بسم الله الرحمن الرحيم

Puberty

Dr Moamar Al-Jefout,

MD, JBO&G, MMed (HR&HG), Ph.D
Associate Professor in Human Reproduction. Endoscopic Surgeon
UAEU, CM&HS
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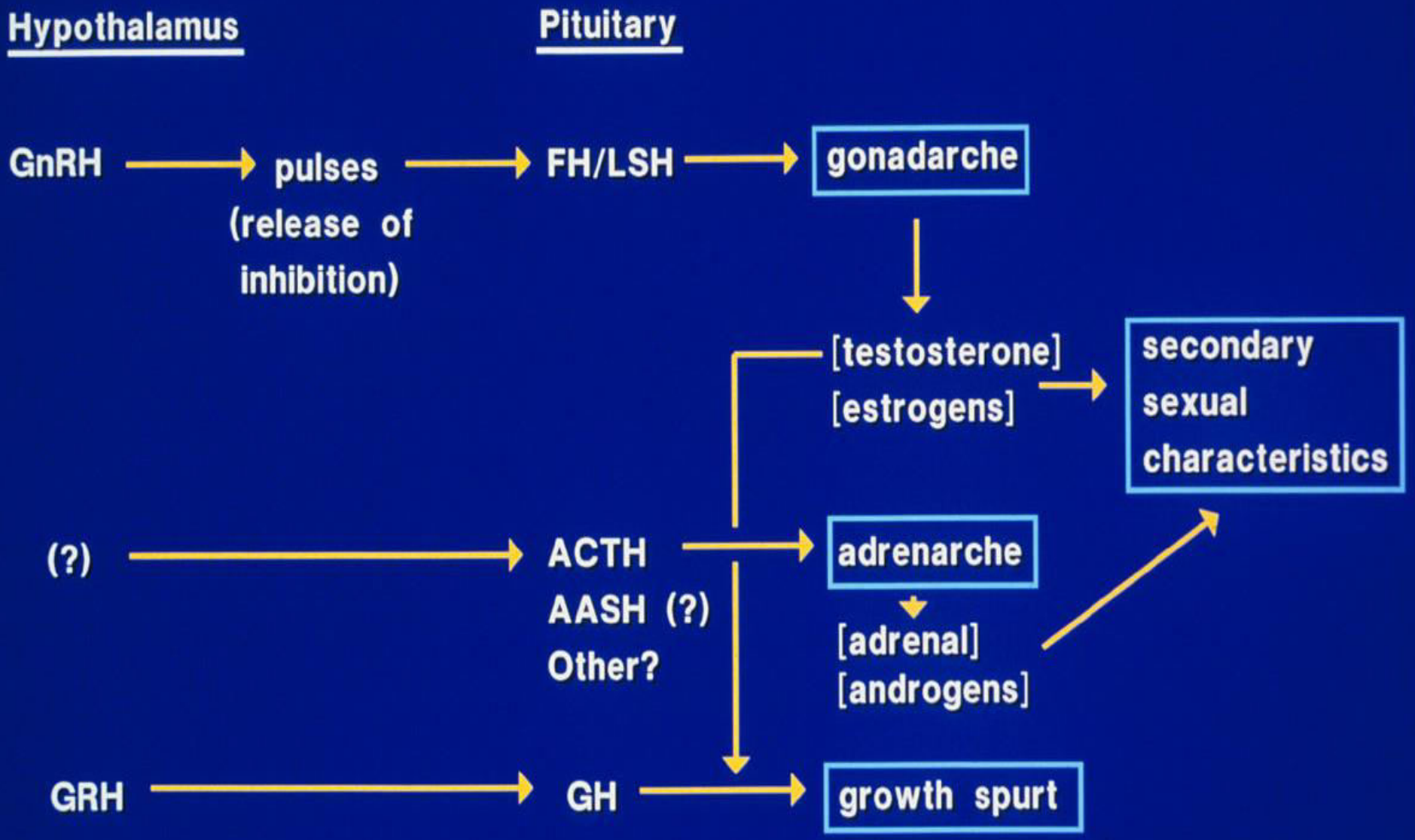
drmoamar@yahoo.co.uk

Puberty

- Puberty is the first stage of adolescent .
- The process of sexual maturation requires approximately 4 years.
- It is an endocrine process that involves the physical, emotional, and sexual transition from childhood.
- There is a strong relationship between body fat content and the onset of puberty.
- From a biologic perspective, the beginning of adolescence is marked by the onset of puberty .
- Cultural influences on puberty include nutrition, the quality of health care and living conditions.

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

Hormones and hormonal changes during puberty:

The Gonadotropins:

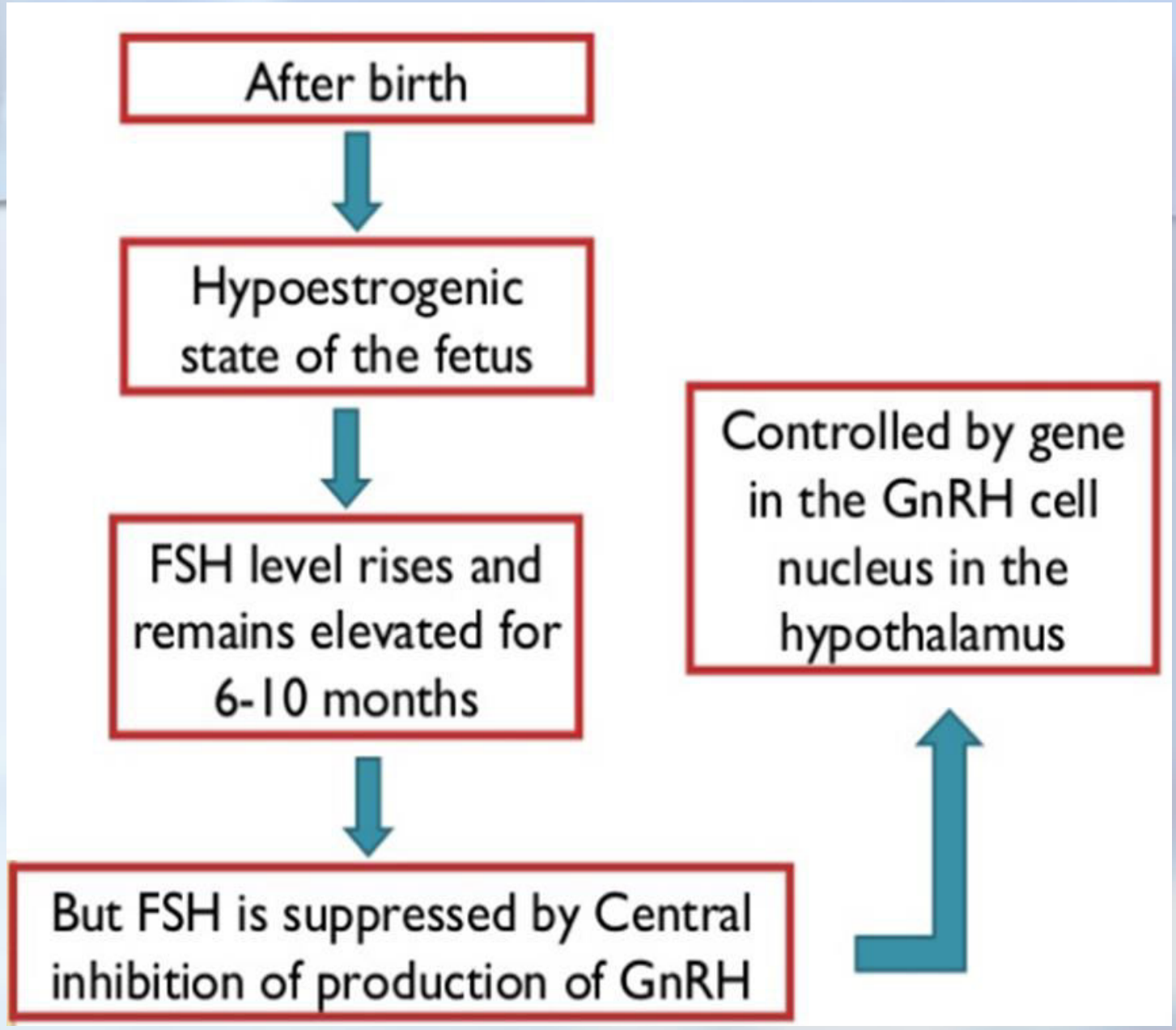
- LH: Increases steadily through puberty
- FSH:
  - Plateaus at Sexual Maturity Rating (SMR).
  - Rise during puberty in males and females.

