

Puberty and Its Disorders

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Disclosures

- None

Objectives

- State normal timing of puberty
- Describe the work up for precocious puberty
- Report the etiologies of delayed puberty
- Perform basic work up for pubertal pathologies

Pretest Question

What is the best indicator of precocious puberty in girls?

- A. Body odor
- B. Growth spurt
- C. Pubic hair
- D. Breast development
- E. Advanced bone age

Thelarche

- 10-11 yrs of age

➤ Menarche

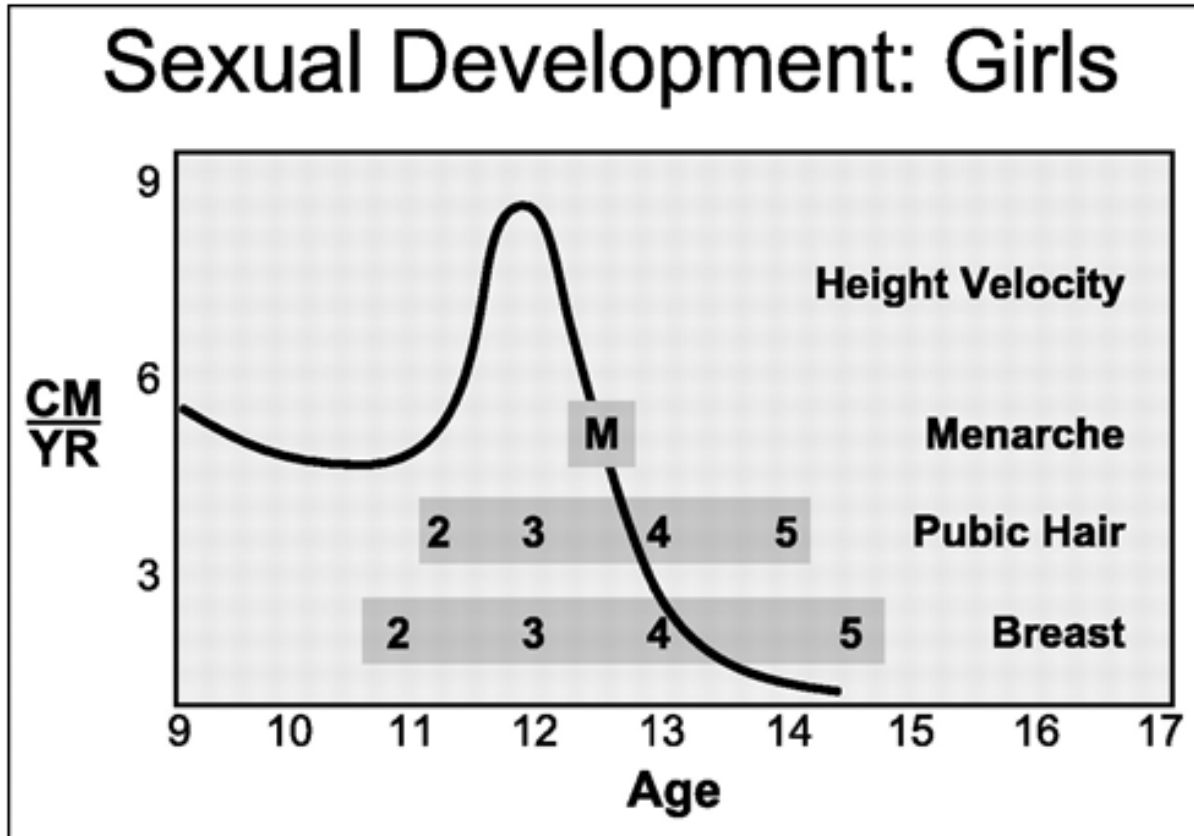
- 2-2.5 years after
- Tanner 4

➤ Adrenarche

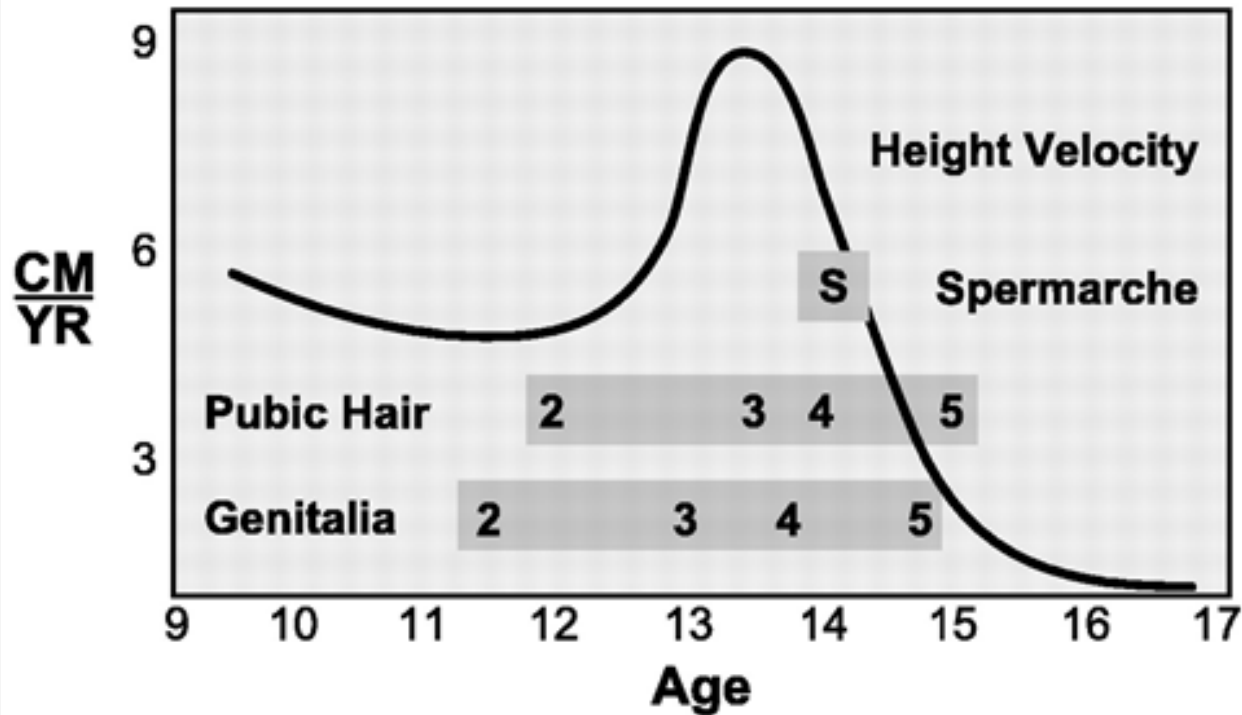
- 6-12 mo after

◆ Peak Growth Velocity

- Tanner 2-3
- Precedes menarche
- Growth complete
2 yrs from menarche

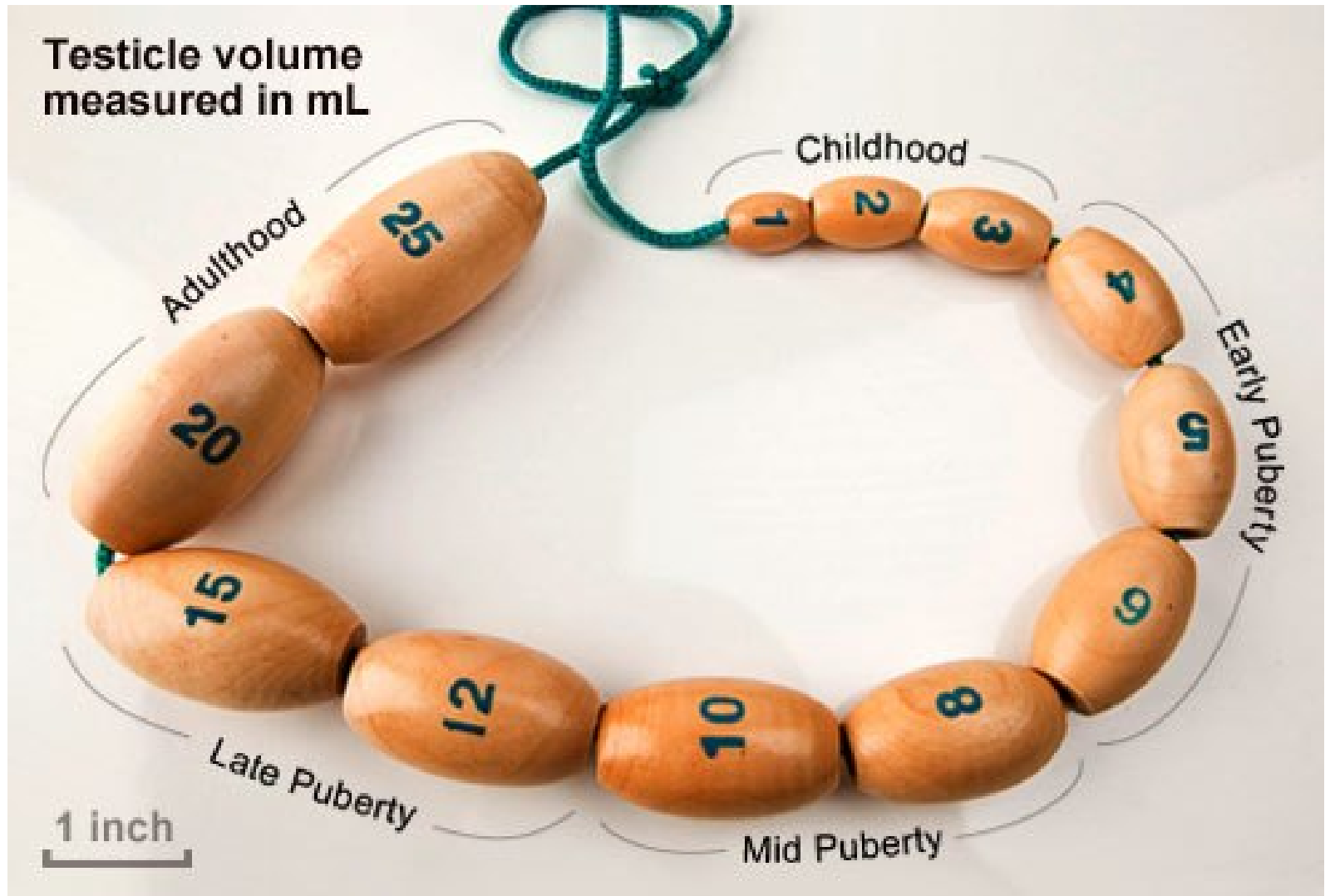


Sexual Development: Boys



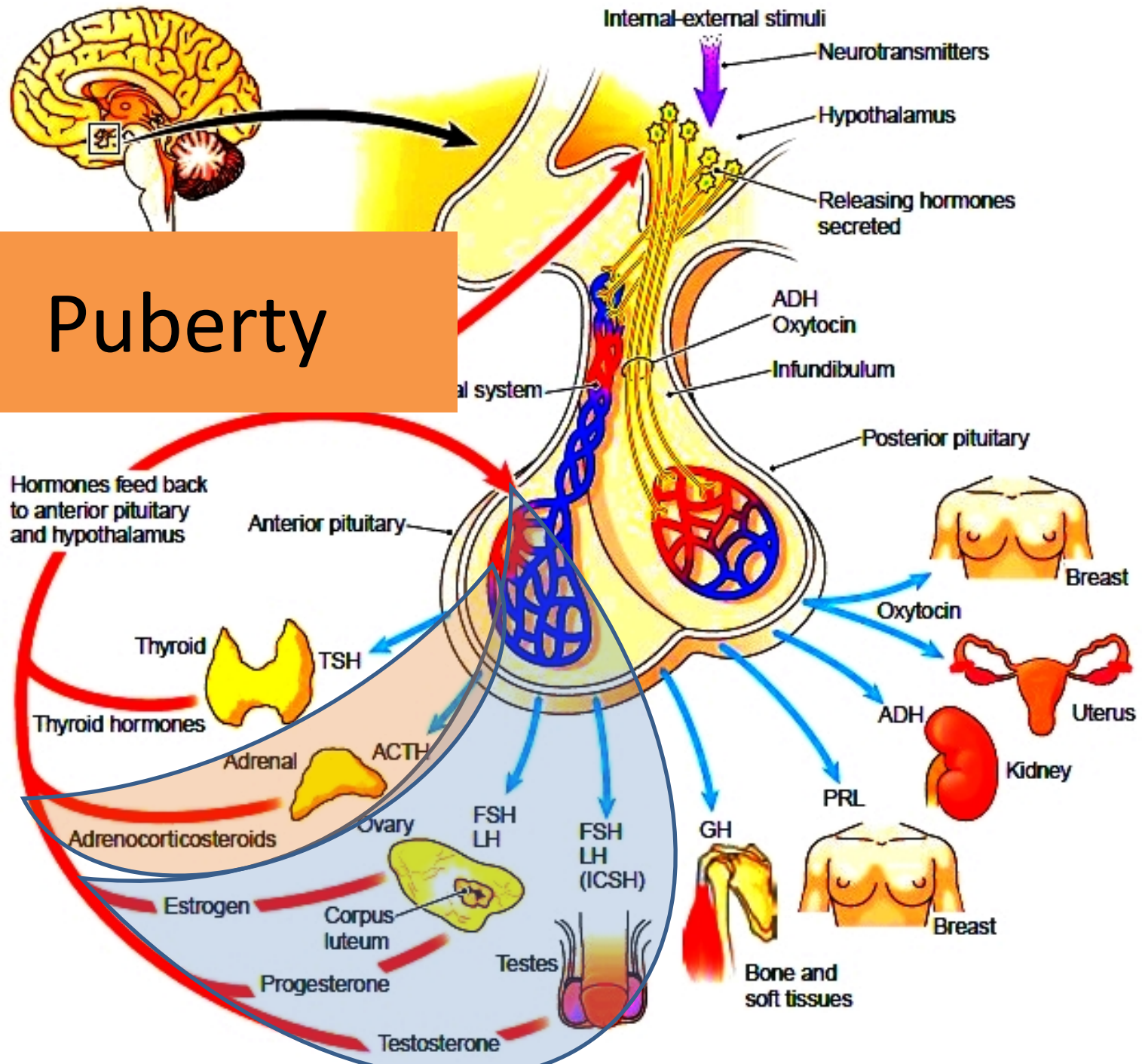
David S. Rosen Pediatrics in Review 2004;25:194-200

