, GnRH pulses occur during sleep** > LH pulses.
  2) The frequency of LH pulses increase with further maturation.
  3) LH pulses appear during day time & increase in amplitude.
  4) **As menarche approaches > the pulses are detected all the time (no diurnal variation).** Adult-type secretory pattern, with GnRH pulses occurring every 90-120 minutes throughout the 24-hour day
  5) Similar changes occur in FSH pulses.
  6) LH/FSH ratio increase.



Normally LH and FSH are impulsively secreted not constant

In prepubertal stage its very low
In early puberty we start to get it during sleep
In late puberty it's happening all the time

- **Initiation of puberty:**
  - Factors responsible for the initiation of the puberty are **UNKNOWN**.
  - **Frisch theory:** A **critical body fat & body weight** are required for the initiation of menarche. Supported by :

    1-Highly competitive athletic training > delayed puberty.

    2-Delayed menarche in malnutrition.

    3-Overweight girls have early menarche.
    - **Leptin:** An adipose derived protein may play a role in the initiation of puberty.

[2] By 20 weeks' gestation, levels of gonadotropins (LH and FSH)rise dramatically in both male and female fetuses

[3] In both male and female fetuses, serum estradiol is primarily of maternal and placental origin.

4-Patients with anorexia nervosa revert to prepubertal pattern of Gonadotropin secretion as body weight decreases.

- **Against the theory:** Changes in body composition occurs simultaneously with gonadotropin increase & does not precede it.

★ **Gonadostat** begins to lose its sensitivity to the –ve feedback by **estrogen** > reactivation of GnRH pulsatility > puberty.

★ CNS inhibitory mechanism (on the hypothalamus) wane "decreases" > **Increased GnRH**, **FSH & LH and estrogen** (gonadarche).

★ Increased sensitivity of the pituitary to GnRH.

★ Increased sensitivity of the ovary to LH & FSH > Increased estrogen secretion.

Adrenarche[4] (pubarche)	- The maturational increase in **adrenal androgens** secretion (DHEA, DHEAS, AND)[5] ➔ **development of pubic & axillary hair** ➔ adult type body odor ➔ acne ➔ oily skin & hair - DHEAS: First detected at 7 Y, maximum at 15 Y. - The mechanism of initiation is unknown - Adrenal androgens > increased bone age & linear growth - Premature adrenarche > **decreased adult height** - Adrenarche & gonadarche are NOT associated.
Gonadarche (maturation of the hypothalamic pituitary ovarian axis)	- The onset of pubertal gonadal activity due to reactivation of HPO axis > Increased estrogen (at the beginning it is anovulatory it has to reach a certain level of estrogen to stimulate LH surge to cause ovulation) - 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 - Reactivation of HPO axis > increased gonadotropin pulses sustained follicular development to antral stage > significant estrogen production (normally estrogen has a negative feedback on LH and FSH but when it reaches a certain high levels it turns into positive feedback and stimulate the LH surge) - There is direct relationship between follicular size & estrogen secretion.
Menarche	When there is sufficient gonadotropin stimulation of the ovaries > follicular growth (~16mm) > Increased estrogen > proliferation of the endometrium (until it outgrows the estrogen capacity to maintain it or the follicle undergo atresia) > decreased estrogen > menstruation (MENARCHE): ➢ **Anovulatory cycles** occur during the first 6-18 months **"endometrium is not exposed to progesterone"** > irregular unpredictable menstrual flow.reassure the mothers this is normal unless there is an obvious problem and very heavy bleeding it is caused of the immaturity of the axis (hypothalamic) ➢ **Ovulatory menstrual cycles:** - Requires further maturation of the HPO axis > development of the +ve feedback mechanism > LH surge ovulation & corpus luteum formation > **progesterone production**. - Early ovulatory cycles have short or inadequate luteal phase because HPO axis has not achieved full maturity.

