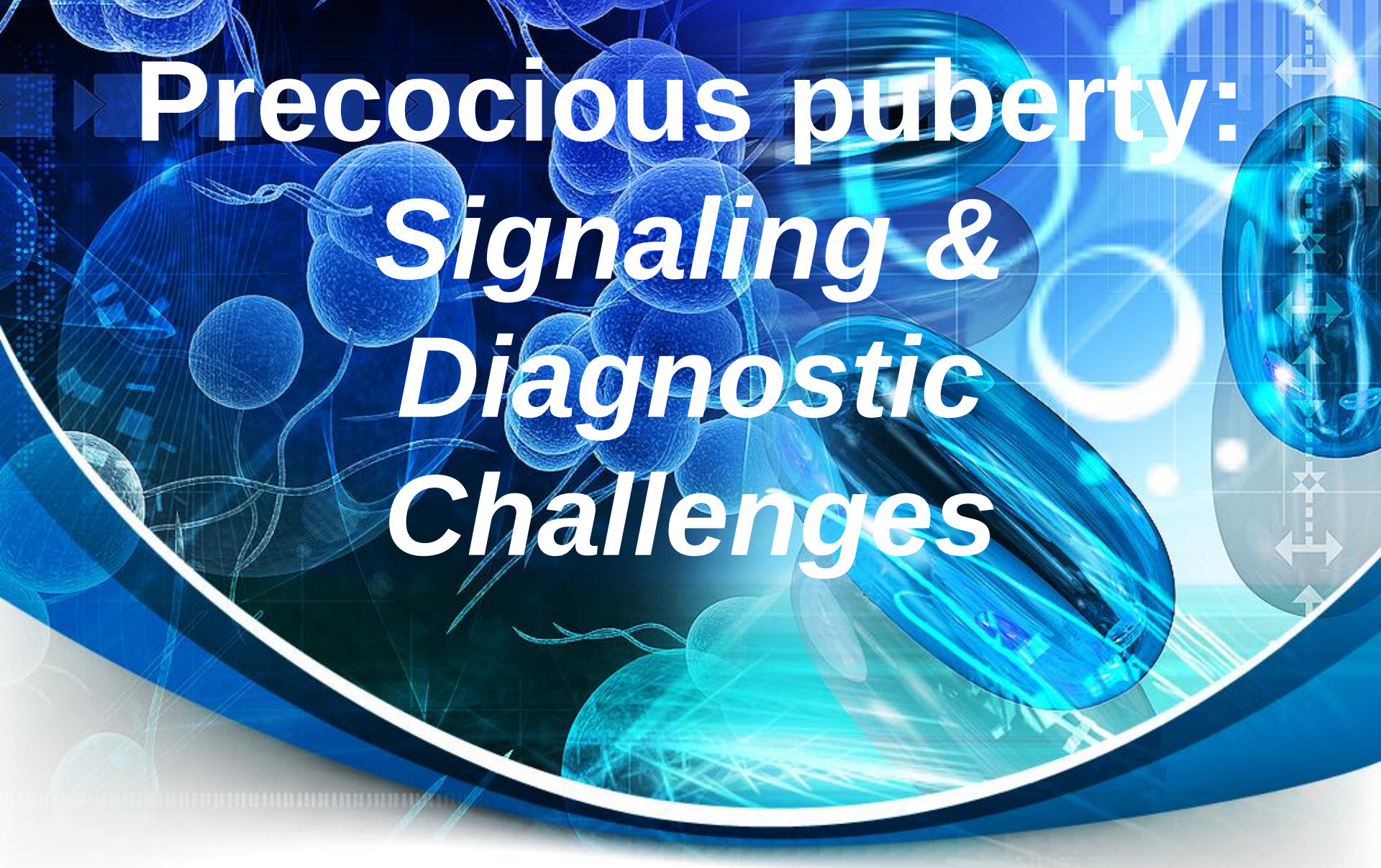


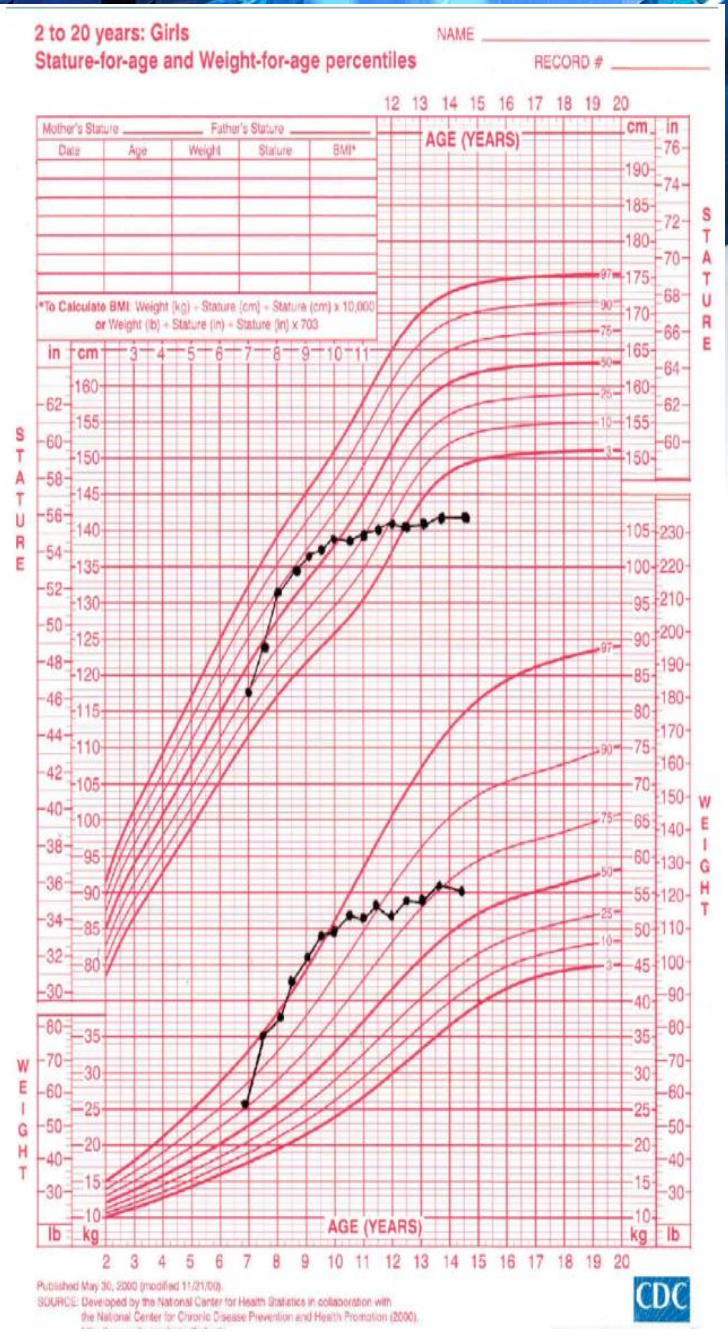
Precocious puberty: *Signaling & Diagnostic Challenges*

December 12, 2020

Francisco Nieves-Rivera, MD, FAAP

Disclosure

The speaker does not have conflicts with the information to be presented.



- Males maybe ~8’’ shorter than average
- Females tend to be ~4.7 shorter than average.

Vignette

- **CC**: Vaginal bleeding
- **HPI**: 4 y/o female w/ bilateral breast tissue enlargement since one month before initial evaluation.
- Brought to ER with history of vaginal bleeding since the day before the visit.
- Saw two days later and bleeding had stopped on its own.
- ROS was negative for headaches.

Vignette

- Her physical significant for:
  - Ht 100.4 cm (40th), Wt 17.8 Kg (83th), HR 82/min, RR 24 /min, BP 83/53 mmHg.
  - Breast tissue was a Tanner/SMR stage III (5.5 cm diameter)
  - Pubic hair Tanner/SMR I.
  - Vaginal wall was pale with whitish secretion → evidence of estrogen stimulation.