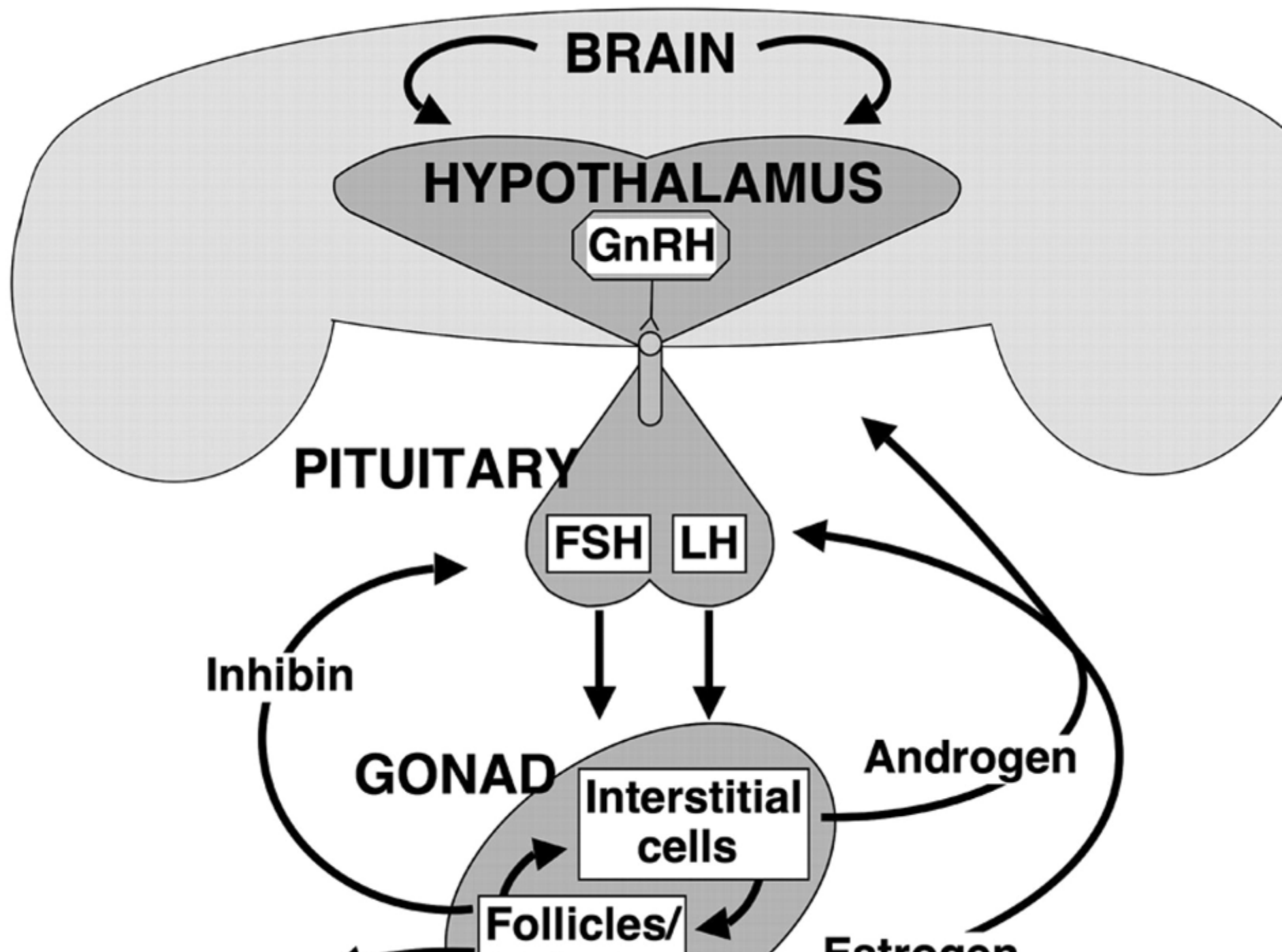
- Testicular growth first with thinning of scrotal skin
 - Average age 11-12 yo
- Penile lengthening & Pubic hair follow
- Peak Growth Velocity at Tanner 4



<https://mlb.nbcsports.com/2011/03/25/bonds-trial-update-whats-an-orchidometer/>

Puberty



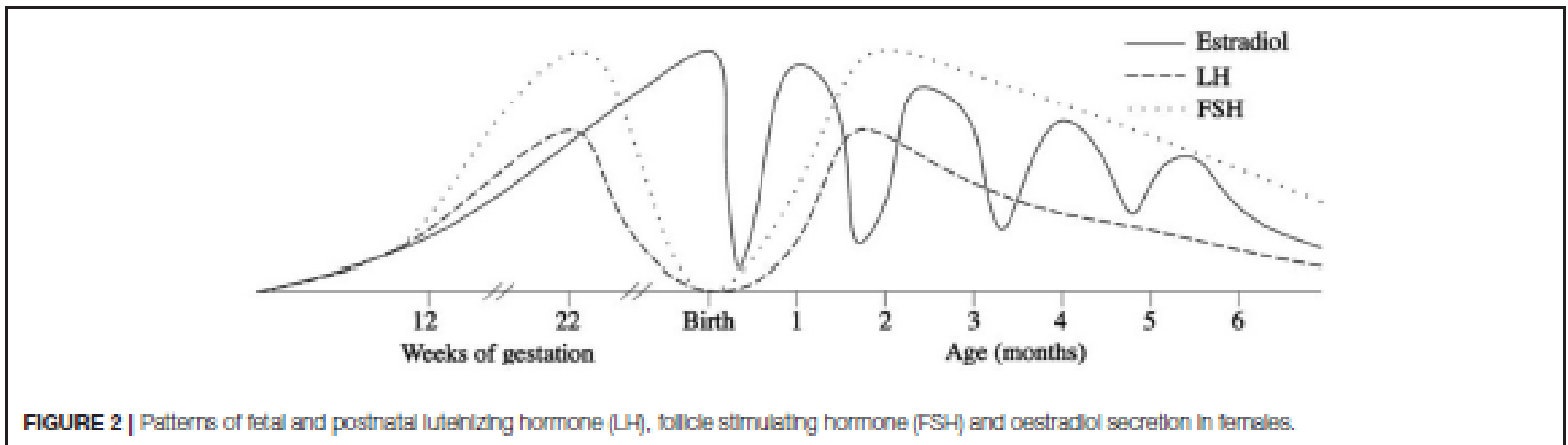
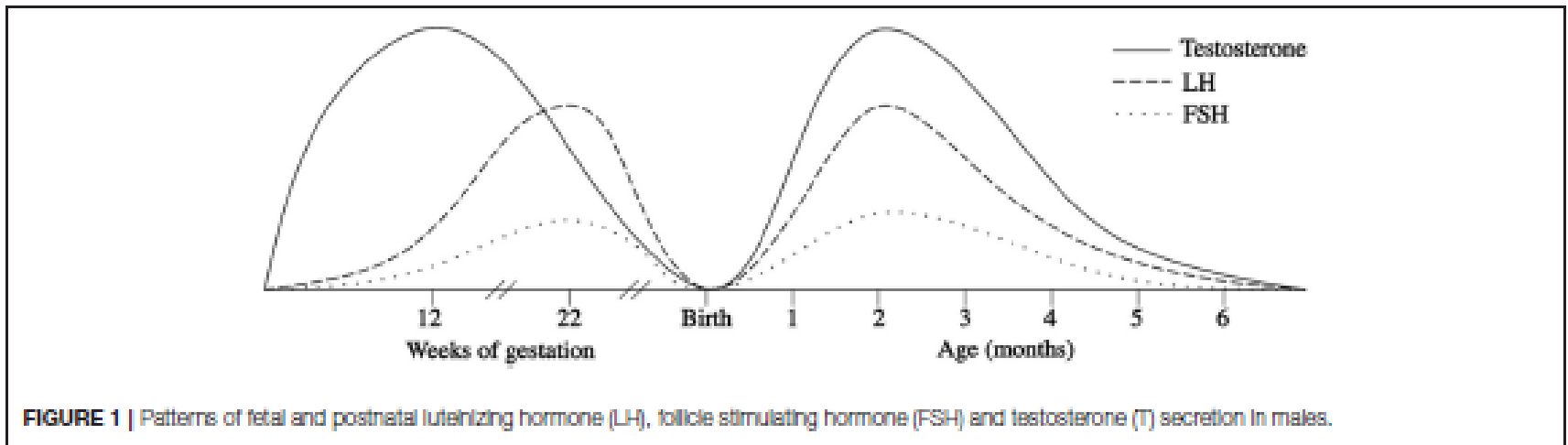