[4] girls who undergo premature pubarche are more likely than other girls to develop PCOS as adults

[5] Dehydroepiandrosterone, DHEA sulfate, Androstenedione

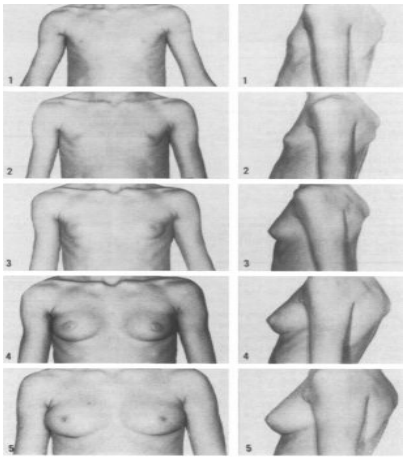
1- Breast development:

Thelarche:

- **The FIRST visible change of puberty.** Growth spurt starts before the breast budding but you cannot notice it.
- Thelarche is induced by **estrogen**. Normal breast development = normal production of estrogen
- Starts at **10.6 years** and completed in almost 3 years.
- Effects of estrogen on the breast:
  a) **Ductal proliferation**
  b) **Site specific adipose deposition**
  c) **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 of breast development (depends on gonadarche = estrogen)

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** (breast elevates beyond the borders of the areola, which remains in contour with surroundings)
STAGE 4	**Areola and nipple form a mound atop breast tissue** (increased breast size & elevation, **areola forms a secondary mound**)
STAGE 5	**Adult configuration areola & breast having smooth contour** (final adult size, areola return to contour of the surrounding breast)



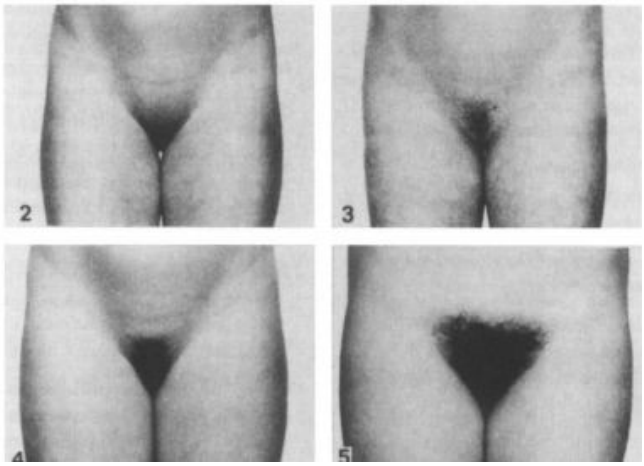
2-Maturation of the genital organs

	Prepubertal	Pubertal (Adult)
Uterus	- Ratio of corpus:cervix (cx) > 1:2 -Tubular shape -Length: 2-3 cm -Volume: 0.4-1.6 -Endometrium: single layer of cuboidal cells	-Ratio of corpus:cervix (cx) > 2:1 -Pear shape -Length : 5-8 cm -Volume: 3-15 -Endometrium: increased thickness
Ovaries	-Volume: 0.2-1.6 ml -Non functional	-Volume: 2.8-15 ml -Multicystic
Vagina	-Reddish in color -**Thin atrophic columnar epithelium** -PH: neutral -Length: 2.5-3.5 cm	-Dulling of the reddish color -Thickening of the epithelium & Cornification (keratinization) of the superficial layer > **stratified squamous epithelium** -PH: acidic (3.8-4.2) -Length: 7.5 cm -Secretion of clear whitish discharge in the months before menarche

External genitalia	-	**Under the effect of <u>estrogens</u>:** 1-Labia majora & minora increase in size & thickness. 2- Rugation & change in color of the labia majora 2-The hymen thickens 3-Clitoris enlarge 4-Vestibular glands begin secretion **Under the effect of <u>adrenal androgens & ovarian androgens</u>**: growth of pubic & axillary hair.

Tanner staging of pubic hair development (most of the time tanner will be the same for breast and pubic hair but **pubic hair depends on adrenarche (androgen)**, while breast depends on gonadarche (estrogen))

STAGE 1	**No** pubic hair.
STAGE 2	Sparse downy hair on the medial aspect of the **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 pubis** but sparing medial thighs)
STAGE 5	Hair spreads to **medial aspect of thighs**.