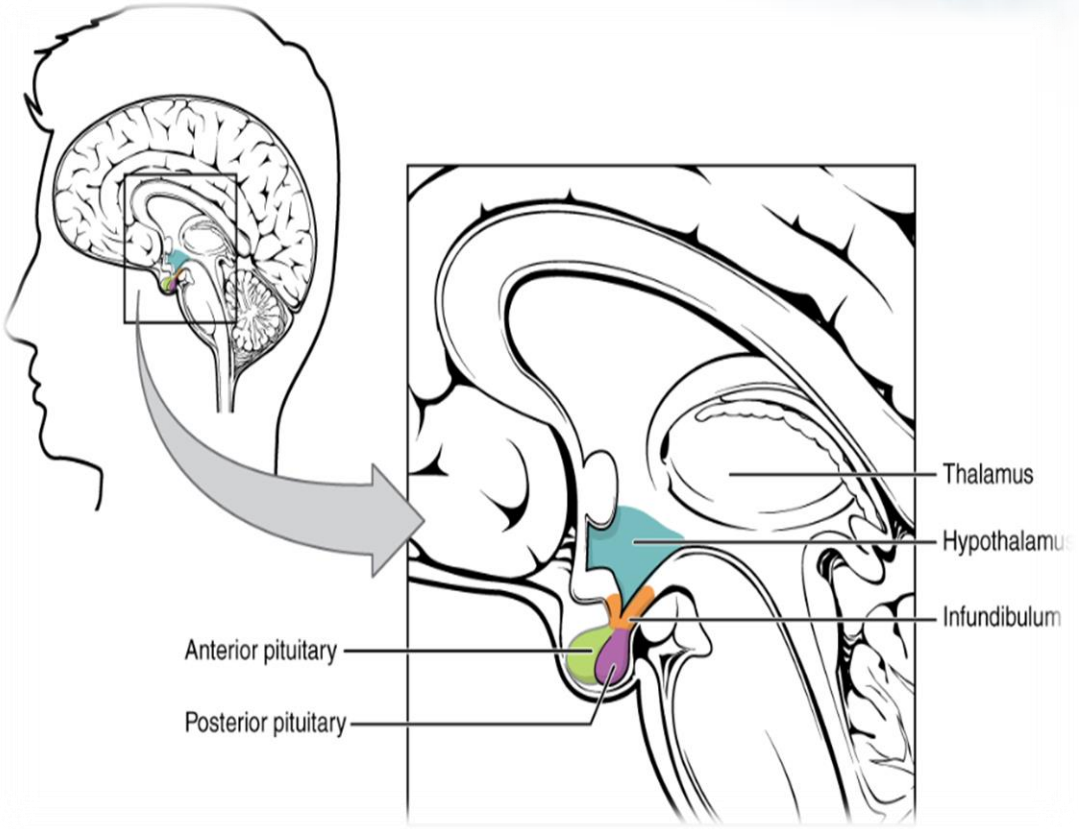
Vignette

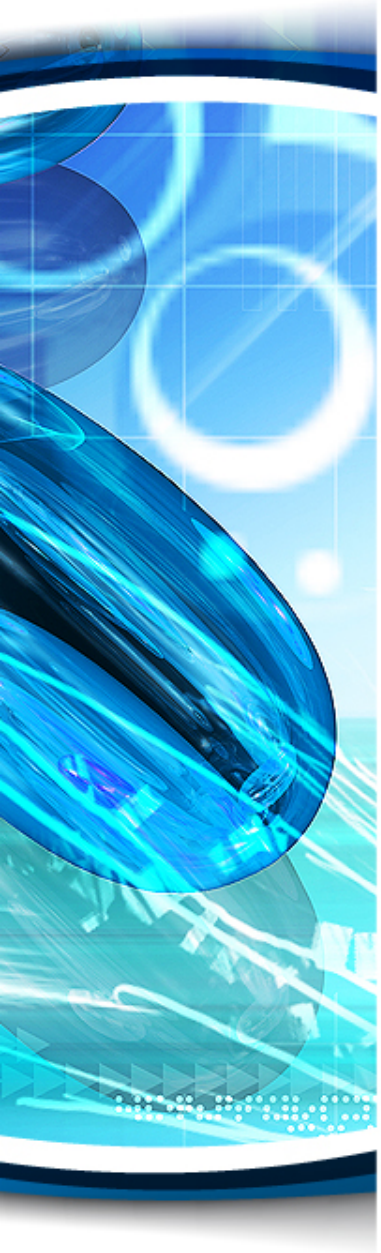
Hormone	Baseline	1 hour	2 hour	3 hour
E_{2} (pg/ml)	39.5	-	-	-
FSH (mIU/ml)	2.92	11.3	12.7	16.6
LH (mIU/ml)	2.68	21.2	22.1	25.0

GnRH test biochemically confirmed that precocious puberty was of central origin: **10X** *vs* FSH 5X–

Vignette

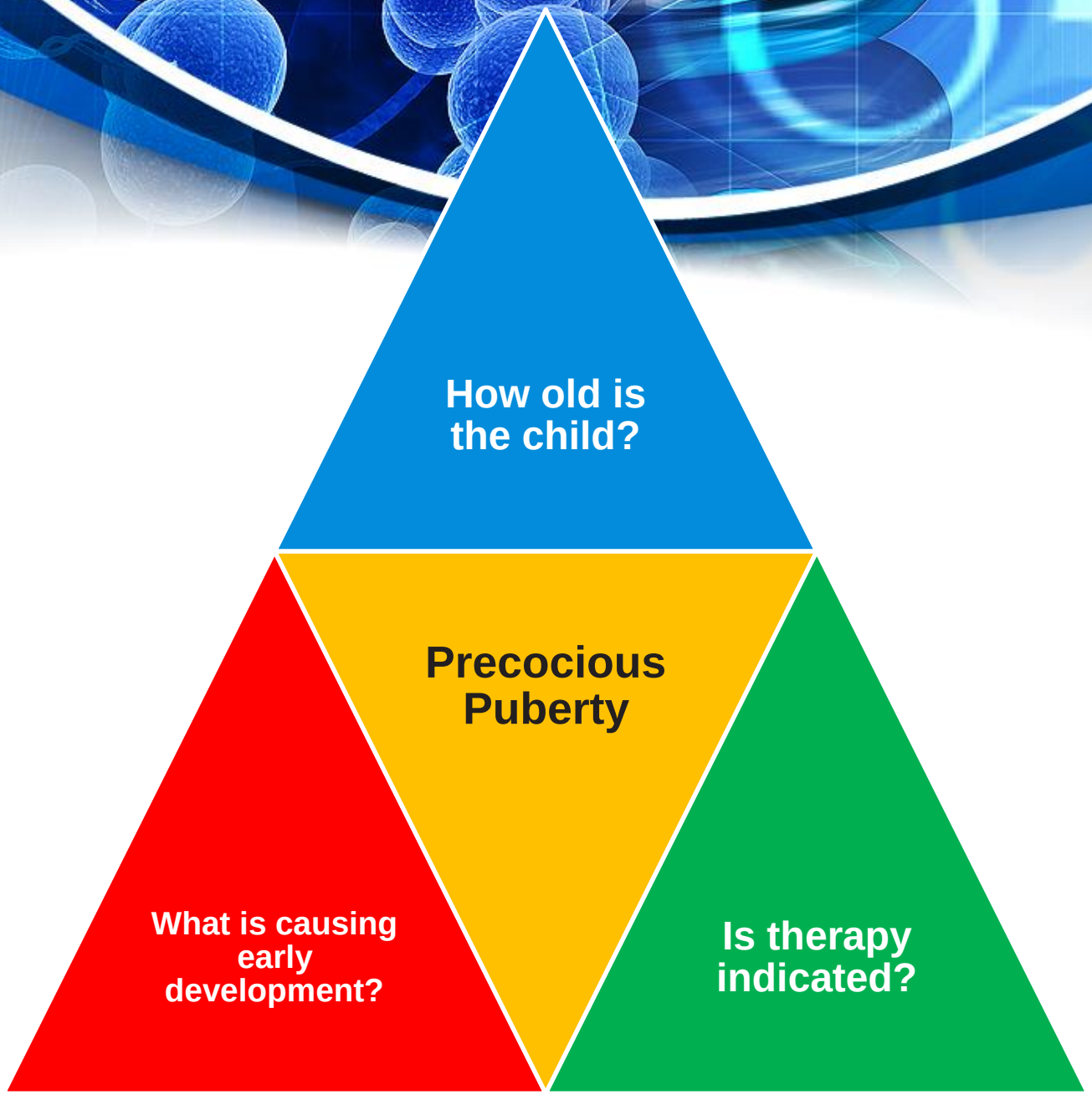
- Brain MRI revealed a suprasellar, oval shape lesion felt most compatible w/ a harmatoma of ***tuber cinereum***.
- Bone age **6** years at a chronological age of **4** years.
- Pelvic US showed a stimulated uterus: **5.1** x 1.7 x 2.1 cm



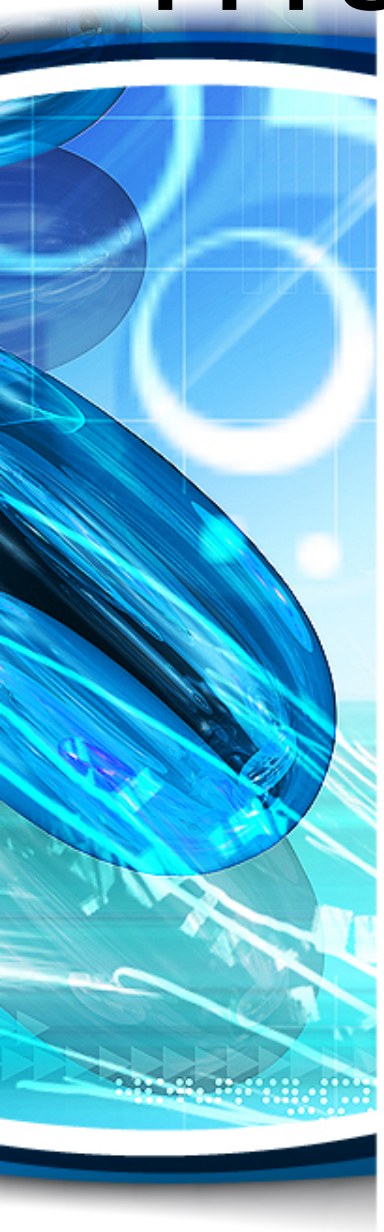


Objectives

- Review Precocious puberty (PP) & variants
- Reexamine mechanisms/signaling in PP & variants
- Diagnostic challenges in PP


How old is the child?
Precocious Puberty
What is causing early development?
Is therapy indicated?

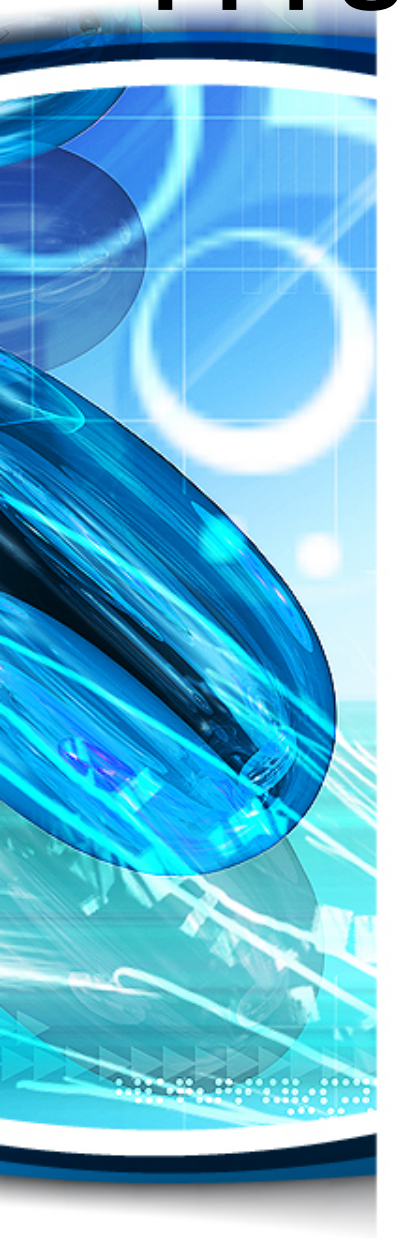
PP: Signaling & diagnostic challenges



- Precocious puberty - onset of 2^{ry} sexual characteristics before the age of 8 years in girls & 9 years in boys.
- 2 to 2.5 SD below the mean age of onset of puberty.
- mean age of onset of puberty of ~ 10.5 years in girls & 11.5 years in boys.

Herman-Giddens ME, Steffes J, Harris D, et al. Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network. Pediatrics 2012; 130:e1058.

PP: Signaling & diagnostic challenges



- Hypothalamic-pituitary-gonadal (HPG) axis is biologically active in utero & briefly during the 1st week of life.
- It then becomes more active again during infancy, with peak activity between 1-3 months of age → **mini puberty**.