Benign Abnormalities of Puberty in Young Children

Mini-Puberty of Infancy

- Activation of HPG axis during neonatal period
- Occurs in 2 weeks of life up to 6 months
- Develops genital organs
 - Boys: penile and testicular growth
 - Girls: breast tissue development
- Creates basis for future fertility
 - Primes pituitary LH and FSH response to GnRH during reproduction.
- May impact growth and adipose tissue development in boys

Timing of Mini Puberty of Infancy



Isolated scrotal hair of infancy



R Bragonier et al. Postgrad Med J 2005;81:412

- Occurs between 8-15 months of age
- Diminished by 13-21 months of age
- No underlying pathological cause found
- No other signs of androgenisation found

Benign Premature Thelarche



Leung A.K.C. (2009) Premature Thelarche. In: Lang F. (eds) Encyclopedia of Molecular Mechanisms of Disease. Springer, Berlin, Heidelberg

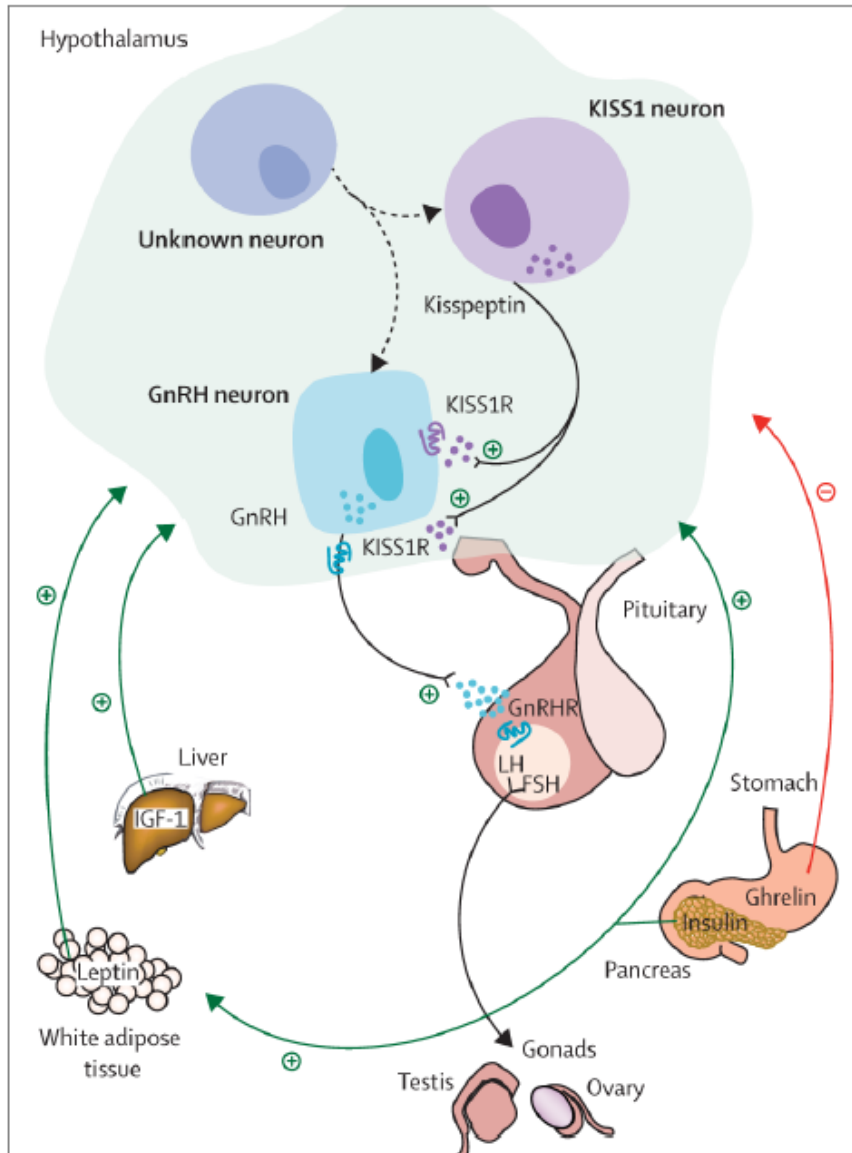
- Nonprogressive, isolated breast development
 - Unilateral or bilateral
- Usually occurs before 3 yrs
 - may persist up to 8 yrs
- Prepubertal LH, FSH, and estradiol
 - FSH \sim 2x LH
- Menarche at normal age
- 10% may progress to CPP

Neonatal Galactorrhea (Witch's Milk)



- Colostrum like milk production
- Occurs 3-4 days after birth
- Lasts no longer than 2 wks of life
- Occurs in 5% of newborns

What Starts Puberty?