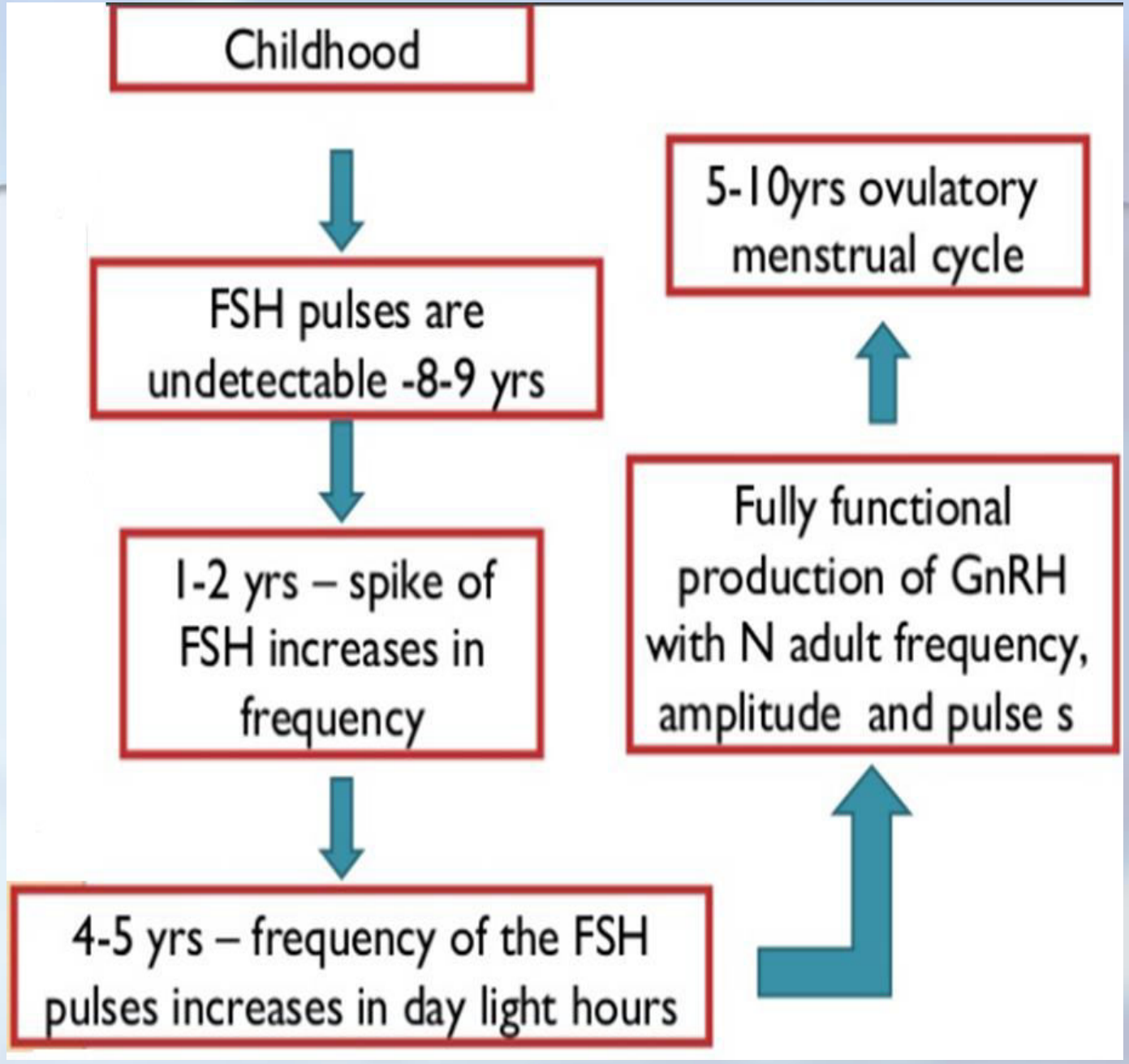
The hypothalamic–pituitary–gonadal axis

- Begins to function during fetal life and remains active during the first few weeks following birth, after which time the axis becomes quiescent secondary to enhanced negative feedback of estrogen.
- The hypothalamic–pituitary–gonadal axis again becomes active during puberty, triggering the production of gonadotropin-releasing hormone (GnRH).

Fetal and Infancy

- During the latter half of fetal life , the hypothalamus pituitary ovarian axis is functional completely .
- FSH levels are suppressed from 20 weeks gestation by the production of estrogen by the placenta and by the fetus itself.
- At birth , the fetus is separated from its placenta and therefore the major source of estrogen is removed.


After birth
Hypoestrogenic state of the fetus
FSH level rises and remains elevated for 6-10 months
But FSH is suppressed by Central inhibition of production of GnRH
Controlled by gene in the GnRH cell nucleus in the hypothalamus


Childhood
FSH pulses are undetectable -8-9 yrs
1-2 yrs – spike of FSH increases in frequency
4-5 yrs – frequency of the FSH pulses increases in day light hours
Fully functional production of GnRH with N adult frequency, amplitude and pulse s
5-10yrs ovulatory menstrual cycle

At puberty – increase secretion of releasing factors by the hypothalamus

↓

Pituitary glands

↓

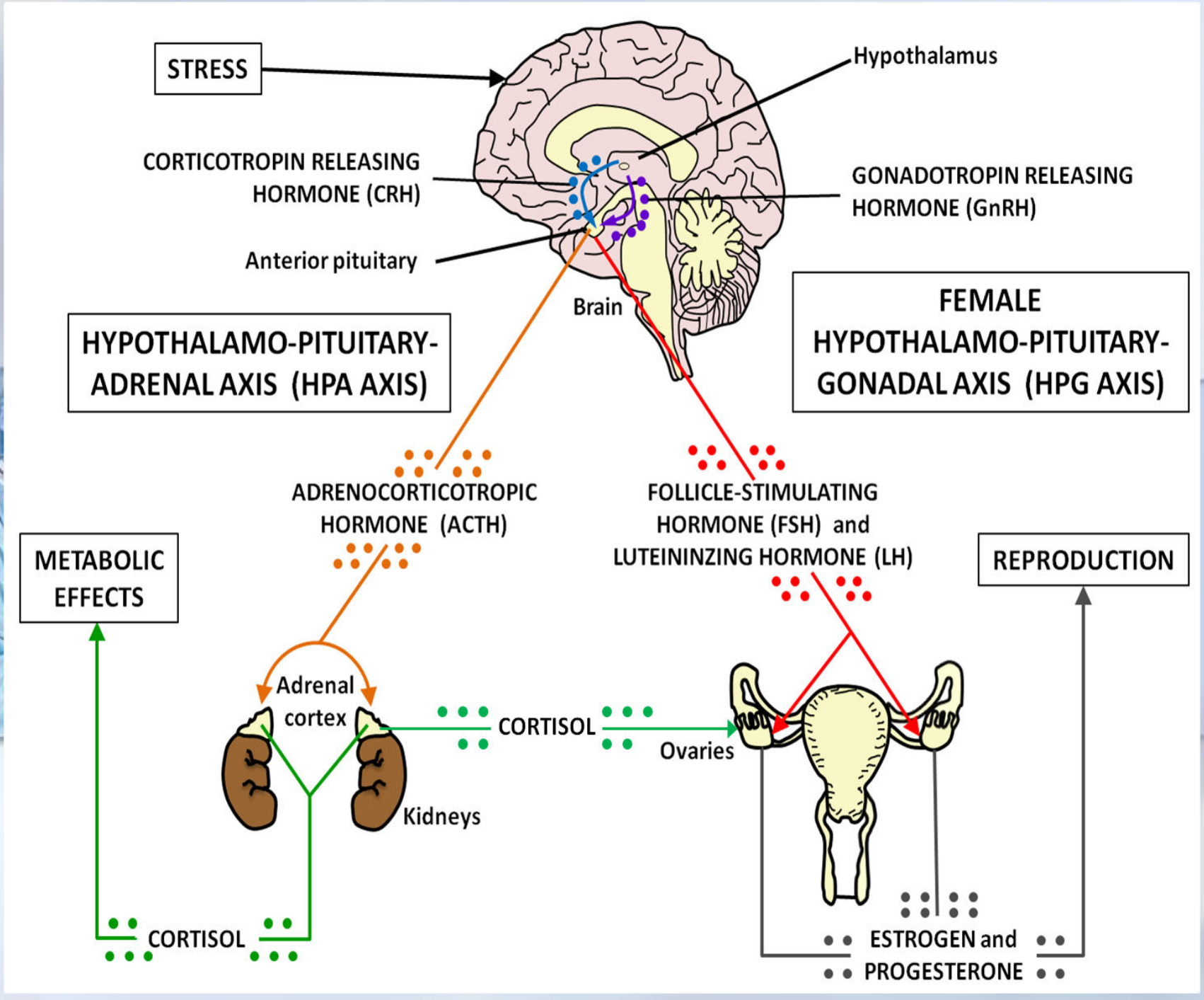
All activities increases

↓

Manifested by sudden spurt in height, enlargement of thyroid, adrenal cortex activity, skin pigmentation