"mini puberty of infancy"

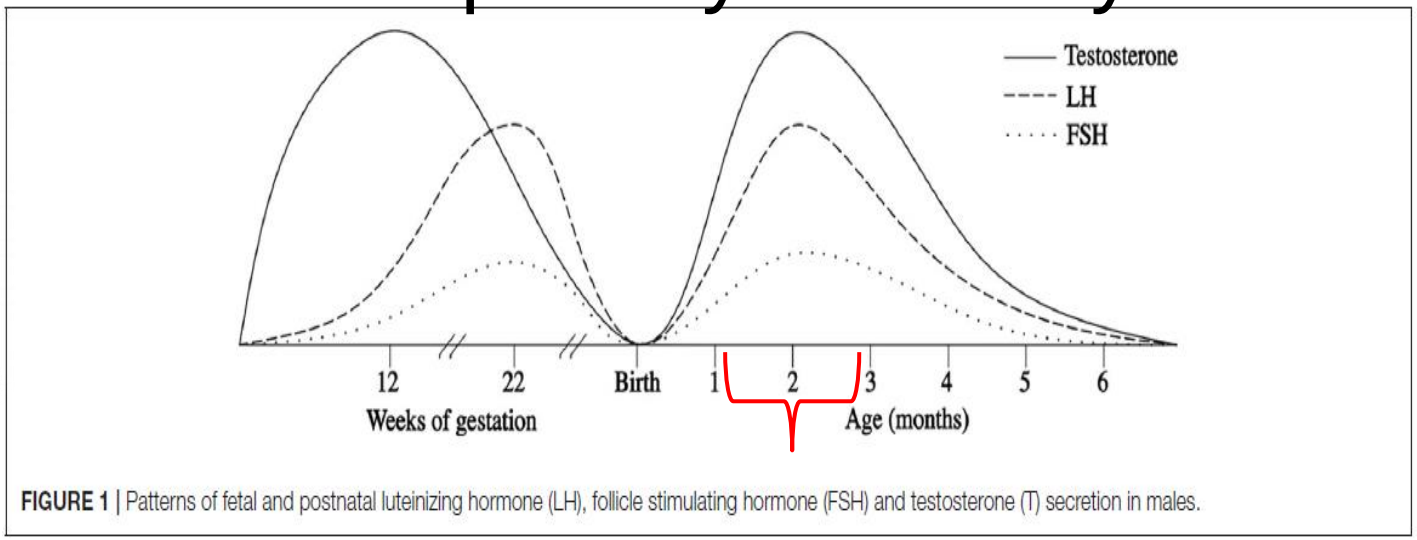


FIGURE 1 | Patterns of fetal and postnatal luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone (T) secretion in males.

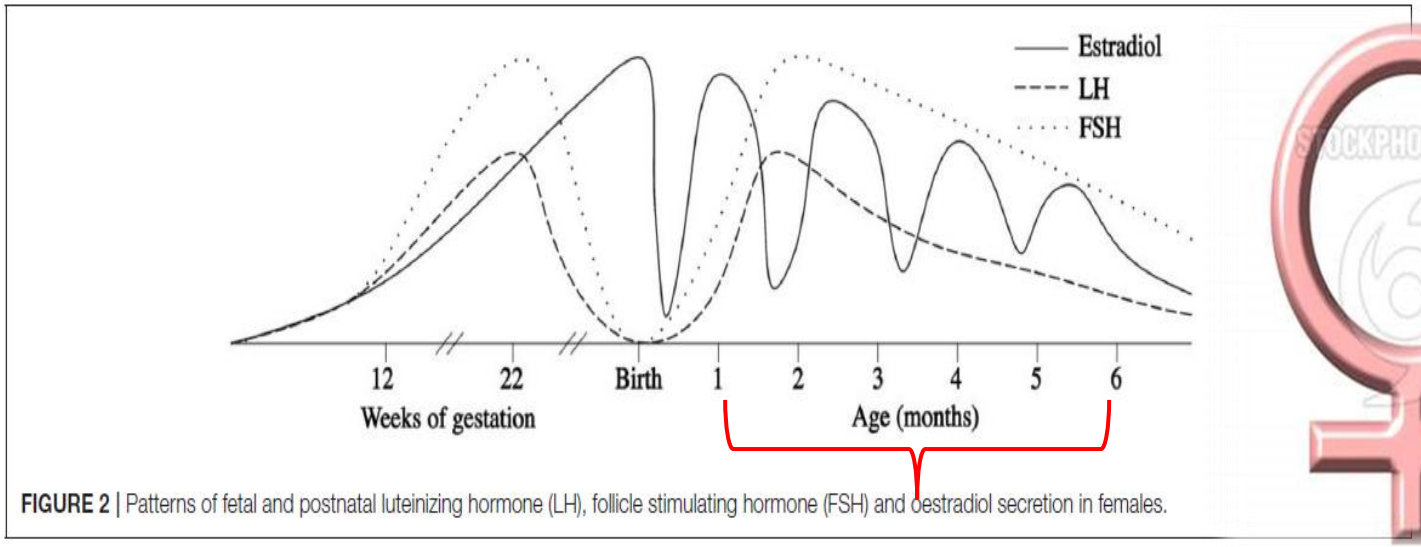
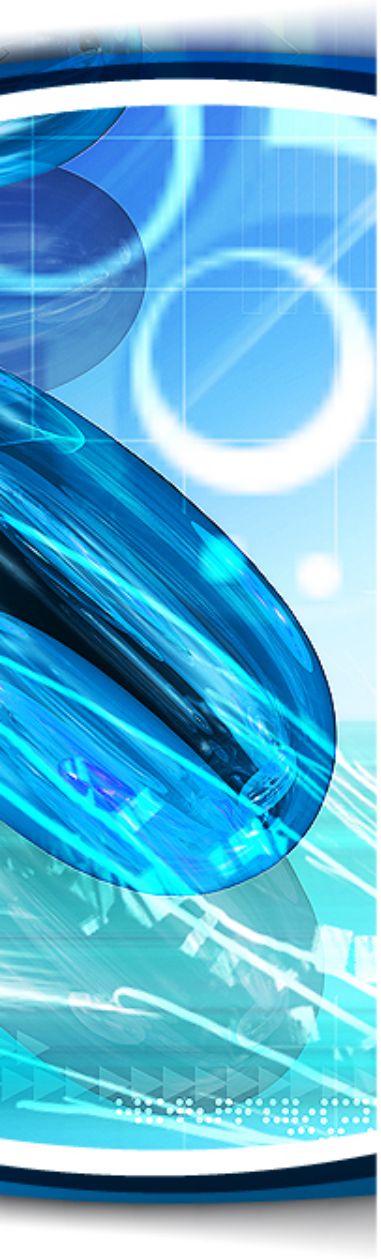


FIGURE 2 | Patterns of fetal and postnatal luteinizing hormone (LH), follicle stimulating hormone (FSH) and oestradiol secretion in females.

Lanciotti L, Cofini M, Leonardi A, Penta L, Esposito S. Up-To-Date Review About Minipuberty and Overview on Hypothalamic-Pituitary-Gonadal Axis Activation in Fetal and Neonatal Life. *Frontiers in Endocrinology*, July 2018 (Vol 9), Article 410 (doi: 10.3389/fendo.2018.00410)



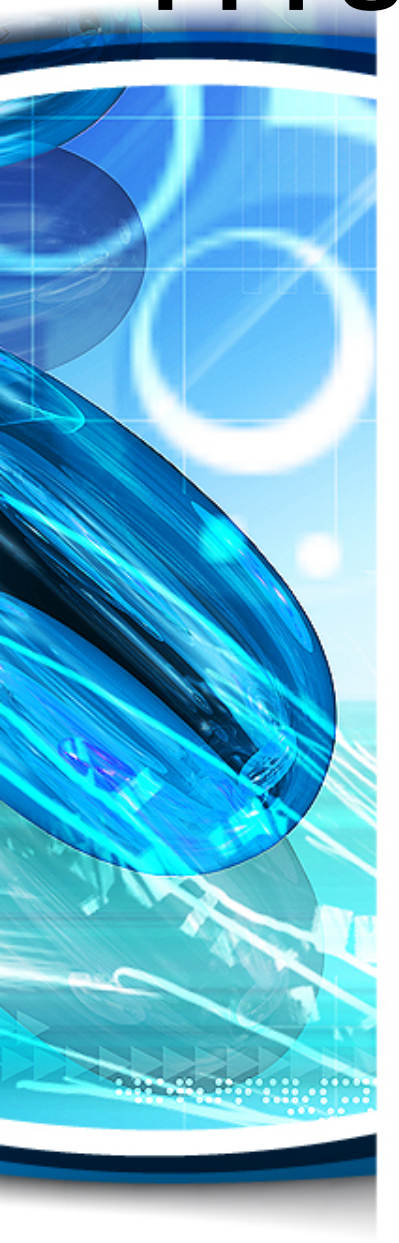
Sexual maturity rating (Tanner stages) of secondary sexual characteristics

Boys – Development of external genitalia
Stage 1: Prepubertal
Stage 2: Enlargement of testes and scrotum; scrotal skin reddens and changes in texture
Stage 3: Enlargement of penis (length at first); further growth of testes
Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker
Stage 5: Adult genitalia
Girls – Breast development
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: Projection of papilla only, related to recession of areola
Boys and girls – Pubic hair
Stage 1: Prepubertal (the pubic area may have vellus hair, similar to that of forearms)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
Stage 3: Darker, coarser, and more curled hair, spreading sparsely over junction of pubes
Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5: Adult in type and quantity, with horizontal upper border

11.5 yrs

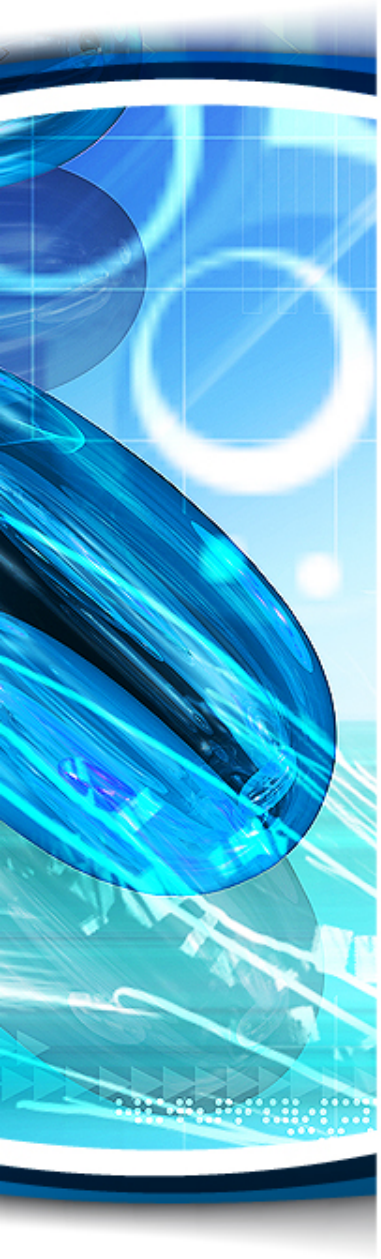
~11 yrs

PP: Signaling & diagnostic challenges



- Since these reports by Marshall and Tanner, several studies in the US & other countries suggest that children, especially **overweight** children, now enter puberty at a younger age than previously.