- Unknown exact trigger
 - Genetic factors of KISS1 leading to Kisspeptin release
- Sustained increase in pulsatile release of GnRH
 - Genetic input association known by parents age at puberty
 - Metabolic signals

Abnormal Puberty

Precocious

- Girls:
 - Before 8 yrs
 - Thelarche
- Boys
 - Before 9 yrs
 - Testicular development

More common in girls

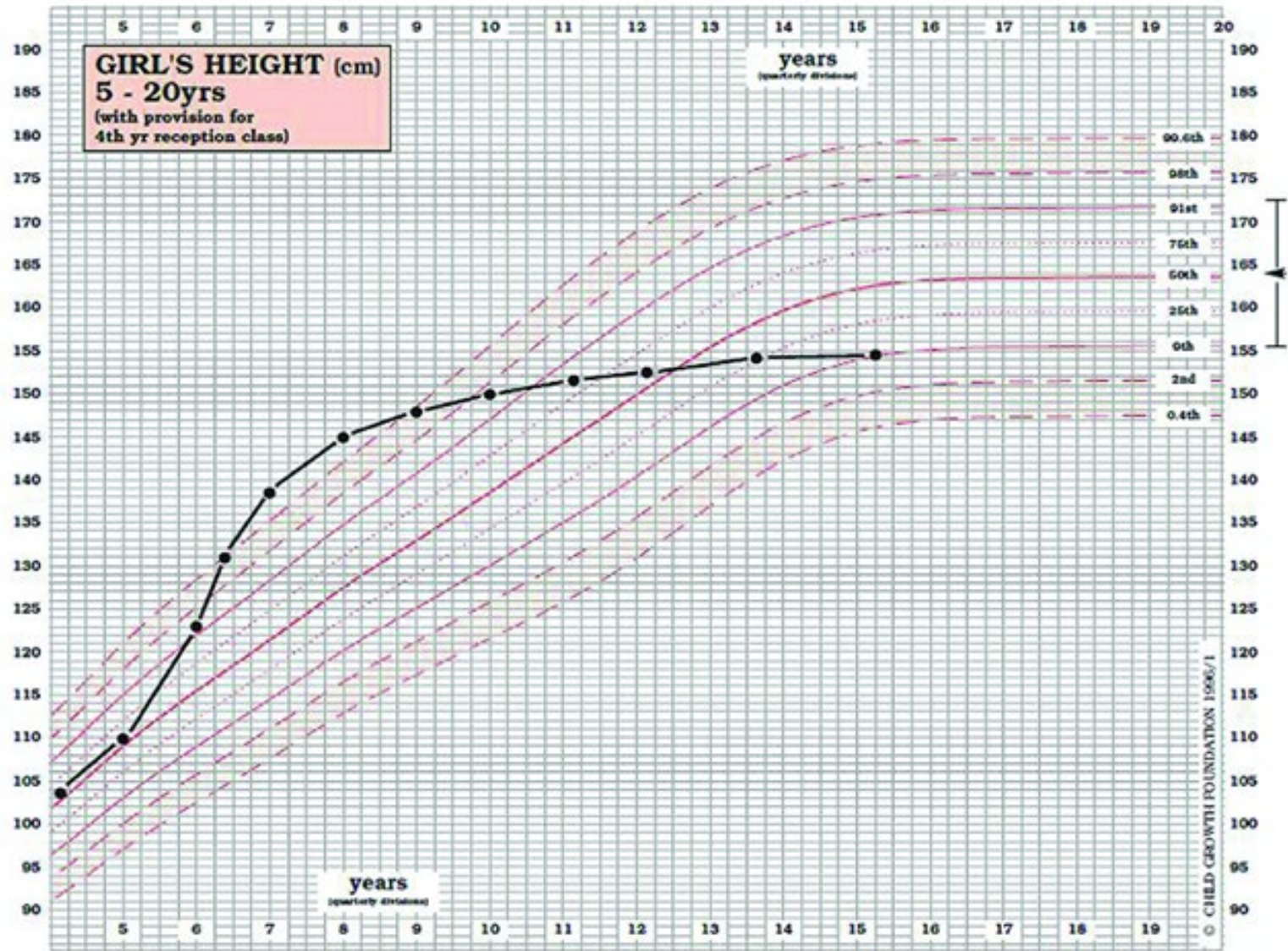
Delayed

- Girls:
 - No thelarche by 13 yrs
 - Menarche by 16 yrs
 - Over 4 yrs from thelarche to menarche
- Boys
 - No Testicular development by 14 yrs

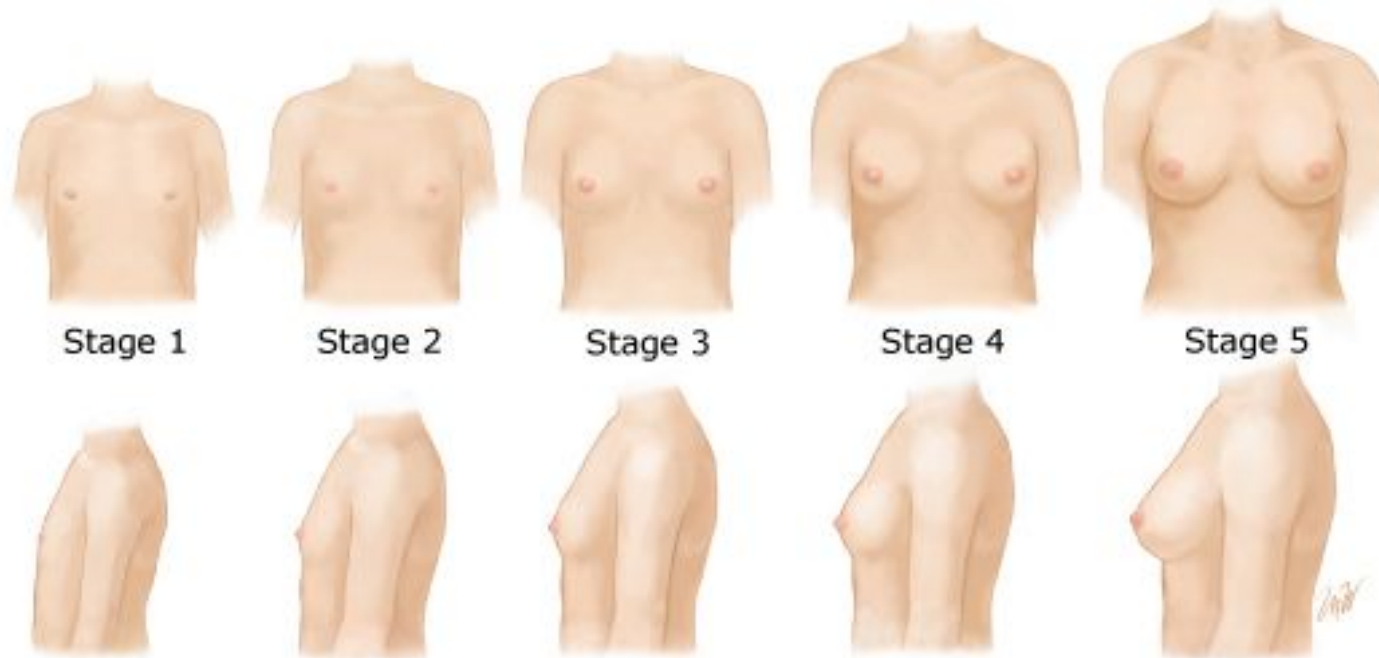
More common in boys

Precocious Puberty

- Signs
 - Rapid advancement through Tanner Stages
 - Bone age advanced
 - Short predicted height
- Causes
 - Exogenous: soy, lavender, tea tree oil
 - Central Precocious Puberty
 - Gonadotropin Independent Precocious Puberty



Tanner staging of breast development in girls



Stage 1: Prepubertal.