↓

Cyclical production of gonadotrophin and estrogen in amount

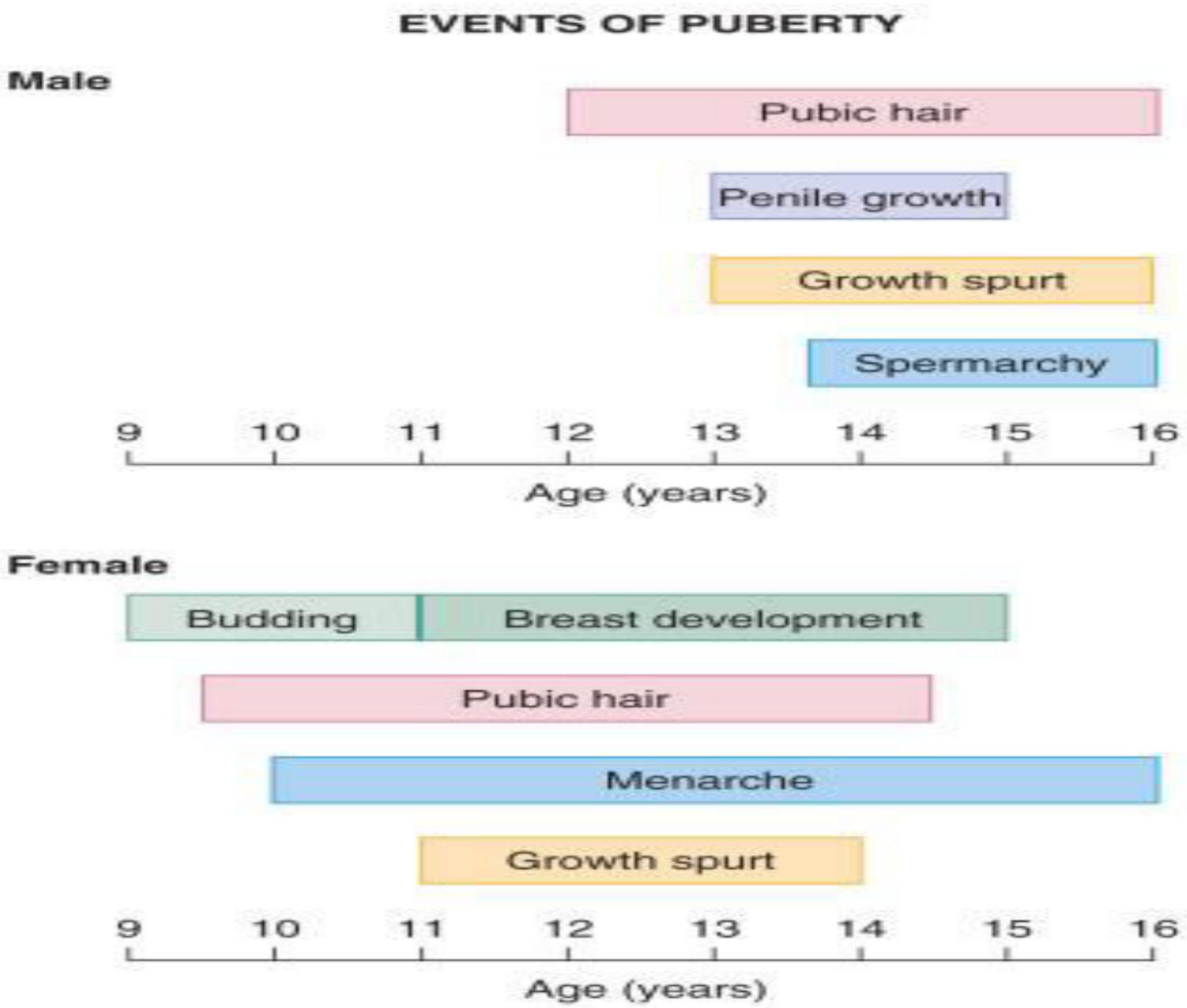

STRESS
Hypothalamus
CORTICOTROPIN RELEASING HORMONE (CRH)
GONADOTROPIN RELEASING HORMONE (GnRH)
Anterior pituitary
Brain
HYPOTHALAMO-PITUITARY-ADRENAL AXIS (HPA AXIS)
FEMALE HYPOTHALAMO-PITUITARY-GONADAL AXIS (HPG AXIS)
ADRENOCORTICOTROPIC HORMONE (ACTH)
FOLLICLE-STIMULATING HORMONE (FSH) and LUTEININZING HORMONE (LH)
METABOLIC EFFECTS
REPRODUCTION
Adrenal cortex
CORTISOL
Ovaries
Kidneys
CORTISOL
ESTROGEN and PROGESTERONE

The predominant factors influencing pre-natal, childhood and pubertal growth rate.

Growth phase	Predominant factors		Hormonal regulators					
	Nutrition	Genetics	GH	IGF-1	IGF-2	Insulin	TH	Sex steroid
Prenatal	**+++**	+	+	+	++	++	+	
Infancy	**+++**	++	++	++	+	++	++	
Childhood	++	**+++**	++	++	+	+	**+++**	
Pubertal	++	**+++**	**+++**	++	+	+	++	**+++**

Stages of puberty

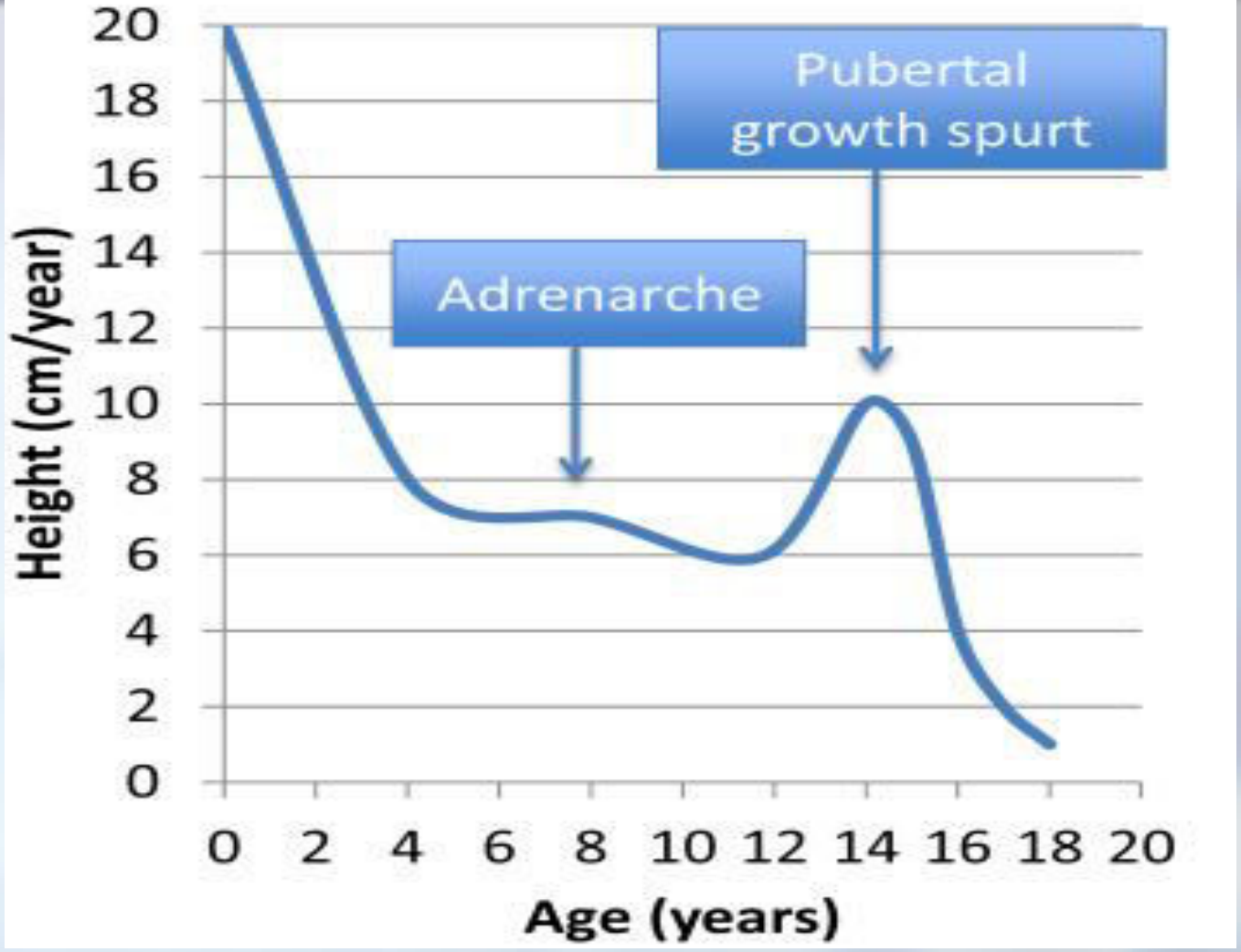
- Growth spurt
- Breast development (thelarche)
- Pubic hair growth (Adrenarche)
- Menstruation (Menarche)
- Axillary hair growth.
- 70% of girls , variation often occur in Tanner.
- Definite signs of puberty are usually present by the age 9 or 10 years .