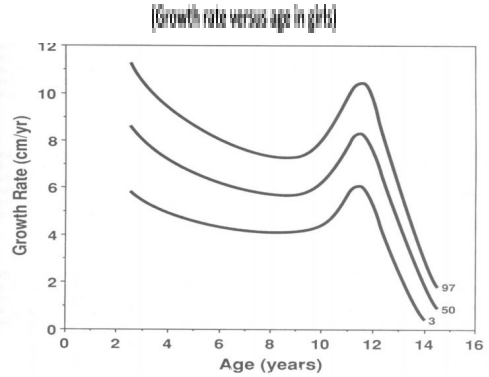


3- Growth spurt

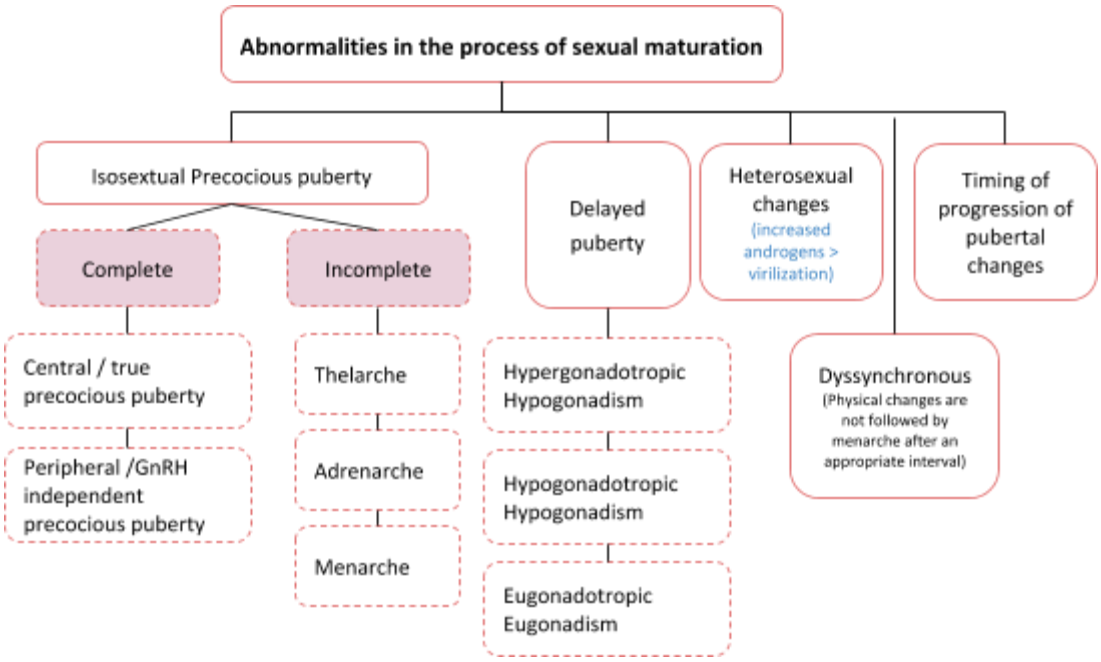
- A global process involving increased skeletal growth rate and muscle mass, & growth of all internal organs.
- Dependent on mainly on **estrogen & growth hormone**. However **adrenal androgens** also play a role
- **Estrogen has:** 1) Direct anabolic effect. 2)Increase growth hormone. 3)Increase insulin like growth factors.
- The onset of growth spurt antedates thelarche & pubarche.
- Coincident with increased shoe size!
- **Peak Height Velocity (PHV):**

➔ 8.1 cm/year (before puberty 3-6 cm/y).
➔ Occurs in midpuberty.
➔ by the time PHV is achieved > 90% of adult height has been achieved.
➔ The average increase in height from the onset of growth spurt to cessation of growth = 25 cm.
➔ Girls who start the growth spurt early will have a shorter adult height.

- Bone age is more closely correlated with pubertal events than chronological age.