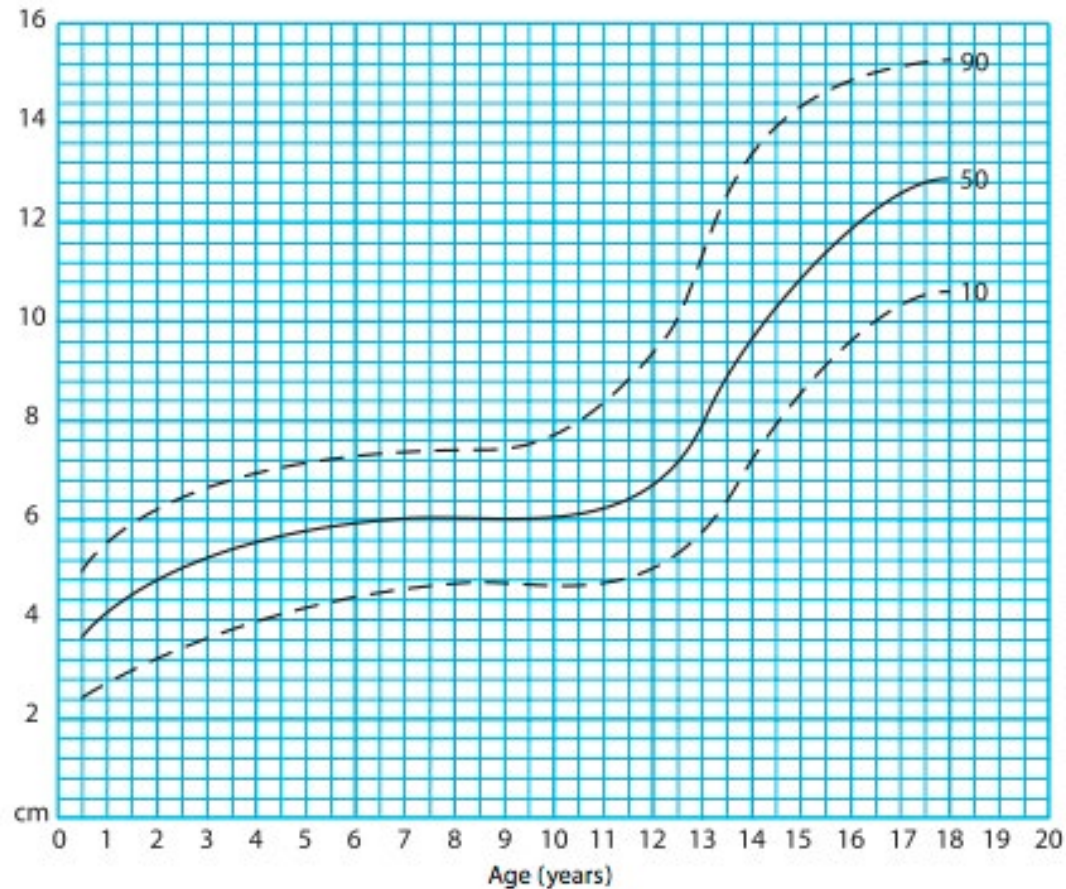
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola.

Stage 3: Further enlargement of breast and areola; no separation of their contour.

Stage 4: Areola and papilla form a secondary mound above level of breast.

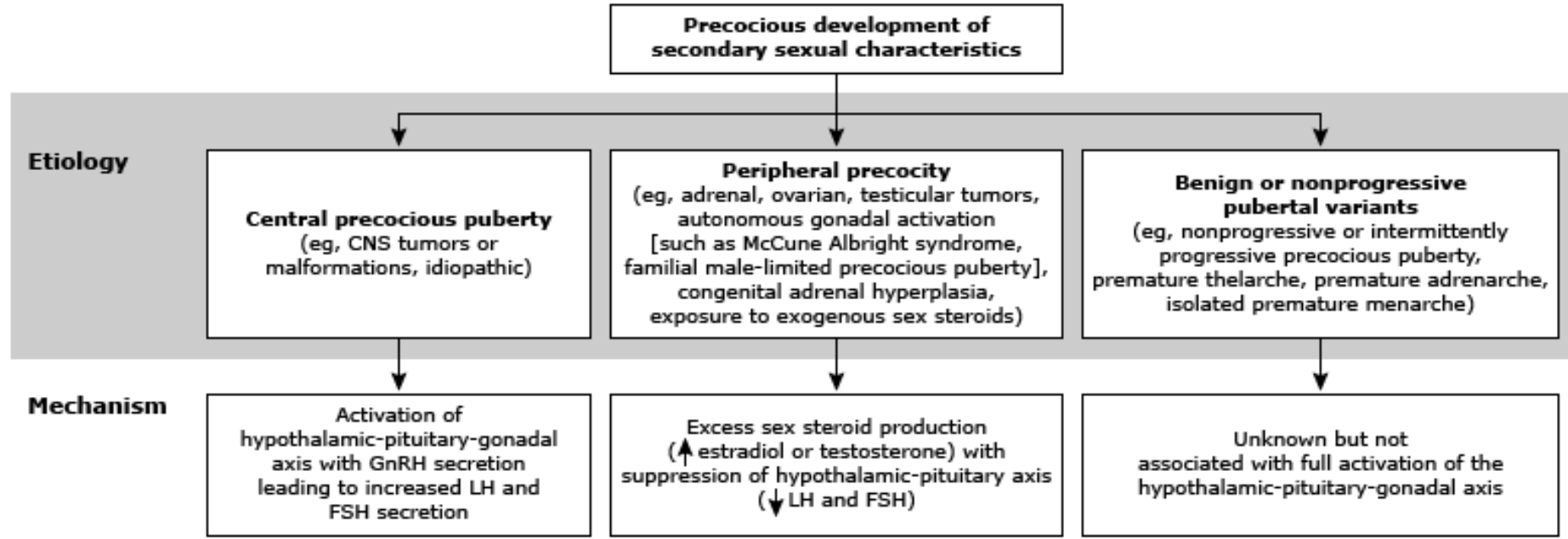
Stage 5: Mature stage with projection of papilla only, related to recession of areola.

Testicular/Penile Enlargement



(Reproduced from Shonfeld & Beebe. 1942, *Journal of Urology*, 48, 759-777;
http://www.caah.chw.edu.au/resources/gpkit/1841_Boys_2-18_Version_3_June_13_08.pdf).

Etiology and mechanisms of precocious puberty



CNS: central nervous system; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone.

From: Harrington J, Palmert MR, Hamilton J. Use of local data to enhance uptake of published recommendations: an example from the diagnostic evaluation of precocious puberty. Arch Dis Child 2014; 99:15. Reproduced with permission from BMJ Publishing Group Ltd. Copyright © 2014.