EVENTS OF PUBERTY
Male
Pubic hair
Penile growth
Growth spurt
Spermarchy
9
10
11
12
13
14
15
16
Age (years)
Female
Budding
Breast development
Pubic hair
Menarche
Growth spurt
9
10
11
12
13
14
15
16
Age (years)

Growth spurt

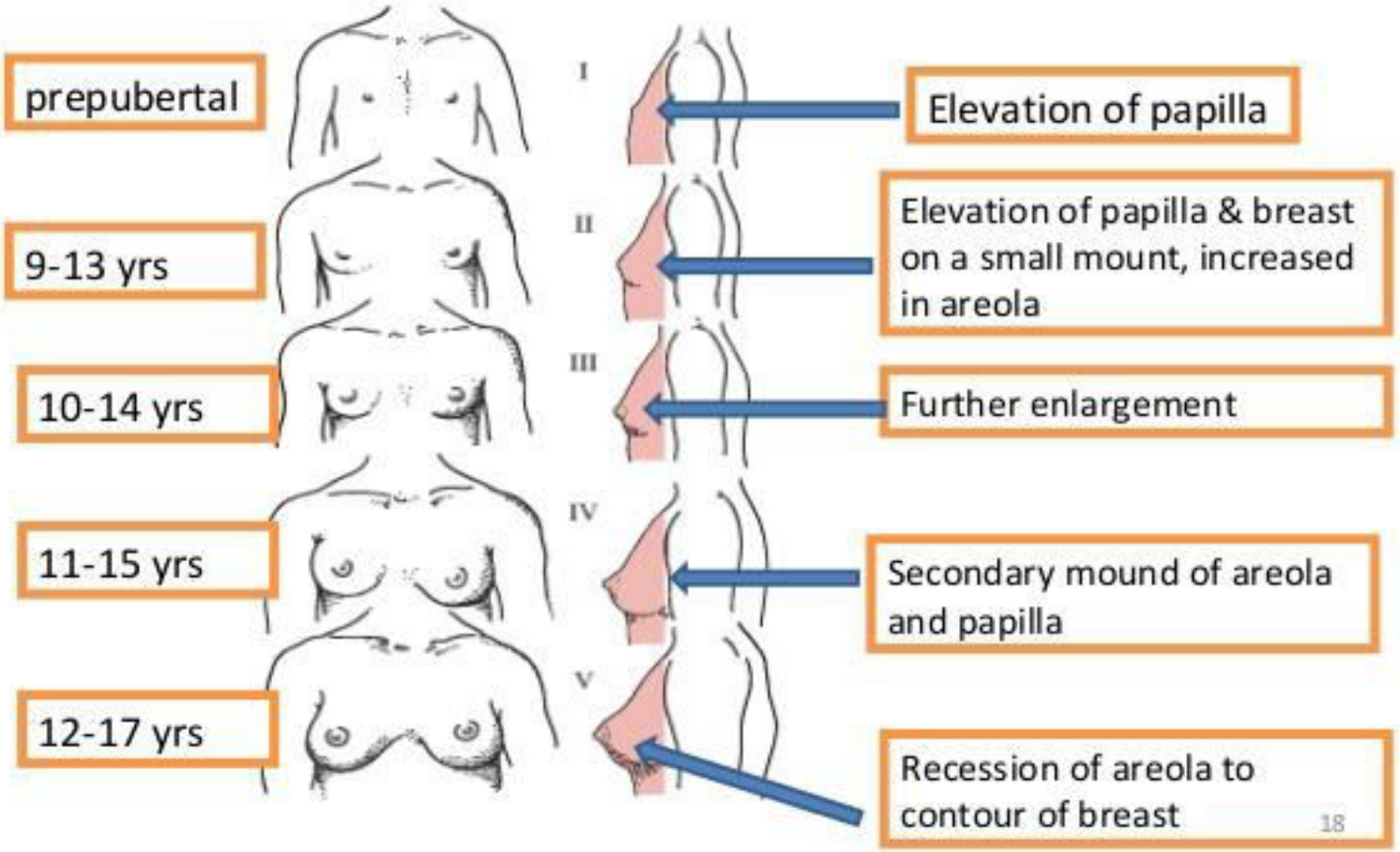
- Approximately 17 to 18 % of adult height accrues during puberty.
- It begins around the age of 11 years in girls.
- 6-10 cm/year for around 2 years.
- The timing of the growth spurt (peak height velocity) varies by gender, occurring approximately two years earlier in girls than in boys.
- The increase in height affects both axial (trunk) and appendicular (limb) components .
- The limbs accelerate before the trunk, with the distal portions of the limbs accelerating before the proximal portions; thus, the adolescent in early puberty is "all hands and feet." In later puberty, however, the growth spurt is primarily truncal .