Herman-Giddens ME, Steffes J, Harris D, et al. Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network. Pediatrics 2012; 130:e1058.



Cell Metabolism

Available online 19 October 2020

In Press, Corrected Proof

Article

Central Ceramide Signaling Mediates Obesity-Induced Precocious Puberty

Violeta Heras [1, 8], Juan Manuel Castellano [1, 2, 8] ✉, Daniela Fernandois [3], Inmaculada Velasco [1], Elvira Rodríguez-Vazquez [1], Juan Roa [1, 2], Maria Jesus Vazquez [1, 2], Francisco Ruiz-Pino [1, 2], Matias Rubio [3], Rafael Pineda [1], Encarnacion Torres [1], Maria Soledad Avendaño [1], Alfonso Paredes [3], Leonor Pinilla [1, 2], Denise Belsham [4], Carlos Diéguez [2, 5], Francisco Gaytán [1, 2], Nuria Casals [2, 6] ... Manuel Tena-Sempere [1, 2, 7, 9] ✉

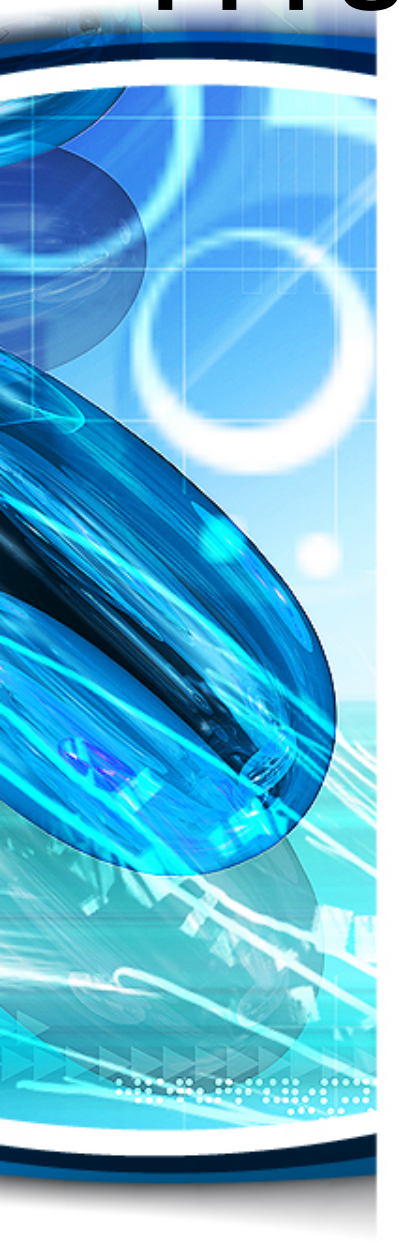
Highlights

- Early-onset obesity increases hypothalamic ceramide content and advances puberty in rats
- Blockade of ceramide synthesis delays puberty and prevents kisspeptin effects
- Obesity alters PVN ceramide synthesis and the maturation of ovarian sympathetic input
- Obesity-induced early puberty is reversed by blocking a ceramide synthetic enzyme in PVN

PP: Signaling & diagnostic challenges

- In addition, there are **racial** differences, with puberty occurring,
- ***Earlier*** in African-American children compared with non-Hispanic Caucasian and Hispanic children.

PP: Signaling & diagnostic challenges

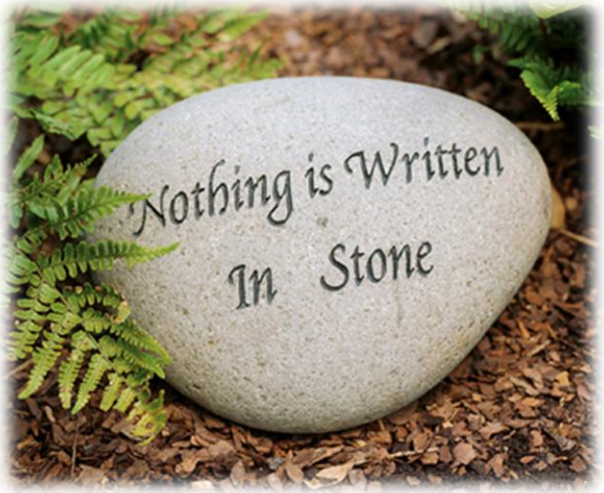


- **Definition** of PP is *problematic*, at least in girls, and that selection of children for evaluation should not only depend on **age** but also clinical features, **race/ethnicity**, and presence/absence of **obesity**.

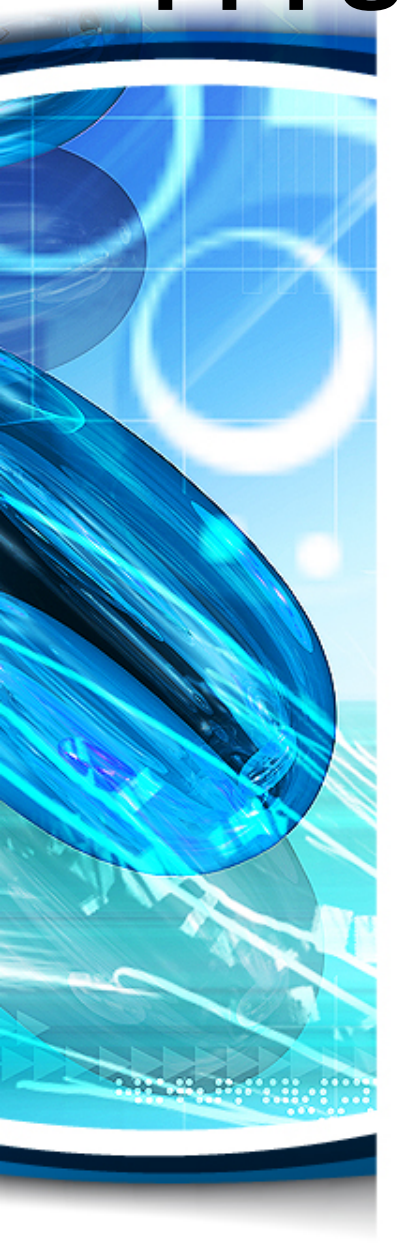
Rosenfield RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics 2009; 123:84

PP: Signaling & diagnostic challenges

- Children presenting w/ signs of 2^{ry} sexual development younger than the age of 8 years in girls or 9 years in boys.
- The level of concern & extent of evaluation should increase w/ **<u>younger</u>** age at presentation.



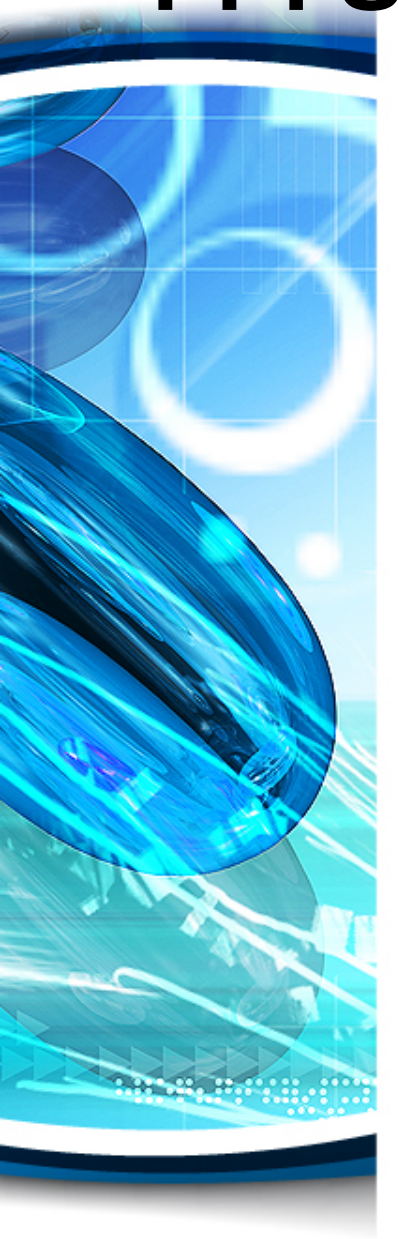
PP: Signaling & diagnostic challenges



- Given the trend towards earlier pubertal development in girls who are between the ages of 7-8, a comprehensive history, physical examination, and clinical follow-up may be **sufficient** if the clinical evaluation does not raise any additional concerns.

Kaplowitz P, Bloch C, Section on Endocrinology, American Academy of Pediatrics. Evaluation and Referral of Children With Signs of Early Puberty. Pediatrics 2016; 137.

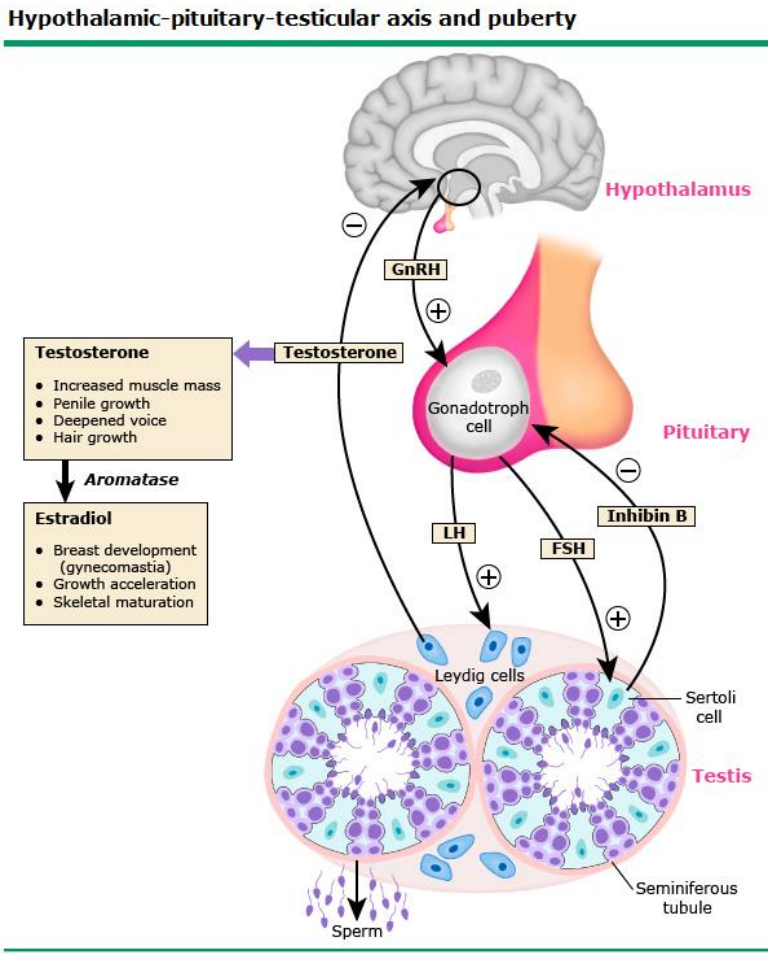
PP: Signaling & diagnostic challenges



- CPP is characterized by **sequential** maturation of breasts and pubic hair in girls and of testicular and penile enlargement and pubic hair in boys.
- In these patients, the sexual characteristics are appropriate for the child's gender (**iso**sexual).