PART 2: Pubertal disorders (Cases from dr slides)



❖ Precocious puberty:

- **What is precocious puberty[6] ?**
  - **Early onset** of puberty before **8 years of age in girls** and 9 years in boys [7]
  - Difficult to ascertain the early age limit because:
    A) 15% of black girls, 5% of white girls > Breast development at 7 Y of age without associated early menarche
    B) 17.7% of black girls, 2.8 % of white girls > Pubic hair development at 7 Y of age.
  - Precocious puberty is either:
    - **GnRH dependent (high FSH) (central PP)**
    - **GnRH independent (low FSH) (peripheral PP)**

Most cases (75%) of PP are 2ry to **idiopathic** premature maturation of the HPO axis with GnRH release.

So the commonest cause is simply premature maturation of hypothalamus and production of the gonadotropin releasing hormones.

Quick Triads:
-CPP + 6 or 7 y/o + Normal head MRI= Idiopathic CPP
-CPP + 4 y/o + Abnormal head MRI= CNS lesion
-CPP + 6 y/o + Cafe-au-lait skin lesions= McCune-Albright Syndrome
-CPP + 6 y/o + Pelvic mass= Granulosa Cell Ovarian Tumor

- **Psychological consequences of precocity:**

1. Children with PP are taller & appear older than their peers > unrealistic expectation 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.

[6] development of any sign of secondary sexual maturation at an age 2.5 standard deviations earlier than the expected age of pubertal onset.
[7] PP is 5 times more in girls than boys.

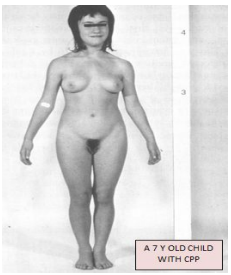
1- Central precocious puberty (CPP)(there is maturation of the HPO axis)

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

1) **Idiopathic** (80-90% of PP): MRI is normal. Rx: GnRH agonist.
2) **CNS tumors :** MRI is abnormal. Rx: variable



A. 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
- GnRH Rx is satisfactory & safe (it is benign. Does not require excision. Respond to GnRH treatments)

B. Optic gliomas C. Craniopharyngioma D. Dysgerminoma E. Ependymoma F. Ganglioneuroma

3) CNS dysfunction[8]:

A. Space occupying lesion eg. Arachnoid cyst **B. Hydrocephalus C. Irradiation D. Trauma E. Infection F. Septo-optic dysplasia (congenital) G. Von Recklinghausen disease H. Excessive exposure to sex steroids (congenital adrenal hyperplasia)**

Treatment

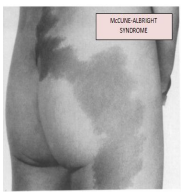
Purpose of treatment:
1) To gain normal adult height (Pt with CPP will have an ultimately shortened adult height[9])
2) Amelioration of the psychosocial consequences of increased size > unrealistic adult expectations
Who should be treated?
1) Pt. with early puberty (<6Y), accelerated growth & advanced 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.

A) THE TREATMENT OF CHOICE IS A GnRH ANALOGUE (as an injection IM or SC causing GnRH to always be high leading to negative feedback)

- GnRH agonists (zoladex) -leuprolide or lupron- 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 &

[8] always make sure to ask in the history for encephalitis or meningitis or any head trauma or radiation for other problem
[9] due to the premature fusion of the long bone epiphyses.