Schematic representation of the postnatal growth velocity curve



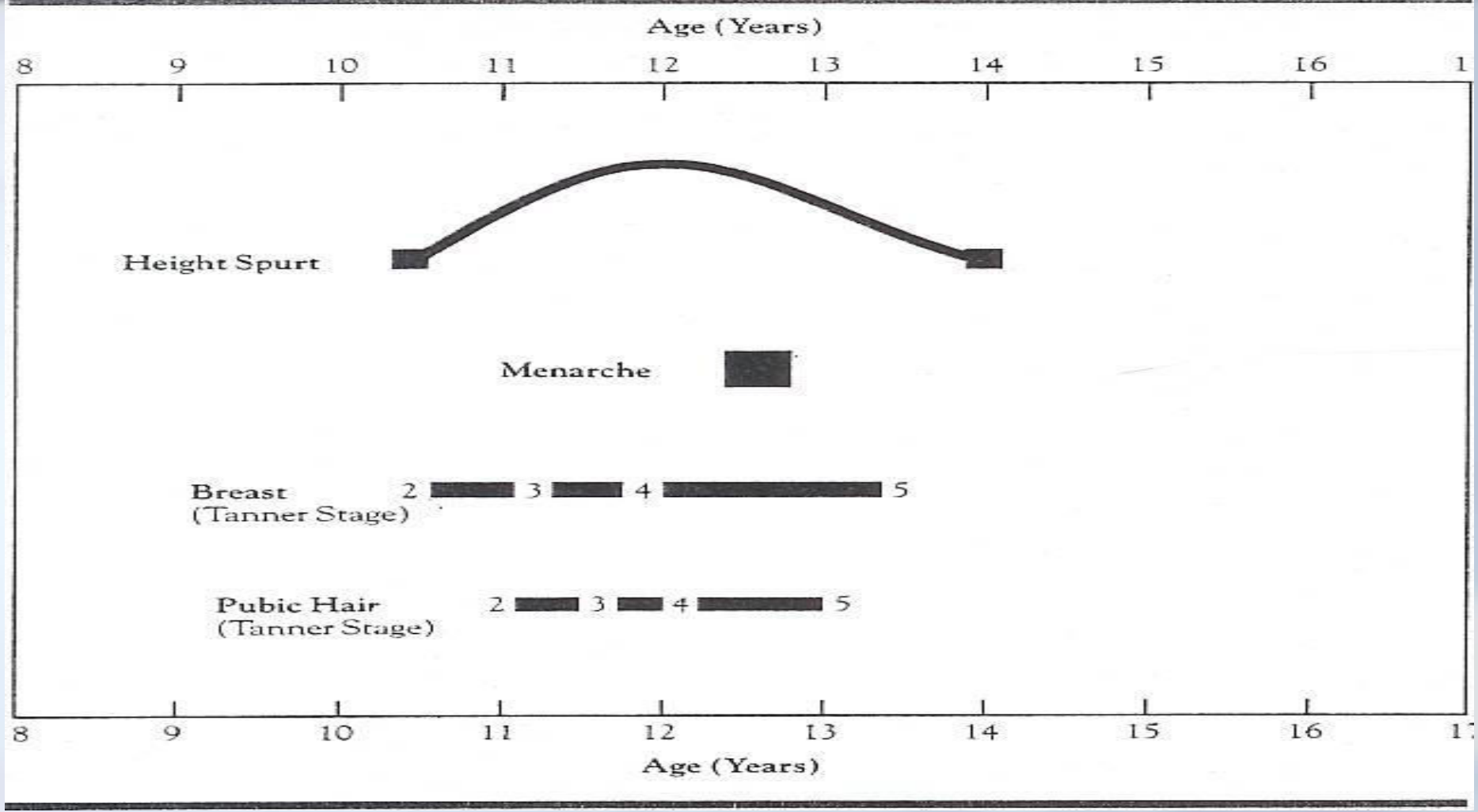
Tanner staging of breast development

– Marshall and Tanner (1969)



Tanner staging of the pubic hair

	In the prepubertal stage 1, there may be fine vellus hair that is no different from that found over the abdominal wall.	
	In stage 2, there is growth of sparse straight hair, primarily at the base of the penis or along the labia.	
	In stage 3, hair increases in quantity and is darker and curlier.	
	Stage 4 is characterized by pubic hair that resembles adult pubic hair, although the escutcheon covers a smaller area than seen in adults	
	Finally, in stage 5, pubic hair has increased further in volume, spread onto the medial thighs, and taken on characteristic male or female configuration.	


Age (Years)
8
9
10
11
12
13
14
15
16
Height Spurt
Menarche
Breast
(Tanner Stage)
2
3
4
5
Pubic Hair
(Tanner Stage)
2
3
4
5
8
9
10
11
12
13
14
15
16
Age (Years)

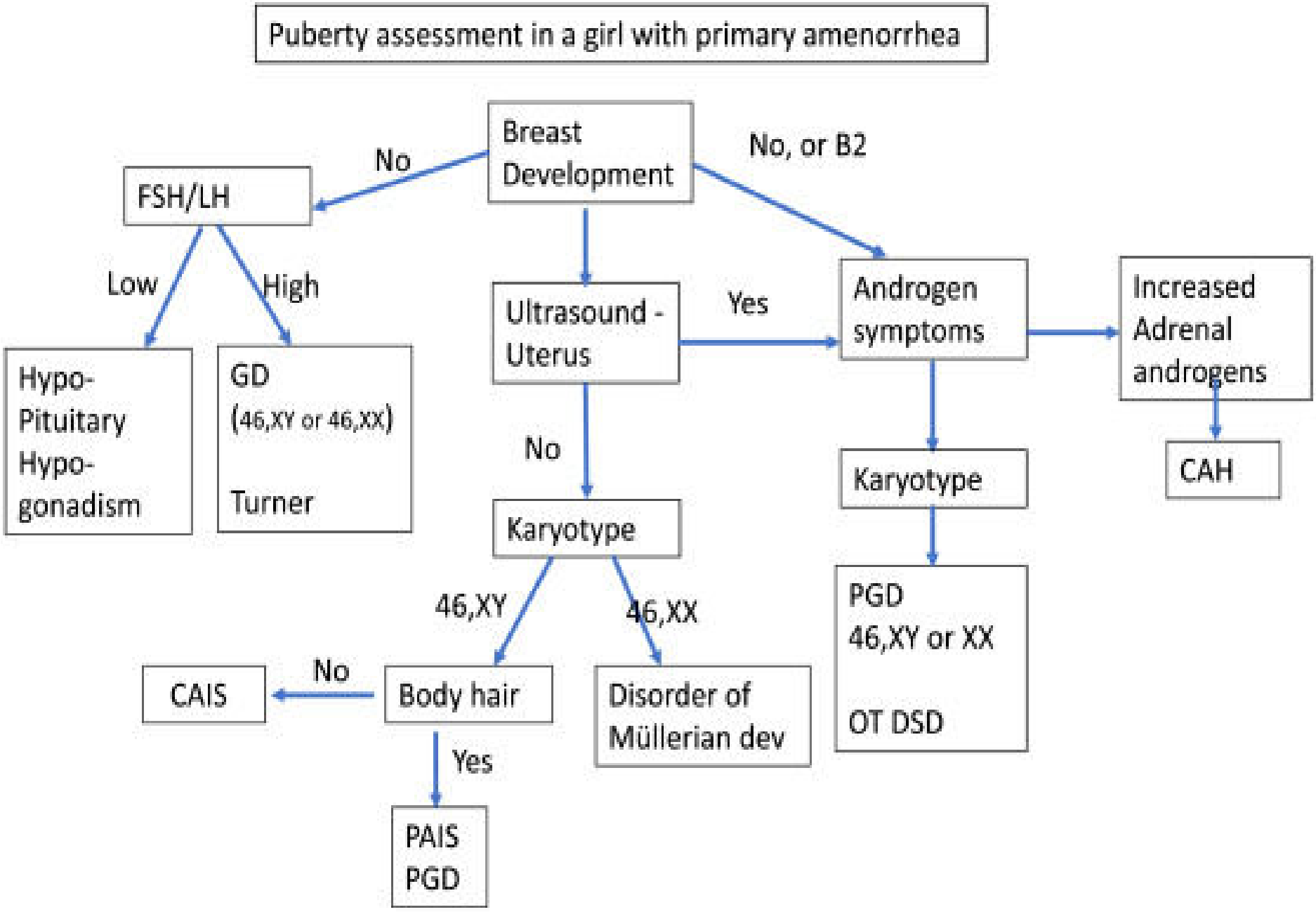
Thelarche (F)	Onset of female breast development, or budding (Tanner stage 2), usually first sign of puberty in girls	Usually occurs after 8 years of age (mean 10–11, range 8–13 years)	Rising oestrogen levels
Gonadarche	Growth of ovaries and testes and increased sex steroid production (true central puberty).	Testicular enlargement in M usually signals pubertal development. Ovarian growth can't be directly seen but usually coincides with thelarche	Activation of gonads by LH and FSH to increase T and oestrogen levels
Pubarche	Development of first pubic hair	First pubic hair occurs at adrenarche (can be transient) and then again at Tanner stage 3. In F usually 6 m after thelarche.	Rising levels of androgens (during adrenarche) and sex steroids during central puberty
Growth spurt	Peak growth velocity seen in childhood after infancy. Occurs shortly before final height is reached.	Usually occurs at Tanner stage 2 in F and 3–4 in M. Always occurs before menarche in F.	Multiple hormones involved. Rising Oestrogen levels cause GH secretion and act directly at GP. Occurs later in M as T needed in higher conc to convert to oestradiol via aromatase
Menarche (F)	Onset of menstruation (Often thought of as culmination of pubertal development in F)	Usually occurs 2 years after thelarche and soon after growth spurt	Oestrogen stimulated growth of uterus and vascularity of endometrium, leading to sloughing of part of the lining. Most menstrual cycles are initially anovulatory.

Menarche

- Occurs at any age between 9-17 years.
- Age of menarche varies :
  - Family
  - Race
  - Social class
  - Environment
  - Diet
  - General health

Factors :

- Geographical
- Genetic
- Body weight- most important
- Health
- Socioeconomic
- Family background


Puberty assessment in a girl with primary amenorrhea
Breast Development
No
No, or B2
FSH/LH
Low
High
Hypo-Pituitary Hypo-gonadism
GD (46,XY or 46,XX)
Turner
Ultrasound - Uterus
Yes
No
Karyotype
46,XY
46,XX
CAIS
No
Body hair
Yes
PAIS PGD
Disorder of Müllerian dev
Androgen symptoms
Increased Adrenal androgens
CAH
Karyotype
PGD 46,XY or XX
OT DSD

Abnormalities of pubertal development:

- The abnormalities of puberty include:
  - **precocious puberty, primary amenorrhea, delayed sexual maturation, and incomplete sexual maturation.**
- The presence of any of these disorders requires investigation of both the **hypothalamic–pituitary–gonadal axis** as well as the **reproductive outflow tract**.
- The initial evaluation should begin with measurement of pituitary gonadotropin (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) levels, which helps distinguish a hypothalamic–pituitary etiology from a gonadal etiology.