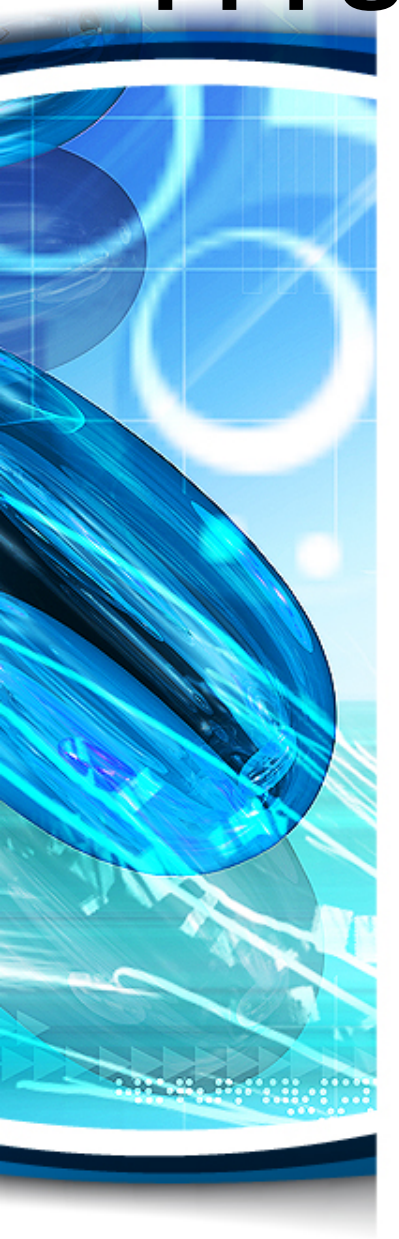
PP: Signaling & diagnostic challenges

- CPP is pathologic in up to 40 to 75% of cases in boys, compared with 10 to 20% in girls



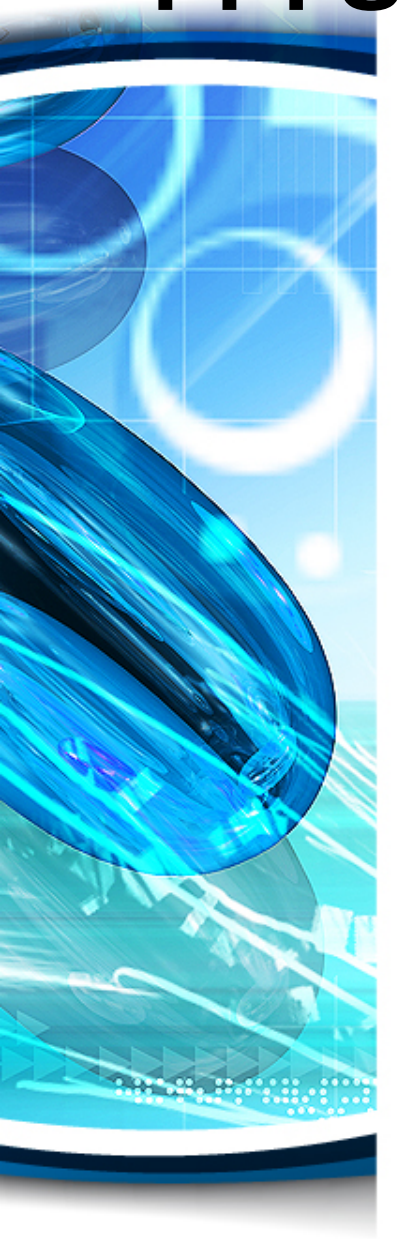
Pedicelli S, Alessio P, Scirè G, et al. Routine screening by brain magnetic resonance imaging is not indicated in every girl with onset of puberty between the ages of 6 and 8 years. J Clin Endocrinol Metab 2014; 99:4455.

PP: Signaling & diagnostic challenges



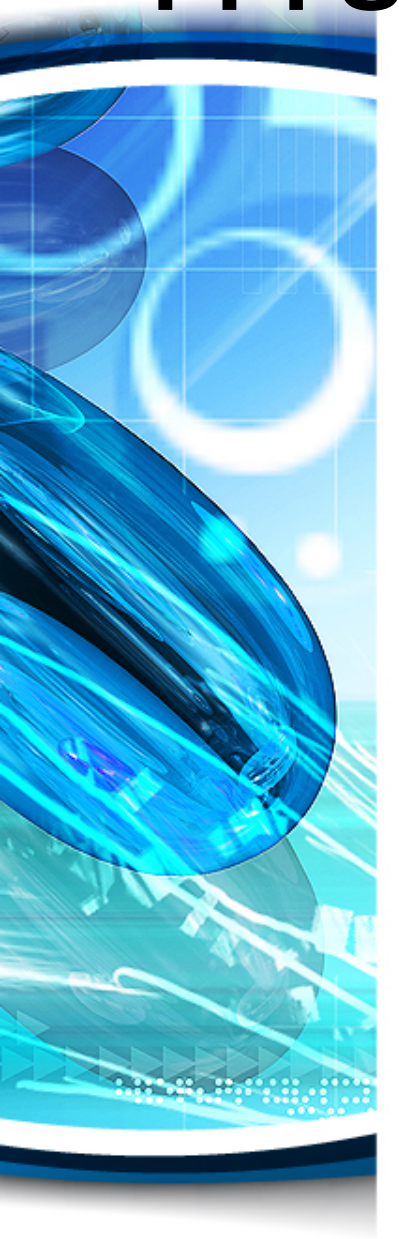
- **<u>Peripheral</u> precocity** – *AKA* peripheral PP, gonadotropin-***<u>in</u>***dependent PP is caused by excess secretion of sex hormones (estrogens or androgens) from:
  - Gonads
  - or adrenal glands,
  - exogenous sources of sex steroids, or
  - ectopic hCG production (e.g., germ-cell tumor).

PP: Signaling & diagnostic challenges



- **Precocity** - used instead of puberty because true puberty requires activation of the HPG axis, as occurs in CPP.
- Precocity may be:
  - appropriate for the child's gender (***iso***sexual)
  - or inappropriate, w/ virilization of ♀ & feminization of ♂ (***contra***sexual).

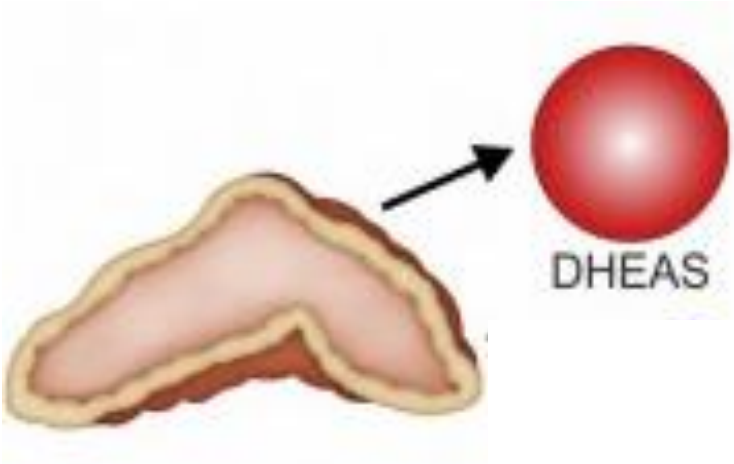
PP: Signaling & diagnostic challenges



- Benign clinical pubertal variants include:
  - Isolated breast development in girls (premature thelarche)
  - Pubarche - Isolated androgen-mediated sexual characteristics (such as pubic and/or axillary hair, acne, and apocrine odor) in boys

PP: Signaling & diagnostic challenges

- Benign clinical pubertal variants:
  - Girls (premature adrenarche, which results from early activation of the hypothalamic-pituitary-**adrenal** axis, as confirmed by mildly elevated levels of DHEA***S*** for age).



PP: Signaling & diagnostic challenges

F/U?

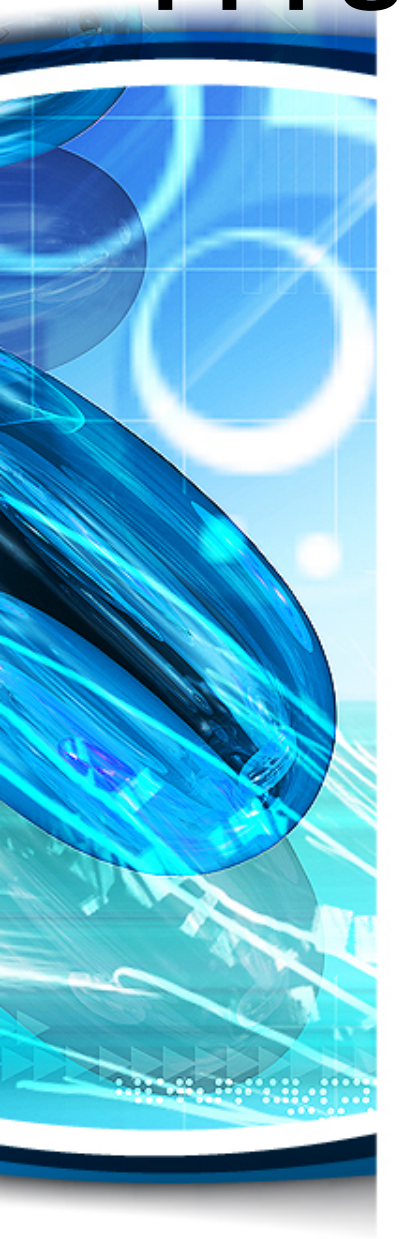
- However, **repeat** clinical examination, which could be performed by the PCP, is warranted to ensure there is no rapid &/or expanded pubertal progression & that the diagnosis is correct.