	menses. NO effect on skeletal maturation & adult height. (may cause atrophy of the endometrium)
2- Peripheral precocious puberty/ Pseudo PP (PPP)(no maturation of the HPO axis)	
Facts	-**GnRH independent** (low FSH, increased estrogen from **autonomous ovarian production**) - 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) eg. 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[10] - 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 (folliculoma) tumors:** 70% present with PP - Malignant ovarian tumor are responsible for 2-3% of all cases of precocious pseudopuberty (PPP) in girls. - The most common are the granulosa cell tumors -Pelvic mass **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 bleed (like the withdrawal bleeding the occurs with normal period) - Surgery should be avoided! (spontaneous resolution) (but sometimes it is large, leading to cyst accident which is a cyst rupture leading to **intraperitoneal hemorrhage** or bleeding in the cyst causing severe pain, in this case we have to interfere surgically) **5) Adrenal tumors** (RARE) (could cause excessive hormonal secretion) **6) Congenital adrenal hyperplasia** -Defect in 21-hydroxylase- > embryology lecture **7) CHRONIC 1RY HYPOTHYROIDISM[11]:** TSH acts on FSH receptors (because of the similarity between the amino acids) > PPP. RX: thyroxine > resolution of the PPP. **8) McCune-Albright syndrome** (congenital)**:** (AKA polyostotic fibrous dysplasia) - Multiple cystic bone lesion - Café-au-lait spots - Autonomous functioning ovaries[12] with 1 or 2 ovarian cysts > increased estradiol. - Endocrine disorder (hyperthyroidism, hyperparathyroidism, Cushing syndrome). - **Rx: Testolactone** inhibit aromatase activity > decreased estrogen synthesis. **9) Peutz-Jeghers syndrome:** a rare sex cord tumor with annular tubules, which secrete estrogen 
Treatment	**1) Treat the cause (if possible)** e.g. excision of tumor. **2) Drugs:** (estrogen inhibiting 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)

[10] The normal vagina is glistening and glossy, here there is a change in color from bright to dull
[11] May also cause delayed puberty (primary amenorrhea in females): high TRH > high TSH and prolactin.
[12] By simulation of aromatase enzyme. *Remember that aromatase converts androgens to estrogen

	- **Medroxyprogesterone acetate** * Girls with prolonged PPP > prolonged exposure of the CNS to estrogen > central precocious puberty

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.
- Management is mainly conservative -

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 bilateral, **without areolar development** - < 2 years of age & non progressive. - Follow up should distinguish cases of slow progressing CPP - No Rx is indicated & subsequent normal puberty occur. (when you see it you have to rule out CPP and PPP)	- 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. (might end up with short adult hight) - **Puberty occur normally at the appropriate age** - **Dx: by exclusion of CAH, androgen secreting tumors & CPP.** see below - CPP can occur 2ry to late Dx or inadequate Rx of CAH.	- Uncommon - We should rule out serious cause of bleeding. **1- Neonatal period** - Due to withdrawal of estrogen produced by the fetoplacental unit. (this is normal> reassure the mother. but if it occurs later after neonatal period you have to take it seriously) **2- Spontaneous regression of ovarian cysts** **3- Hypothyroidism** **4- McCune Albright Syndrome**. -DDx : ➢Vulvovaginitis ➢Foreign body in the vagina ➢Trauma ➢Sexual abuse ➢Vaginal tumors

HETEROSEXUAL PRECOCITY - will be discussed in the embryology lecture (intertextuality)

1- Exposure to exogenous androgens.

2- Androgen-secreting neoplasms (very rare)

Dx: physical and radiologic examinations of the abdomen Rx: by surgical removal.

ADRENAL TUMORS (RARE)	**OVARIAN TUMORS**
- Function autonomously - Elevated DHEA , DHEAS, testosterone - Elevated Cortisol - Could be benign or malignant with poor prognosis	- Most commonly Arrhenoblastoma - lipoid cell tumors - Elevated Testosterone & AND - DHEA, DHEAS > NORMAL

3- Congenital adrenal hyperplasia most commonly results from a defect of the adrenal enzyme **21-hydroxylase** that leads to excessive androgen production.

- More severe forms of this defect cause the birth of a female with ambiguous genitalia. If untreated, progressive virilization during childhood and short adult stature will result.
  Rx: replacement of cortisol and surgical correction of any anatomic abnormalities in the first few years of life.
- A less severe form of this defect, referred to as nonclassic (late onset) adrenal hyperplasia **can cause premature pubarche and an adult disorder resembling PCOS.**
- Late onset CAH may have a similar presentation to pubarche

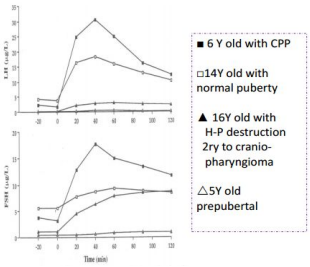
Dx: ACTH stimulation test > Marked elevation of 17-OH progesterone, increased plasma level of 17-OH progesterone, AND, DHEA.