Abnormalities of pubertal development

Precocious Puberty

GnRH-dependent Central

develops secondary to early activation of the hypothalamic–pituitary–gonadal axis.

Causes :

1-Idiopathic

(arcuate nucleus in the hypothalamus is prematurely activated.

2- infection , inflammation, injury in the CNS .

(elevated estrogen →Short stature

GnRH-independent Peripheral

results from sex hormone production (androgens or estrogens) independent of hypothalamic–pituitary stimulation

Causes:

ovarian cysts or tumors, McCune–Albright syndrome, adrenal tumors, or iatrogenic causes. Some tumors, such as granulosa cell tumors, teratoma, or dysgerminomata, directly secrete androgen.

Delayed puberty

causes :

1-hypergonadotropic hypogonadism

2-hypogonadotropic hypogonadism

3-anatomic causes

Precocious puberty

- It is the onset of secondary sexual characteristics prior to the age 6 in black girls and age 7 in white girls.

1-GnRH-dependent, or true (central) precocious puberty:

- A random LH ≥ 0.3 IU/L is considered diagnostic of CPP
- A bone age is usually done when CPP is suspected, because an advance of 2 or more years supports the diagnosis
- Brain MRIs are often done as part of the CPP evaluation to rule out a tumor, such as a glioma or astrocytoma, or a benign developmental defect called a hypothalamic hamartoma.
- develops secondary to early activation of the hypothalamic– pituitary–gonadal axis.
- The most common causes are **idiopathic.**
- other causes include : infection, inflammation, or injury of the central nervous system.
- Occasionally, GnRH-dependent precocious puberty results from neoplasms of the hypothalamic–pituitary stalk.

- Laboratory studies show either an appropriate rise in gonadotropins or a steady gonadotropin level in the prepubertal range.

The arcuate nucleus in the hypothalamus is prematurely activated. This causes early sexual maturation with early reproductive capability. The elevated estrogen levels affect the skeleton, resulting in short stature in adulthood secondary to premature closure of the epiphyseal plates.

Preparations of gonadotropin-releasing hormone analogues currently in use

Brand name (chemical name)	Dose formulations (mg)	Frequency of administration	Advantages	Disadvantages
Lupron Depot-Ped (leuprolide)	7.5, 11.25, or 15	Monthly	Possibly more rapid onset of effect	Need for frequent injections
Lupron Depot-Ped (leuprolide)	11.25 or 30	Every 3 mo	Fewer injections than 1 mo form with similar efficacy	No less expensive than monthly
Triptodur (triptorelin)	22.5	Every 6 mo	Fewer injections than Lupron	No less expensive than 1 mo and 3 mo formulations
Supprelin (histrelin)	50	Implant is designed to last at least 12 mo	No injections; effect may last for up to 2 y	Needs to be placed and removed by a simple surgical procedure

Precocious puberty

2-GnRH-independent sex hormone production:

-It results from sex hormone production (androgens or estrogens) independent of hypothalamic–pituitary stimulation.

This condition can be caused by:

ovarian cysts or tumors.

McCune–Albright syndrome

adrenal tumors.

iatrogenic causes.

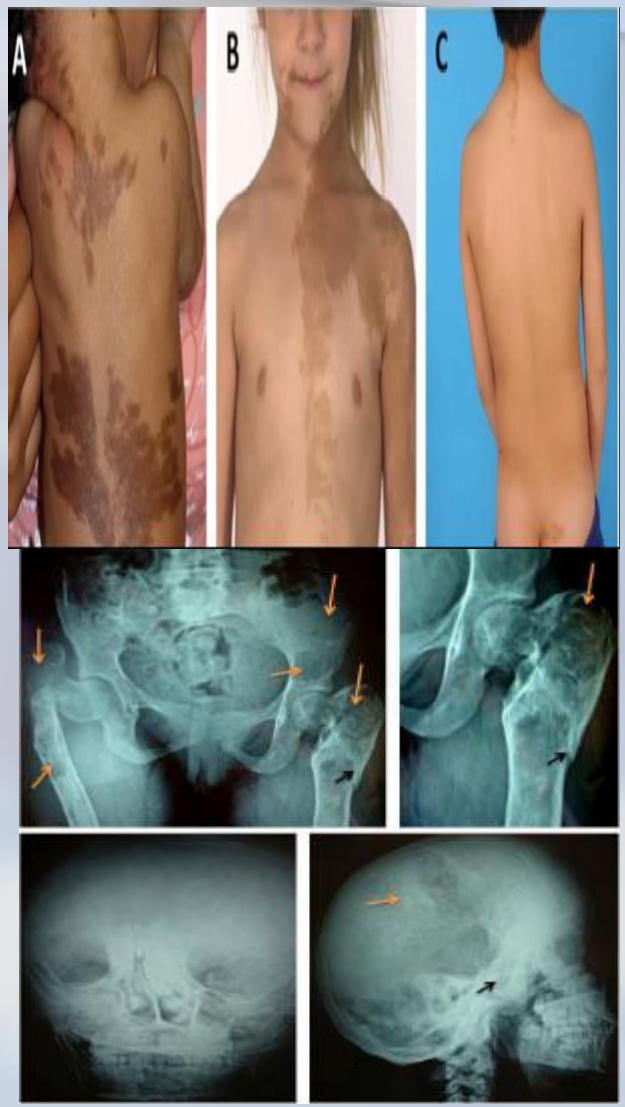
Some tumors, such as :

granulosa cell tumors, teratoma, or dysgerminomata, directly secrete androgen.

- **Physical examination usually reveals a palpable pelvic mass and leads to further evaluation/imaging studies.**

McCune–Albright syndrome (polyostotic fibrous dysplasia)

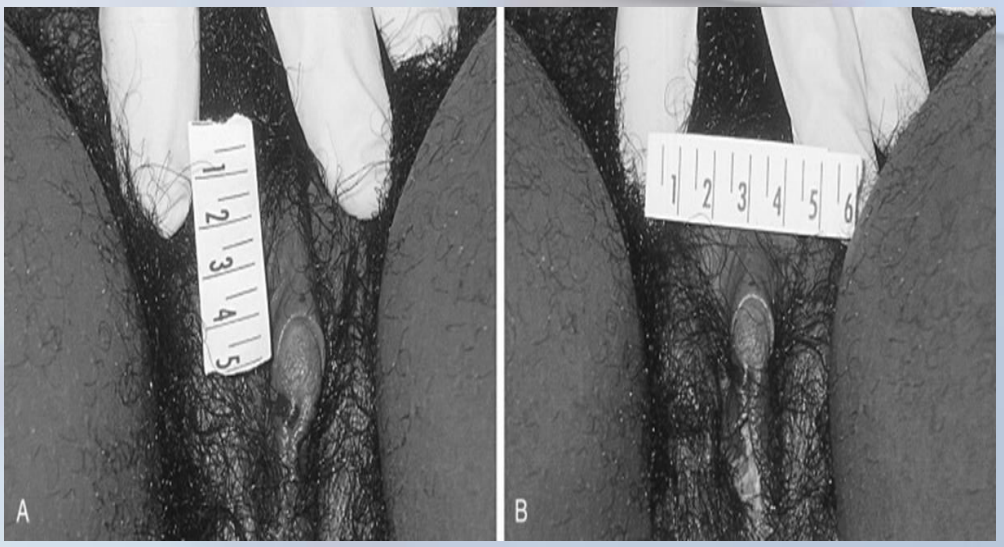
- It is characterized by:
  - multiple bone fractures.
  - café-au-lait spots,
  - precocious puberty.
  - Premature menarche can be the first sign of the syndrome.
- Numerous organs potentially affected, including the adrenal glands, parathyroid glands, pituitary gland, thyroid gland, and gonads
- The syndrome is thought to result from a defect in cellular regulation with a mutation in the alpha subunit of the G protein that stimulates cAMP formation, which causes affected tissues to function autonomously.
- This mutation causes the ovary to produce estrogen without the need for FSH, resulting in sexual precocity.