PP: Signaling & diagnostic challenges

- ***True* PUBERTY**
  - These children have accelerated linear growth for age, advanced bone age, and pubertal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

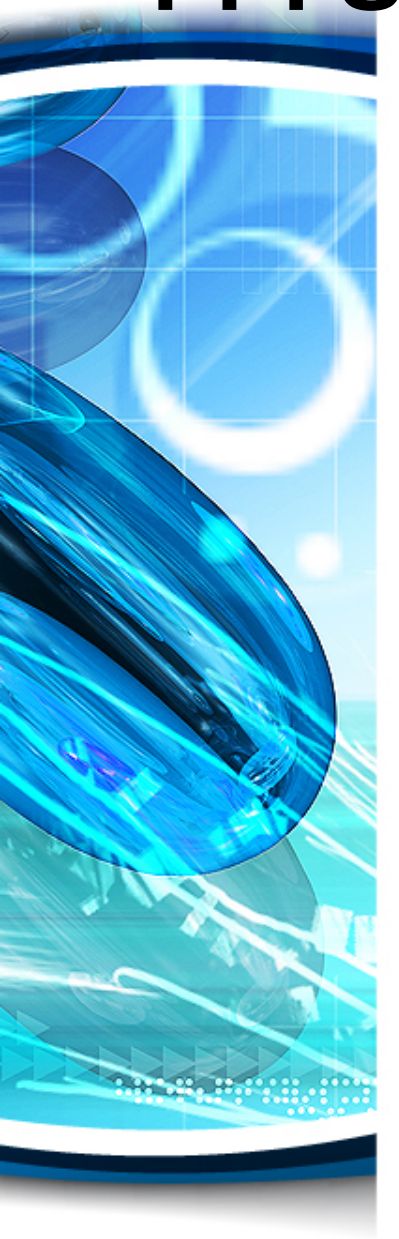
Bangalore Krishna K, Fuqua JS, Rogol AD, et al. Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium. Horm Res Paediatr 2019; 91:357.

PP: Signaling & diagnostic challenges

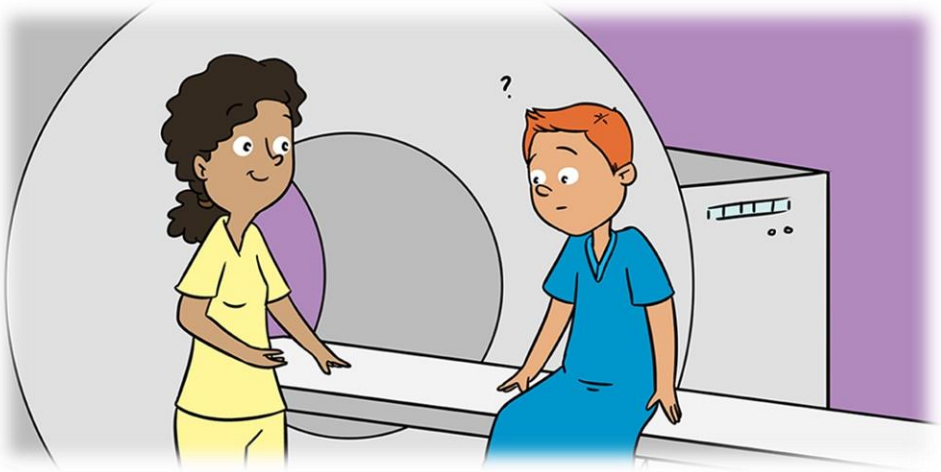


- CPP is idiopathic in 80 to 90% of cases of girls but in only 25 to 60% of boys.
- In some cases, especially those w/ other affected **family** members, cases designated as idiopathic CPP may be due to presence of genetic variants that are associated with early puberty.

PP: Signaling & diagnostic challenges



- … cases caused by lesions of the CNS, are referred to as **neurogenic** CPP.
- MRI is therefore recommended, even in the absence of clinically evident neurologic abnormalities.

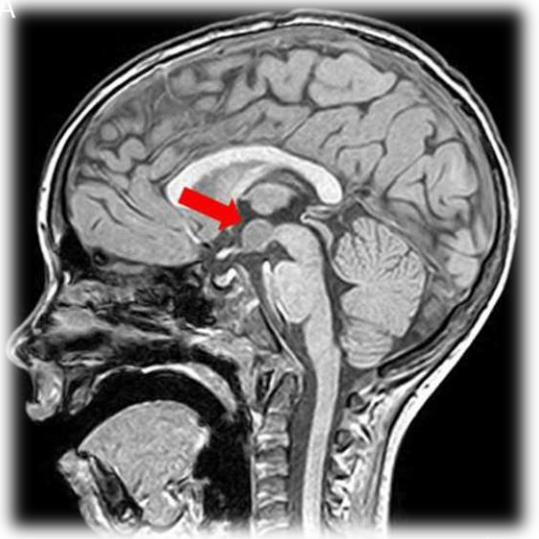


PP: Signaling & diagnostic challenges

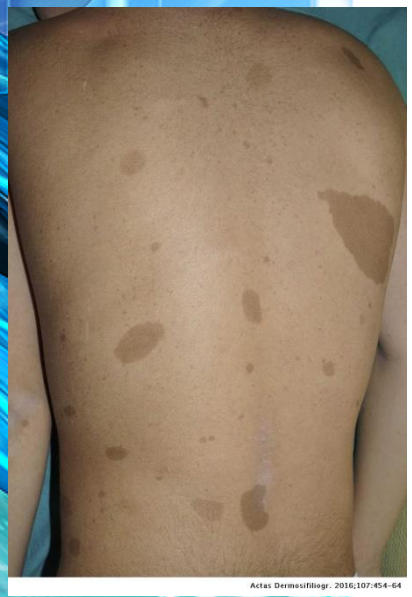
- However, the low prevalence of CNS lesions in girls w/ the onset of puberty that begins after age 6 years raises the question if all girls in this age group need imaging.

PP: Signaling & diagnostic challenges

- Many different types of intracranial disturbances can cause PP:
  - Hamartomas of the tuber cinereum → most CNS tumor to cause PP in very young children, although, the mechanism by which these tumors lead to CPP is unknown.



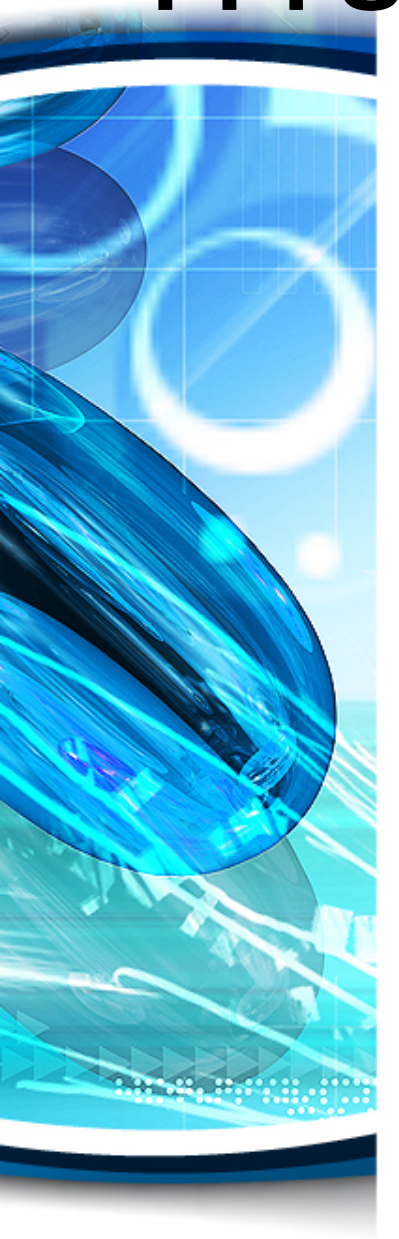
PP: Signaling & diagnostic challenges



- Other CNS tumors associated with PP:
  - astrocytomas, ependymomas, pinealomas, & optic and hypothalamic gliomas.
  - Sexual precocity in pts w/ neurofibromatosis is usually, but not always, associated w/ an optic glioma.

Mogensen SS, Aksglaede L, Mouritsen A, et al. Pathological and incidental findings on brain MRI in a single-center study of 229 consecutive girls with early or precocious puberty. PLoS One 2012; 7:e29829

PP: Signaling & diagnostic challenges

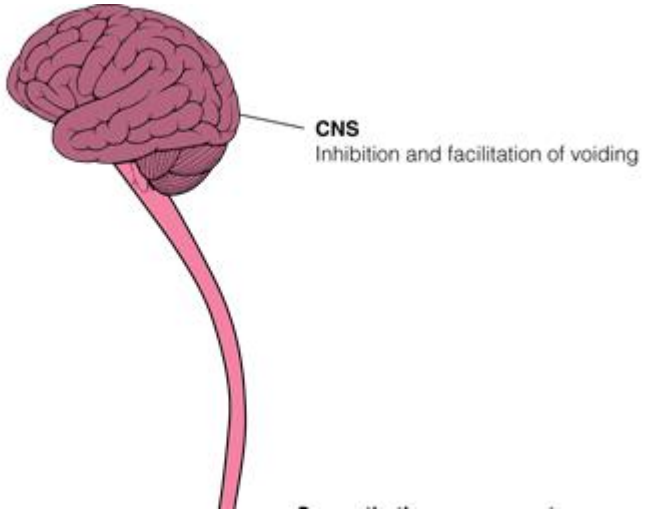


- CNS irradiation & PP
  - ***rare complication***
  - when it occurs, it is commonly associated with GH deficiency (GHD).
  - In this setting, regardless of height velocity, the GH axis should be evaluated.
  - If GHD confirmed, the pt should be treated w/ GH combined w/ GnRH agonist therapy.

van Iersel L, Li Z, Srivastava DK, et al. Hypothalamic-Pituitary Disorders in Childhood Cancer Survivors: Prevalence, Risk Factors and Long-Term Health Outcomes. J Clin Endocrinol Metab 2019; 104:6101.

PP: Signaling & diagnostic challenges

- Other CNS lesions & Precocious puberty:
  - hydrocephalus, cysts, trauma, CNS inflammatory disease, and congenital midline defects, such as optic nerve hypoplasia.