Rx: glucocorticoids

- 50% of pt. with premature pubarche progress to PCOS > Hyperandrogenism & insulin resistance

Evaluation of patients with sexual precocity:

WE HAVE TO DIFFERENTIATE BETWEEN CPP & PPP

1- History	- Onset & progression of symptom (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. (to check for ovarian tumors) - Family Hx > early puberty, short stature.
2- PE	- Tall stature for age / changes in Ht. velocity (it is very important indication for growth spurt, so if we find the height higher than expected at this age maybe an indication for accelerated growth 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): (very important for diagnosis and differentiation between CPP and PPP) ➔ Prepubertal: FSH > LH, LH rise is minimal < 10 IU/ml. ➔ Pubertal: high LH > FSH, LH peak above upper limit for prepubertal. (more than 10) **2) Bone age radiography:** (X-ray of the wrist) - 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:** - Adrenal - Ovaries > rule out ovarian cysts or tumors & to assess size - Uterus > to assess size **5) Vaginal smear for pyknotic index:** (not used much because it is very difficult to take a sample of the vagina for a young girl)

	- 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.

❖ **Delayed puberty:** (within the objectives but not mentioned in the slides). **Source: 433 team**

This topic is discussed in amenorrhea lecture as "Primary amenorrhea"

- Mostly patient come because of delay in the menstruation .
- It is important to establish whether puberty itself is delayed.
- Detailed history is taken about other secondary sexual characters.
- Exclude chronic illness .
- Family history.

Investigations

- Gonadotropins level FSH and LH .
- Karyotyping .
- Pelvic ultrasound to confirm the presence of the uterus and ovaries .
- Possibly X- ray to determine bone age.
- Other like thyroid function test prolactin and 17-alpha- hydroxy-progesterone .

- **Absence of pubertal development** (no breast development by age 13, no menarche by age 15, no menarche by 3 years after the onset of breast development, lack of progression to next Tanner stage in a year).
- Physiologic delays in puberty tend to be **familial.**
- Sexual hair onset does not mean the onset of puberty. It is due to adrenal androgen secretion.

- **Types:** further details in the next page from doctor ahmed

Hypergonadotropic Hypogonadism worse prognosis Give them the estrogen and progesterone	**Hypogonadotropic Hypogonadism** good prognosis because there are ovaries just give hormones	**Euogonadotropic Eugonadism**
FSH / LH ↑ 1-Autoimmune ovarian Failure. 2-Turner's syndrome.[13] 3-Previous radiation or chemotherapy. 4-Galactosemia. 5-Gonadal dysgenesis (XX, XY).	**1-REVERSIBLE CAUSES** -Constitutional (without problems) delay "most common 30%". -Systemic disease (hypothyroidism, prolactinoma, excessive exercise, CAH, anorexia nervosa, brain tumor, chronic diseases، crises or stresses). if she want to get pregnant we can give her gonadotropin , but if she doesn't just estrogen and progesterone (for secondary characteristics , prevent osteoporosis and regulate menstrual cycle) **2-IRREVERSIBLE CAUSES:**	**Normal pubertal onset but lack of menarche** 1-Mullerian agenesis (most common)they have hair، there is high chance that they have kidney problems 2-vaginal septum/ imperforate hymen. 3-Androgen insensitivity the phenotype is female but she has a testis XY and no female internal organ they do not have hair

[13] characterized by loss or structural anomalies of an X chromosome. Its clinical features vary, and multiple organ systems may be affected. Often these patients present with hypergonadotropic hypogonadism and clinical features such as short stature and infertility.

	-Kallmann Syndrome[14](most common) - Hypopituitarism -Congenital CNS lesion -GnRH receptor defects	4-Hypothalamic amenorrhea with onset after puberty (excessive exercise, extreme weight loss, psychogenic stress).