Adrenal hyperplasia (CAH)

- The most common form of **CAH, 21-hydroxylase deficiency**, presents at birth with the finding of ambiguous genitalia.
- However, the nonclassical form, previously known as late-onset CAH, tends to present at adolescence.
- In this disorder, the **adrenal glands are unable to produce adequate amounts of cortisol** as a result of a partial block in the conversion of 17-hydroxyprogesterone to deoxycortisol.
- Deficiency of the 21-hydroxylase enzyme leads to a shunting away from aldosterone and cortisol production in cholesterol biosynthesis toward the production of androgens (testosterone and estradiol), which results in **precocious adrenarche.**
- A pathognomonic finding for 21-hydroxylase deficiency is an **elevated 17-hydroxyprogesterone level**. Plasma renin is also measured to determine the amount of mineralocorticoid deficiency.
- Medical therapy is instituted as early as possible and is aimed at steroid/mineralocorticoid replacement, depending on the severity of the deficiency.
- In the **nonclassical** form of CAH, patients present with premature adrenarche, anovulation, and hyperandrogenism, appearing somewhat like patients with polycystic ovarian syndrome.

clitoromegaly



Severe clitoromegaly resulting from a testosterone-secreting ovarian tumor.

(A) The entire length of the clitoris is approximately 4 cm (normal, <1 cm).

(B) (B) The transverse diameter of the clitoris measures 1.5 cm (normal, <0.7 cm).

Iatrogenic causes

- Drug ingestion must be considered in all children who present with precocious puberty.
- These children may exhibit increased pigmentation of the nipplesandareola of the breast secondary to ingestion of oral contraceptives, anabolic steroids, and hair or facial creams.

Therapy for GnRH-independent precocious puberty:

- The main goals of treatment of precocious puberty are to arrest and diminish sexual maturation until a normal pubertal age, as well as to maximize adult height.

- involves administration of a GnRH agonist. Results occur rapidly and continue during the first year of treatment.
- Treatment for GnRH-independent precocious puberty attempts to suppress gonadal steroidogenesis.

Delayed Puberty

- There is wide variation in normal pubertal development. However, puberty is considered delayed when secondary sex characteristics :
  - have not appeared by age 13.
  - there is no evidence of menarche by age 15 to 16.
  - When menses have not began 5 years after the onset of thelarche.

Causes:

1- Hypergonadotropic hypogonadism .

2- Hypogonadotropic hypogonadism .

3- Anatomic causes.

Hypergonadotropic hypogonadism

- The most common cause of delayed puberty with an elevated FSH(>30 mIU/mL) is gonadal dysgenesis, or Turner syndrome.
- In this condition, there is an abnormality in or absence of one of the X chromosomes in all cell lines. Patients have streak gonads, with an absence of ovarian follicles; therefore, gonadal sex hormone production does not occur at puberty.

Turner's Syndrome (X-)

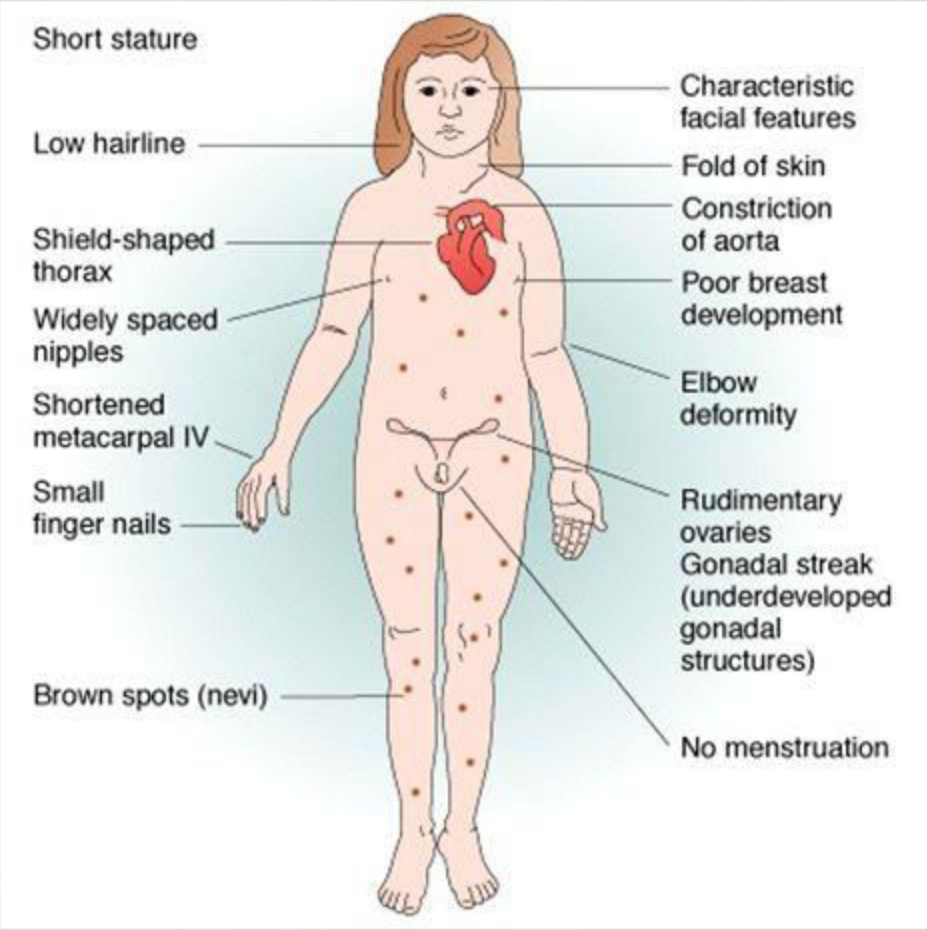
- Missing an X chromosome on 23rd Pair.

Management :

-Obstetrics and Gynecology estrogen is administered initially, epiphyseal closure may begin, and long bone growth is truncated and adult height compromised.

-A delay in estrogen administration can lead to the development of osteoporosis in the teenage years.

-Progestins should not be given until the patient has reached Tanner stage IV, because premature progestin therapy may prevent the breast from developing completely, thus resulting in an abnormal contour.



Hypogonadotropic hypogonadism

-The arcuate nucleus of the hypothalamus secretes GnRH in cyclic bursts (or a pulsatile fashion), which stimulates release of gonadotropins from the anterior pituitary gland.

- Dysfunction of the arcuate nucleus disrupts the short hormonal loop between the hypothalamus and pituitary. As a result, FSH and LH secretion does not occur.
- Consequently, the ovaries are not stimulated to secrete estradiol, and secondary sexual maturation is delayed.
- The most common cause of this type of delayed puberty is constitutional (physiologic) delay.
- Other causes include Kallmann syndrome; anorexia, exercise, or stress; pituitary tumors/pituitary disorders; hyperprolactinemia; and drug use.

Constitutional delay of puberty

-It represents approximately 20% of all cases of delayed puberty.

- It's the most common cause for delayed puberty.

-It is thought to be a normal variant of the development process and trends can be seen within families.

-Children with constitutional delay usually have not only delay of secondary sexual maturation, but also short stature with an appropriate delay of bone maturation.

1-Kallmann syndrome

-The olfactory tracts are hypoplastic, and the arcuate nucleus does not secrete GnRH.

-Young women with Kallmann syndrome have little or no sense of smell and do not have breast development.

-This condition can be diagnosed on initial physical examination by challenging the olfactory function with known odors such as coffee or rubbing alcohol.

-Once the condition is recognized and treated, the prognosis for successful secondary sexual maturation and reproduction is excellent.

-Secondary sexual maturation can be stimulated by the administration of exogenous hormones or by the administration of pulsatile GnRH.

-Patients typically can have normal reproductive function.

-Ovulation is induced by the administration of exogenous gonadotropin, and progesterone is given in the luteal phase to allow implantation of the embryo.

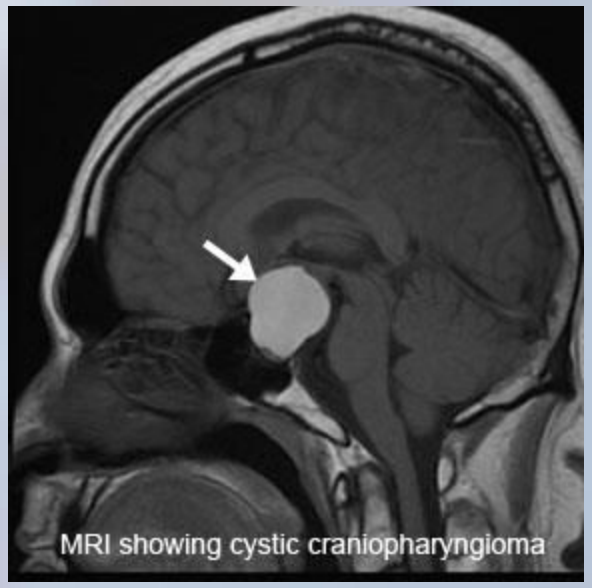
2-Craniopharyngioma

-It is the most common tumor associated with delayed puberty.