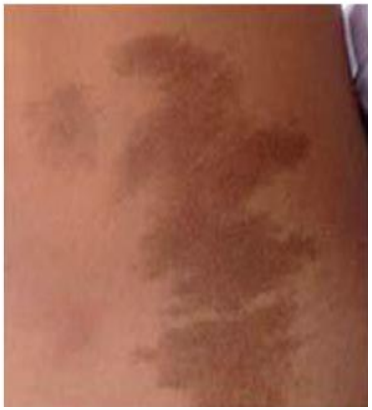


PP: Signaling & diagnostic challenges

- **Genetics** — w/ CPP in only a minority of cases:
  - Gain-of-function mutations in the kisspeptin 1 gene (***KISS1***) & the gene for its G protein-coupled receptor (***KISS1R***, formerly known as *GPR54*) have been implicated in the pathogenesis of some cases of CPP.

Silveira LG, Noel SD, Silveira-Neto AP, et al. Mutations of the KISS1 gene in disorders of puberty. J Clin Endocrinol Metab 2010; 95:2276.

McCune - Albright Syndrome



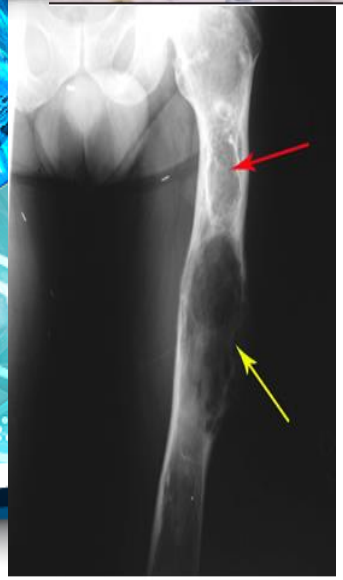
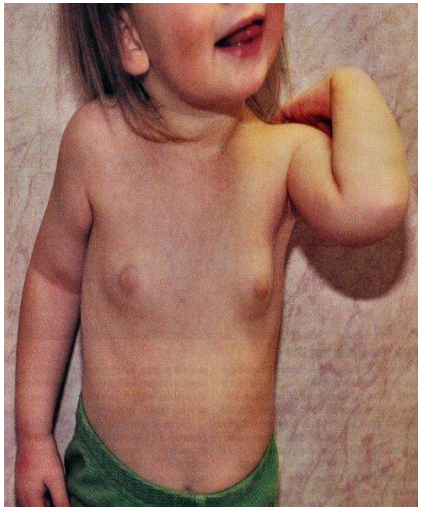
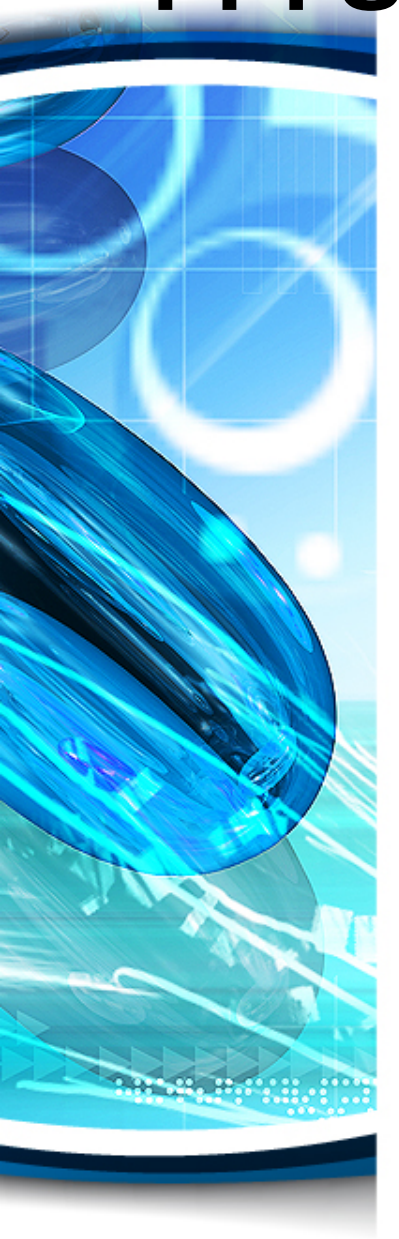


Figure 6b

Somatic activating mutation of the GNAS gene

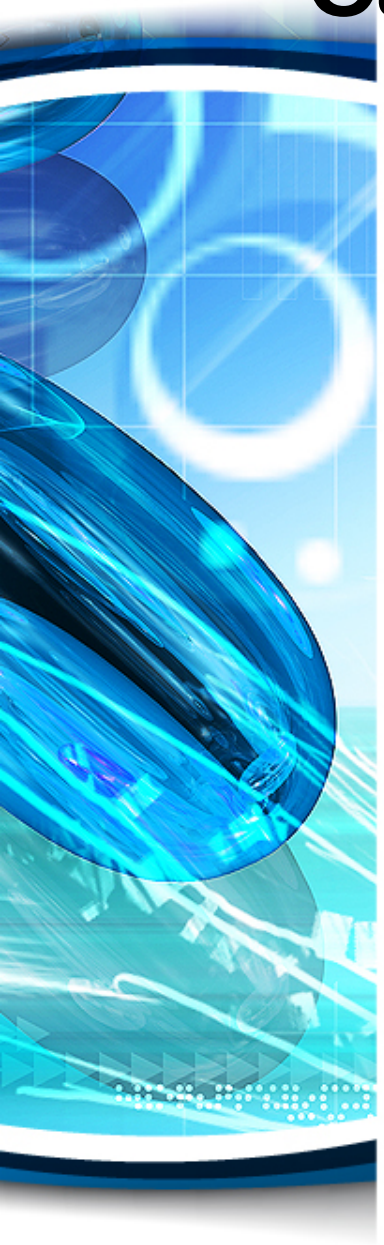


PP: Signaling & diagnostic challenges



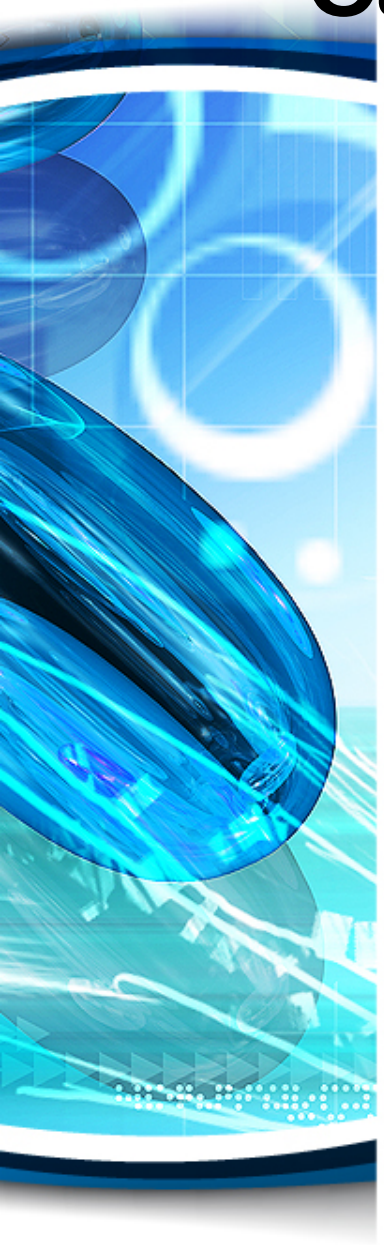
- **Previous excess sex steroid exposure —**
  - Children exposed to high serum levels of sex steroid (eg, those w/ McCune-Albright syndrome & poorly control CAH) may sometimes develop superimposed CPP,
  - either from the **priming** effect of the peripheral precocity-derived sex steroid on the hypothalamus or in response to the **sudden lowering** of the sex steroid levels following improved control of the sexual precocity.

Causes of peripheral precocity



- *AKA* peripheral PP or gonadotropin-**in**dependent PP
- caused by excess secretion of sex hormones (estrogens and/or androgens)
- derived either from the gonads or adrenal glands or from exogenous sources.

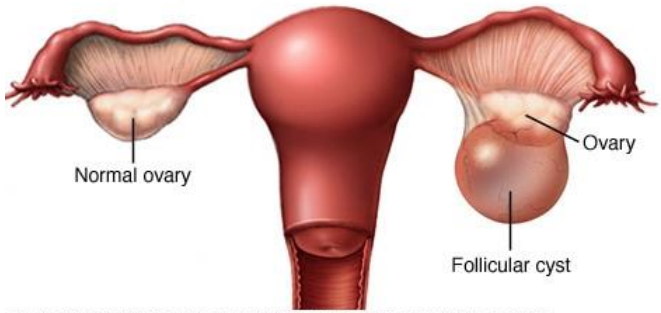
Causes of peripheral precocity



- Characterization is based upon whether the sexual characteristics are appropriate for the child's gender (**iso**sexual) or inappropriate, with virilization of girls and feminization of boys (**contra**sexual).
- FSH & LH levels are typically ↓

Causes of peripheral precocity

- **Ovarian cysts**:
  - A functioning follicular cyst is the most common cause of Peripheral Precocity in girls.
  - Affected pts often present w/ breast development, followed by an episode of vaginal bleeding, which occurs due to E_2 withdrawal once the cyst has regressed.



Causes of peripheral precocity

- **Leydig cell tumors**:
  - Should be considered in any boy w/ **asymmetric** testicular enlargement.
  - The larger testis should be biopsied if it enlarges during follow-up.
  - These testosterone-secreting tumors are almost always benign and are readily cured by surgical removal.

Henderson CG, Ahmed AA, Sesterhenn I, et al. Enucleation for prepubertal leydig cell tumor. J Urol 2006; 176:703.

Causes of peripheral precocity

- **Human chorionic gonadotropin (hCG)-secreting germ-cell tumors:**
- Germ-cell tumors secrete hCG
- In boys, activates LH receptors on the Leydig cells, resulting in increased testosterone production.
- Increase in testicular size usually only to an early pubertal size.

Causes of peripheral precocity

- **Familial male-limited PP:**
  - **rare** disorder (*AKA* **testotoxicosis**), 1-4 y/o
  - caused by an activating mutation in the LH receptor gene, which results in premature Leydig cell maturation & testosterone secretion.
  - AD disorder, girls are <u>not</u> affected clinically
  - the increase in testicular size is usually only to an early pubertal size.

Causes of peripheral precocity

Both girls and boys:

- Physical changes either may be iso- or contrasexual depending on the sex of the child and the type of sex hormone produced.
- Excess estrogen will cause feminization, while excess androgen will result in virilization.