Hypogonadotropic hypogonadism

- Majority is constitutional delay in puberty.
- May be secondary to chronic illness and improvement of underlying condition is the treatment.
- Anorexia nervosa at young age have low levels of gonadotropin .
- Athletic girls .
- Congenital deficiency of gonadotropin with hypoplasia of olfactory lobe Kallmann syndrome
- Acquired damage to hypothalamus and pituitary by tumor, trauma ,infection , radiation , secondary to hydrocephalus and hemochromatosis due to repeated transfusion in sickle cell disease , thalassemia and wilson disease .
- In all cases the ultrasound will confirm the immature uterus and small inactive ovaries,
- Most girls with constitutional delay will proceed to normal development if left untreated.

Otherwise treatment is replacement with gonadotropin or estrogen and progesterone

Hypergonadotropic hypogonadism

- Failure of gonadal development.
- No negative feedback from the gonads .
- Commonest cause is Turner syndrome 45xo .
- Damage to the ovaries by infection , irradiation, chemotherapy, or surgery .
- Autoimmune disease such as Addison , vitiligo, and hypothyroidism.

Treatment by hormone replacement therapy estrogen and progesterone.
Gonadal causes carries a bad prognosis for pregnancy .

- **Evaluation:**

1-History
2-Physical examination
3-Investigations:

- Hormonal profile : (FSH,LH , PROLACTIN , TFT , PROGESTERONE).
- IMAGING: Pelvic US, MRI,CT, Bone Age (X-ray),Brain MRI.

BOX 32-3

RADIOLOGIC AND LABORATORY TESTS USED TO EVALUATE FEMALE DELAYED PUBERTY

Radiologic

Magnetic resonance imaging or computed tomography of the brain with optimal visualization of hypothalamic region and sella turcica (hypogonadotropic hypogonadism)

Laboratory

Follicle-stimulating hormone
Karyotype (delayed puberty, ambiguous genitalia)
Progesterone (delayed puberty secondary to 17-hydroxylase [P450c17] deficiency)
Prolactin (hypogonadotropic hypogonadism)

- **Management: (Treat the underlying cause)**

1-Turner syndrome → hormone replacement therapy.
2-HIGH FSH / NORMAL KARYOTYPE XX → Autoimmune ovarian failure or Gonadal dysgenesis → hormone replacement therapy.

[14] They have isolated GnRH deficiency (no secretion of GnRH → ↓ LH / FSH → ovaries will not produce follicles → ↓ Estrogen.It is associated with anosmia (decreased sense of smell). These individuals may have other anomalies of midline structures of the head. We cannot treat it, but we can treat the symptoms (e.g. LH/FSH for ovulation, or Estrogen as a replacement if she is not planning to get pregnant).

3-HIGH FSH / XY KARYOTYPE (Gonadal dysgenesis) → hormone replacement therapy + Gonadectomy (to prevent malignant changes).

4- LOW / NORMAL FSH → Exclude systemic disease.

If no systemic disease:

- MRI of the brain.
- GnRH stimulation test.

★Q1: A 7-year-old girl achieved her menarche 2 months ago with a good breast development. Which one of the following can be a cause of her condition?

A. Brain tumour.
B. Congenital adrenal hyperplasia.
C. Mullerian agenesis.
D. Turner syndrome.

The answer is: A

BOX 32-2

LABORATORY TESTS USED SELECTIVELY TO EVALUATE FEMALE PRECOCIOUS PUBERTY

Radiologic

Serial bone age (isosexual precocity)

Magnetic resonance imaging (MRI) or computed tomography (CT) of the brain with optimal visualization of hypothalamic region and sella turcica (true isosexual precocity)

MRI, CT, or ultrasonography of abdomen, pelvis, or adrenal gland (heterosexual precocity, pseudoisosexual precocity)

Laboratory

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

Dehydroepiandrosterone sulfate, testosterone (heterosexual precocity)

17-hydroxyprogesterone, 11-deoxycortisol (suspected congenital adrenal hyperplasia causing heterosexual precocity)

Thyroid function tests (thyroid-stimulating hormone, free thyroxine) (isosexual precocious puberty)

Gonadotropin-releasing hormone (GnRH) stimulation test: LH measurement after 100 μg of GnRH is given intravenously (to differentiate gonadotropin-dependent from gonadotropin-independent isosexual precocity)