Early Puberty Work Up

- Luteinizing Hormone
- Follicle Stimulating Hormone
- Estradiol
- Total Testosterone (male)
- TSH and FT4
- Bone Age
- If CPP is real – MRI of brain and pituitary

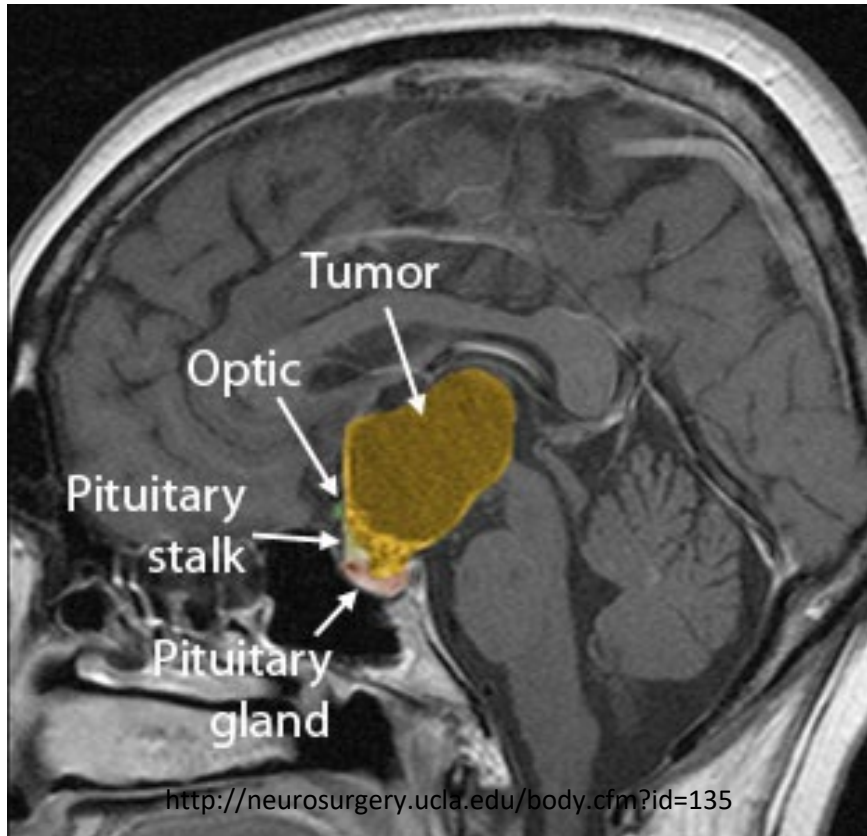
Central Precocious Puberty

- **Idiopathic F > M**
- Premature onset with normal progression
- It's all about the LH
 - Levels surge during sleep – get labs in the morning!
 - Random LH detectable in 50-75% of girls with central precocity
 - LH >0.4 IU/L concerning
 - GnRH stimulation (Leuprolide Stimulation test)
 - LH can still remain low until mid-puberty in girls
 - Stimulated LH > 4 IU/L concerning
 - Increase in FSH >> LH suggests prepubertal status
 - LH:FSH ratio >0.66 suggestive of CPP

Treatment of CPP

- GnRH analog interrupts pulsatile endogenous GnRH
 - Histrelin acetate (Supprelin LA) Implant
 - Lueprolide acetate (Lupron Depot-Ped)
 - Triptorelin (Triptodur)

CNS Lesions Commonly Associated



- **Craniopharyngioma**
 - Benign tumor
 - Papilledema or optic atrophy
 - Visual problems
- **Hypothalamic Hamartoma**
 - Most commonly associated brain lesion
 - Ectopic neural tissue of GnRH secretory neurons
 - Associated with Gestalt sz

Gonadotropin Independent Precocious Puberty

- **Gonadal Tumor**
 - Most common reproductive neoplasm in children
 - < 5% are malignant
 - Majority are germ cell tumors, epithelial cell tumors, and sex cord-stromal tumors
 - Tumor markers: α -fetoprotein, hCG, CEA
 - Secrete estrogen, androgens, or gonadotropin like hCG
- **Ovarian cysts**
 - can grow to 1-6cm
 - precocity regresses when cysts removed

Case

7 year 2 month old AA female c/o pubic hair.

Present and progressive since 5 years of age.

“Always seemed to need deodorant”

No breast development, vaginal bleeding or dc

No exposure to testosterone creams or gels

Fam Hx:

Mother 10 years of age at menarche and has PCOS

Father unknown age of pubertal development

Case

Physical Exam:

- BP: 109/58, pulse 99, height: **131.5 cm**, weight: **36.3 kg**. >99 %ile (Z= 2.39) BMI: 20.99 kg/m² 98^t %ile (Z= 2.00)
- GENERAL APPEARANCE: alert, no dysmorphic features
- SKIN/Eyes/ENT/Resp/CV/ABD/Musculoskeletal: unremarkable
- THYROID: not enlarged, no nodules palpated
- BREAST/CHEST: symmetric, Tanner stage 1 - glandular tissue not palpable. Lipomastia noted
- GU: pubic hair Tanner Stage 3 - very few hairs noted on labia majora, No clitoromegaly
- Axillary: 2-3 Fine hyperpigmented hairs noted

Tanner Staging of Pubic Hair

Tanner I	No pubic hair
Tanner II	Small amount of long, pigmented, downy hair, straight or slightly curled hair along the labia majora
Tanner III	Hair becomes darker, rough and curly. Some hair is also found over the junction of the pubis
Tanner IV	Adult like hair quality in a small and limited area. There is sparing hair in the medial thighs
Tanner V	Adult hair quality which extends to medial surface of the thighs in the shape of an inverse triangle

Case

Differential Diagnosis

- Premature Pubarche/Adrenarche
- Exogenous testosterone
- Non-classic CAH
- Gonadal tumor secreting testosterone or bHCG
- Adrenocortical tumor
- Cushings

Work-up

Total testosterone, DHEAS, androstenedione, 17OHprogesterone, and Bone Age

	Ref. Range		
DHEA Sulfate	Tanner Stage	Mean Age	Reference Range
	I:	>14 d	16-96
	II:	10.5 y	22-184
	III:	11.6 y	11-296
	IV:	12.3 y	17-343
	V:	14.5 y	57-395
Estradiol	I*:	7.1	undetectable-20
	(>14days and Prepubertal)		
	II:	10.5	undetectable-24
	III:	11.6	undetectable-60
	IV:	12.3	15-85
	V:	14.5	15-350
Luteinizing Hormone	<0.1- 6.0		<0.1 mIU/mL
FSH	<0.3 - 3.0		2.2 mIU/mL
Testosterone	<7-20		<7.0 ng/dL
17-OH Progesterone	<100		<40 ng/dL
Androstenedione	I	<9.2	<51
	II	9.2-13.7	42-100
	III	10.0-14.4	80-190
	IV	10.7-15.6	77-225
	V	11.8-18.6	80-240

Bone Age:

FINDINGS: Patient's chronological age is 7 years 2 months. According to the radiographic atlas of skeletal development of the hand and wrist by Greulich and Pyle method, patient's bone age is 8 years 10 months.

IMPRESSION: Advanced bone age.