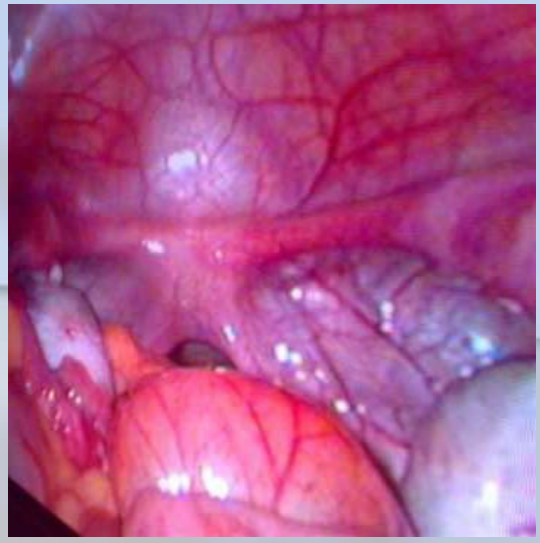
-This tumor develops in the pituitary stalk with suprasellar extension from nests of epithelium derived from the Rathke pouch.

-The radiologic hallmark is the appearance of a (supra)sellar calcified cyst.

-Calcifications are present in approximately 70% of craniopharyngiomas.

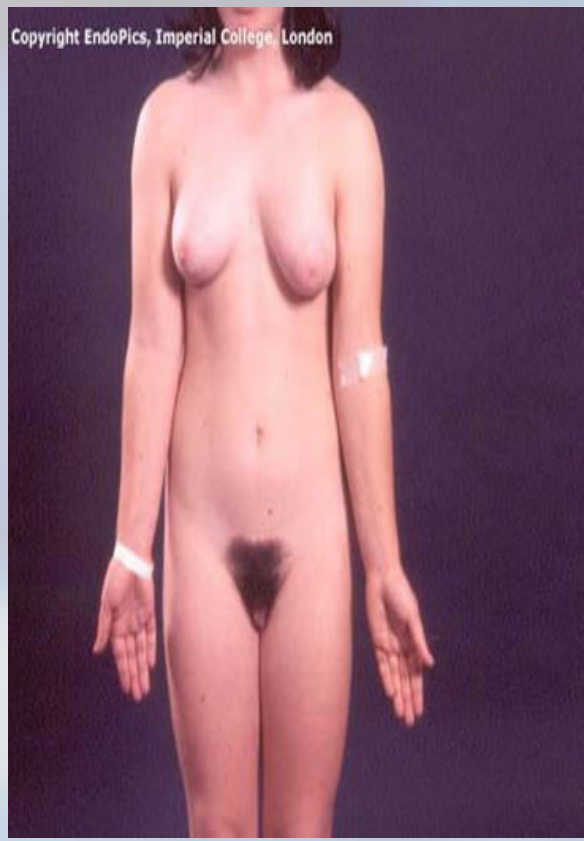

MRI showing cystic craniopharyngioma

3-Anatomic causes



-During fetal life, **müllerian ducts** develop and fuse in the female fetus to form the upper reproductive tract (i.e., the fallopian tubes, uterus, and upper vagina).

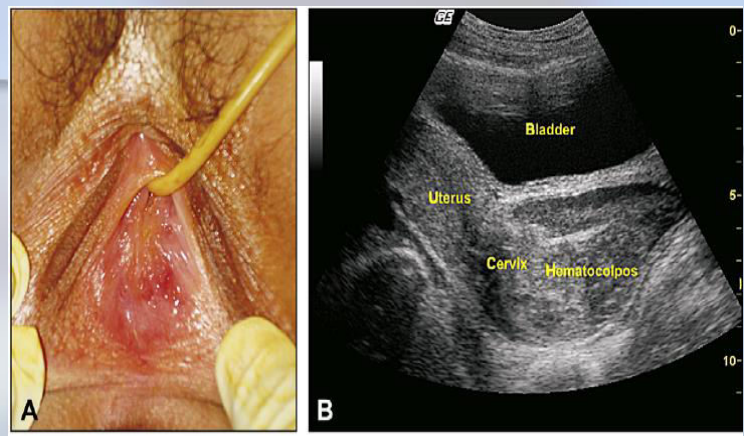
-The lower and midportion of the vagina develop from the canalization of the genital plate.

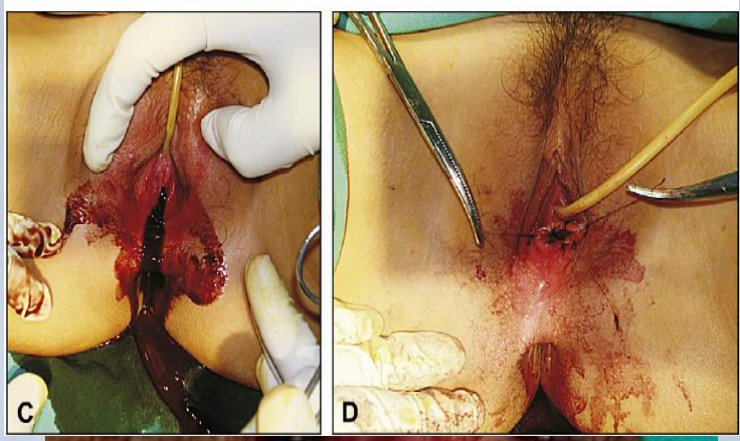


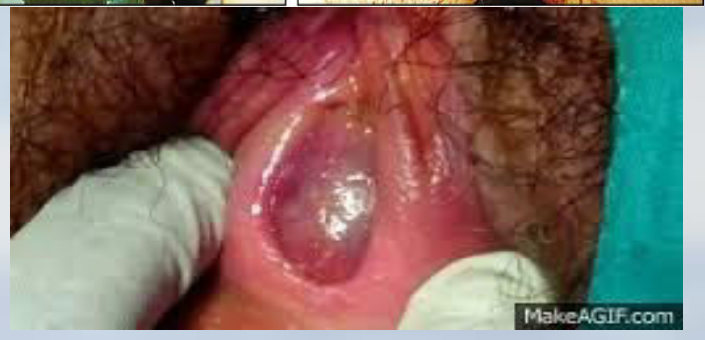
- **Müllerian agenesis, or Mayer-Rokitansky–Küster–Hauser syndrome (46, XX)**, is the most common cause of primary amenorrhea in women with normal breast development.
- In this syndrome, there is congenital absence of the vagina and usually an absence of the uterus and fallopian tubes.
- Ovarian function is normal, because the ovaries are not derived from müllerian structures; therefore, all the secondary sexual characteristics of puberty occur at the appropriate time.
- Physical examination leads to the diagnosis of müllerian agenesis.

Imperforate hymen

- It is the simplest genital tract anomaly.
- In this condition, the genital plate canalization is incomplete, and the hymen is, therefore, closed.
- Menarche occurs at the appropriate time, but because there is obstruction to the passage of menstrual blood, it is not apparent.
- This condition presents with pain in the area of the uterus and a bulging, bluish-appearing vaginal introitus.
- Hymenotomy is the definitive therapy.
- This condition may be confused with a **transverse vaginal septum**. Transverse vaginal septa can occur along the vagina at any level and result in obstruction to outflow of menses.
- A vaginal septum can be resected and primarily repaired via a procedure called a Z-vaginoplasty. P
- rolonged obstruction to menstruation can be associated with an increased incidence of endometriosis.







Key points

- • Differentiating normal from abnormal pubertal development can be challenging for the primary care provider; however, the distinction is important because of the potential for long-term medical and psychosocial complications.
- • Precocious puberty may result from early activation of the hypothalamic-pituitary-gonadal (HPG) axis (central precocious puberty) or exposure to sex steroids independent of HPG axis activation (peripheral precocious puberty).
- • A significant proportion of children with central precocious puberty have no underlying abnormality, but it is important to exclude disorders of the central nervous system.
- • Delayed puberty may result from functional failure of the gonads or impaired function at the level of the hypothalamus or pituitary gland.
- • Although a basic workup is helpful in identifying a possible cause of early or delayed puberty, referral to a pediatric endocrinologist is often indicated for management.