Case Diagnosis

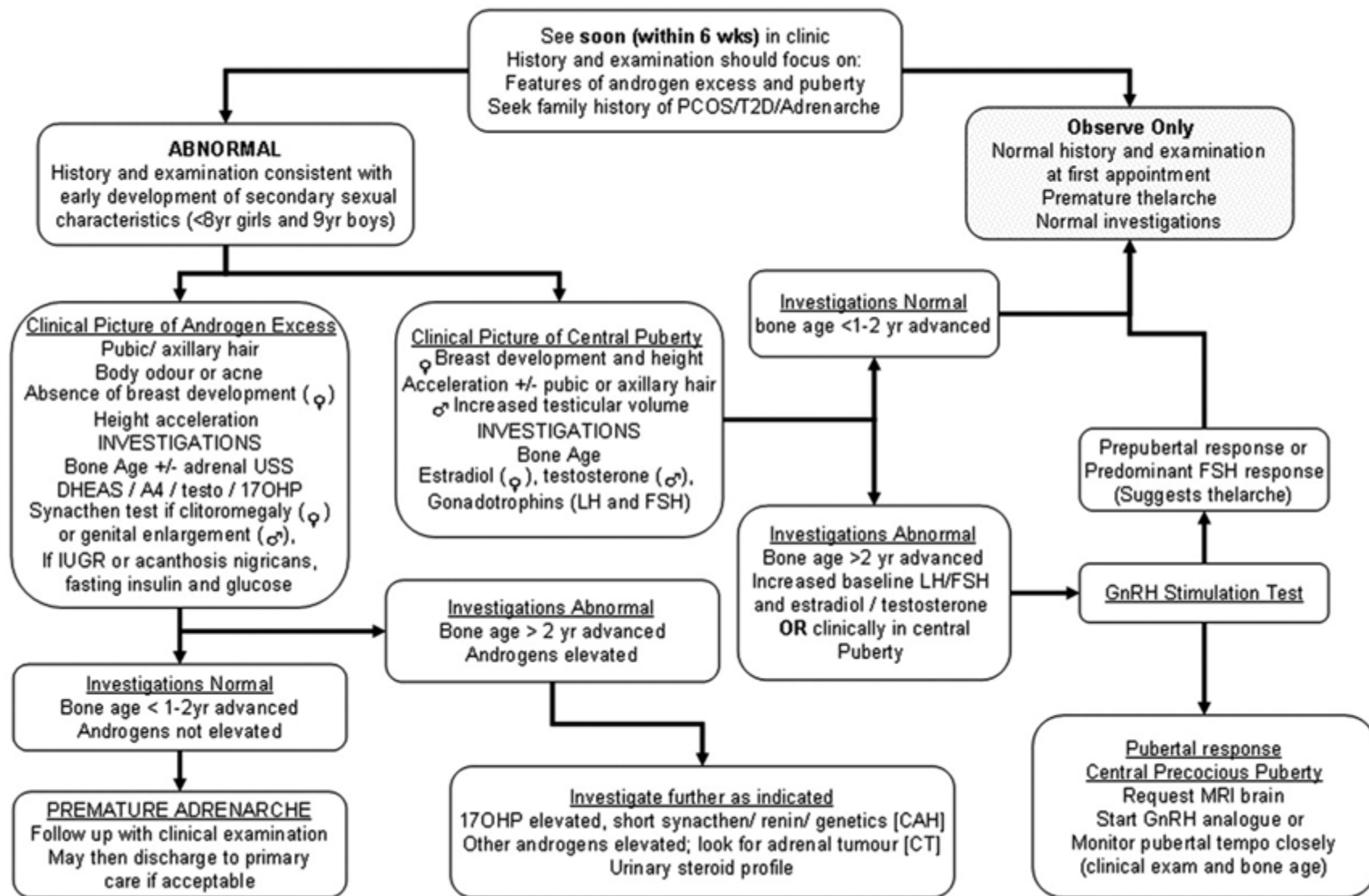
Benign Premature
Adrenarche

Premature Adrenarche

Not “true” precocious puberty

- Secondary sexual hair, acne, body odor
 - No breast development; clitoromegaly
 - Prepubertal to 4 mL testicular size in boys
- Need to monitor for development of CPP
- DHEA-S may be elevated to appropriate Tanner stage
- Increased incidence of hyperandrogenism later
 - PCOS

Algorithm for Investigation of Children Presenting with Adrenarche



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Delayed Puberty – What Could IT Be?

- Primary Hypogonadism
 - Turner Syndrome
 - Klinefelter Syndrome
 - Gonadal injury (chemo, autoimmune, infection, cryptorchidism)
 - DSD (testosterone biosynthesis disorders, CAIS, receptor defects)
- Secondary Hypogonadism
 - Constitutional Delay of growth and puberty
 - GnRH deficiency
 - Kallman Syndrome
 - Hypopituitarism
 - Tumors
 - SOD
 - Functional HH
 - Anorexia, Poorly controlled chronic disease

Delayed Puberty

- Work Up

- LH
- FSH
- Estradiol/Testosterone
- TSH and Free T4
- Bone Age
- Screen for chronic Medical Disease
 - Celiac screen, CBC, ESR, CMP, ?Prolactin
- Consider karyotype

- Treatment

- Time in CDGP
- Testosterone
 - 3-6 months low dose
- Estrogen

* Patient and Family history is most helpful

Question

You are seeing a 16-year-old girl for the first time who complains of amenorrhea. The mother's menarche was at age 12 years. The girl developed pubic hair at age 11 years and breast buds at age 12 years. She has no other symptoms. The mother reports that the girl eats well and has been active all her life. Physical examination reveals a height of 57 in, weight of 89 lb, BMI of 19.3, breast tissue at SMN rating 2, and pubic hair at SMR 4. A urine pregnancy test shows negative results. Laboratory results include: LH of 10mIU/mL (normal adult female, 2-95mIU/mL), FSH of 42mIU/mL (normal adult female, 1-30mIU/mL), and prolactin of 27ng/mL (normal, 5-23ng/mL).

Of the following, the MOST likely cause of this girl's primary amenorrhea is

- A. congenital adrenal hyperplasia
- B. excessive exercise
- C. imperforate hymen
- D. prolactinoma
- E. Turner syndrome

Question

A 7 yr old girl presents to you for concern for precocious puberty with progressive breast development. She is overweight but otherwise healthy. Her mother had menarche at 15 years and is concerned if her daughter is starting puberty now. On PE you were able to palpate a small amount of breast tissue, but an appreciable amount of adipose tissue around her breast area. She has no pubic hair. You are concerned about precocious puberty but also consider that she may simply be overweight and not have true breast tissue. You need to determine if further workup is necessary. Of the following the BEST test to help you make this decision is

- A. Bone age
- B. MRI brain
- C. estradiol level
- D. 17 OHP
- E. LH level

Question

An 8-year-old boy presents for a routine physical. On exam, he has Tanner 2 pubic hair and 5 cc bilaterally descended testes.

Which of the following is the next best diagnostic test?

- A. testicular ultrasound
- B. testosterone level
- C. adrenal CT
- D. bone age
- E. brain and sella MRI

14yo male presents to you clinic with a “swollen left nipple” for 2 weeks. Occasionally it is tender. No discharge. No redness or fever. He has had no chronic illnesses.

On physical examination, he appears healthy. He has a 2cm, firm, freely moveable, subareolar mass on the left breast that is mildly tender. No redness or discharge. No mass is palpated in the right breast.

Which of the following is the most likely diagnosis?

- A. Rhabdomyosarcoma
- B. Liposarcoma
- C. Physiologic pubertal gynecomastia
- D. Subareolar abscess
- E. Breast cancer

Pattern of gonadotropin secretion throughout life