Causes of peripheral precocity

Both girls and boys:

– **Primary hypothyroidism**:

- Girls, findings include early breast development, galactorrhea, and recurrent vaginal bleeding,
- Boys present with premature testicular enlargement.
- “Overlap" or Van Wyk-Grumbach syndrome.
- Mechanism -> cross-reactivity & stimulation of the FSH receptor by high TSH alpha subunit.

Anasti JN, Flack MR, Froehlich J, et al. A potential novel mechanism for precocious puberty in juvenile hypothyroidism. J Clin Endocrinol Metab 1995; 80:276.

Causes of peripheral precocity

Both girls and boys:

– **Exogenous sex steroids and endocrine-disrupting chemicals (EDC):**

- Feminization, including gynecomastia in boys, has been attributed to excess estrogen exposure from creams, ointments, and sprays.
- Caretakers using these topical estrogens to treat menopausal symptoms may inadvertently expose children to the hormones.

Food and Drug Administration safety communication, 7/29/10: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220185.htm (Accessed on October 06, 2010).

Causes of peripheral precocity

Both girls and boys:

– Exogenous sex steroids and EDC

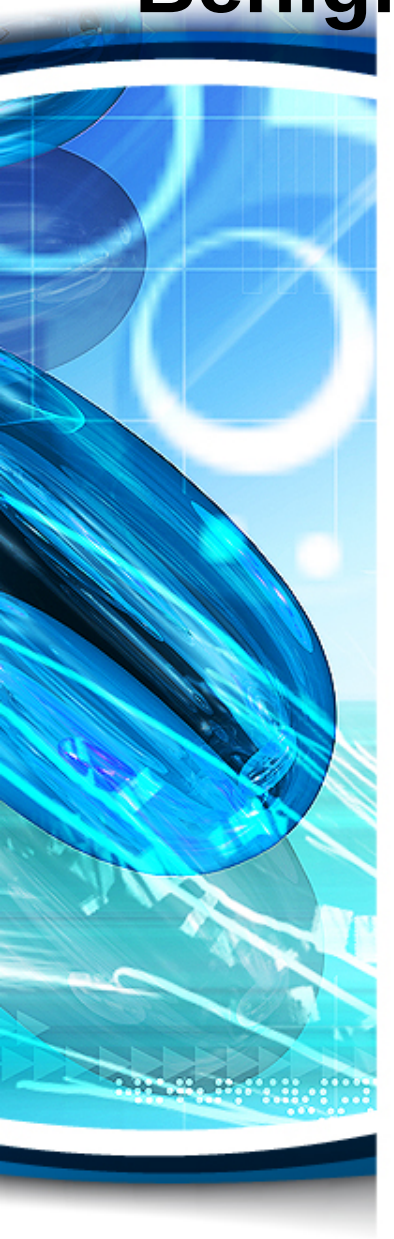
- A food source was suspected for local "epidemics" of early thelarche in Italy and Puerto Rico during the 1980s, but no single causative substance was found in food samples.
- There is ongoing research assessing the influence of EDC on population trends of earlier onset of puberty as well as their potential role as causative agents of precocious puberty.

Sáenz de Rodríguez CA, Bongiovanni AM, Conde de Borrego L. An epidemic of precocious development in Puerto Rican children. J Pediatr 1985; 107:393.

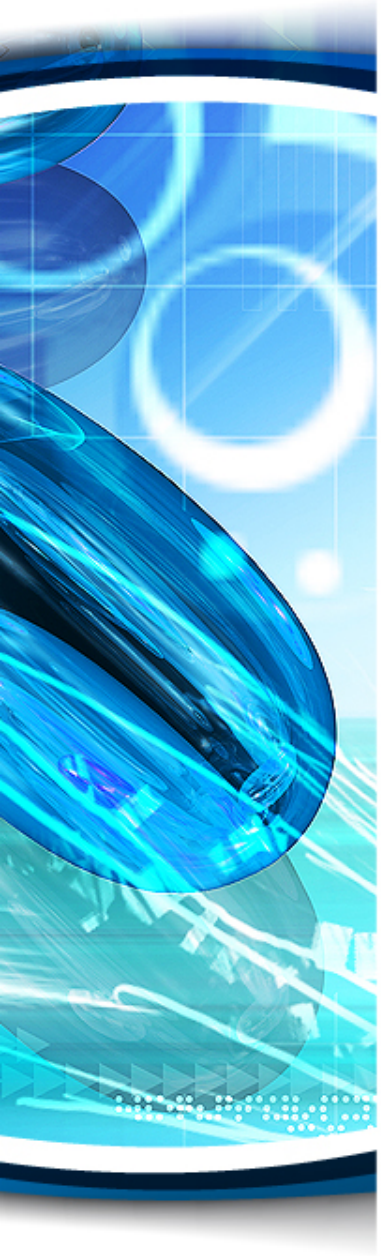
Causes of peripheral precocity

- **Adrenal pathology**:
  - Androgen-secreting tumors
  - Late onset congenital adrenal hyperplasia
  - Boys who have an adrenal cause for their precocity will not have testicular enlargement.

Benign (non-progressive) pubertal variants



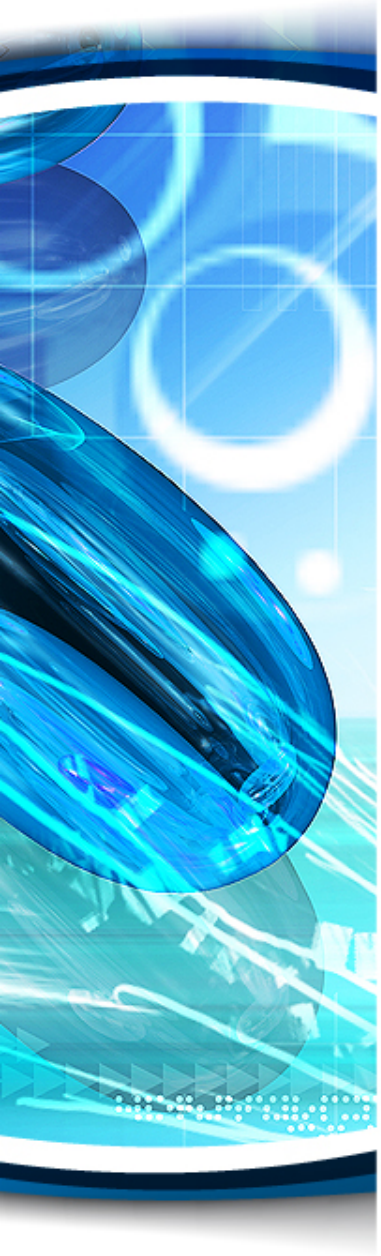
- Non-progressive or intermittently progressive PP
- Premature thelarche
- Premature adrenarche
- Isolated premature menarche
- Not associated w/ full activation of HPG axis but F/U recommended.



Premature thelarche (PT)

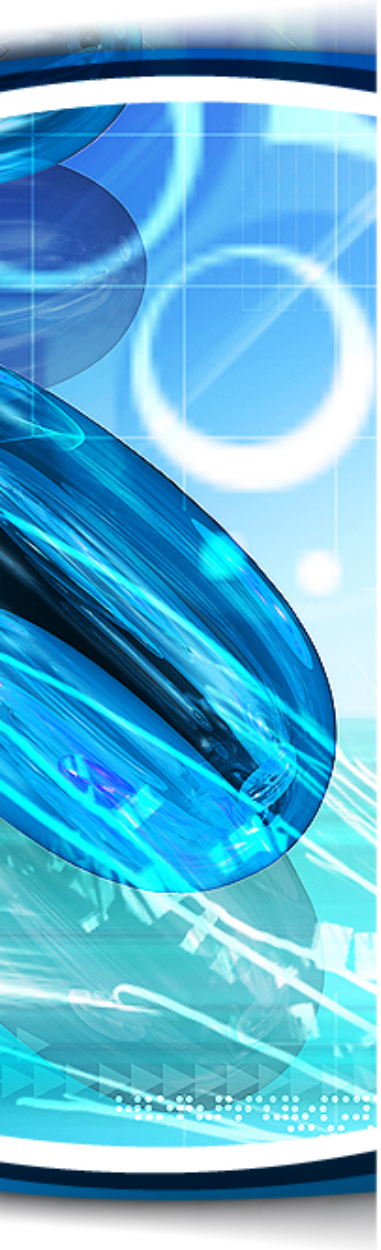
- Most cases are idiopathic & present <2 years of age (may even start at birth).
- Most cases remit spontaneously and do not progress.
- F/U is warranted because PT can represent the initial presentation of true CPP in as many as 10 to 20 % of children referred to pediatric endocrine units.

Premature adrenarche (PA)



- **PA** is characterized by the appearance of pubic &/or axillary hair (pubarche) prior to the age of 8 years in girls & 9 years in boys, in conjunction with a mild elevation in serum DHEAS for age.
- More common in girls, African-American & Hispanic females, & individuals w/ obesity and insulin resistance.

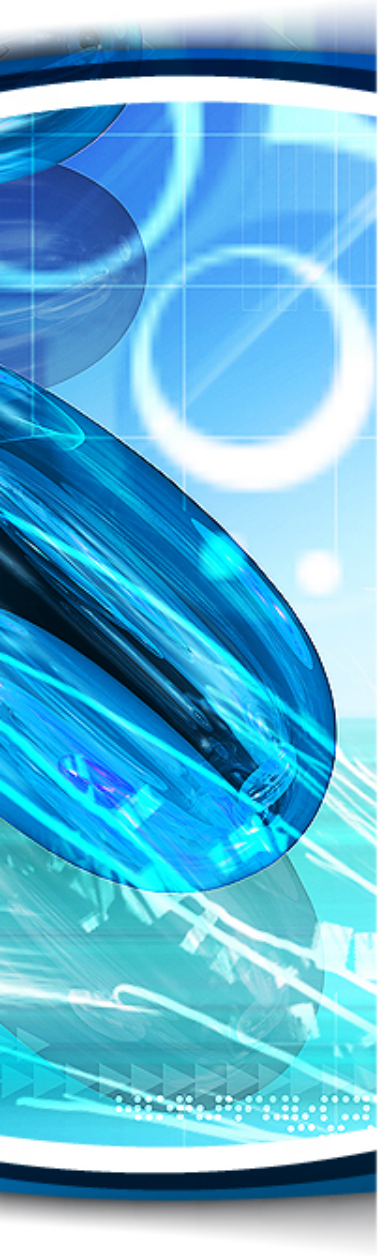
Nonprogressive or intermittently progressive PP



- A subgroup of patients presenting with what clinically appears to be CPP (often with evidence of both gonadarche and pubarche) will either have stabilization or very slow progression in their pubertal signs.

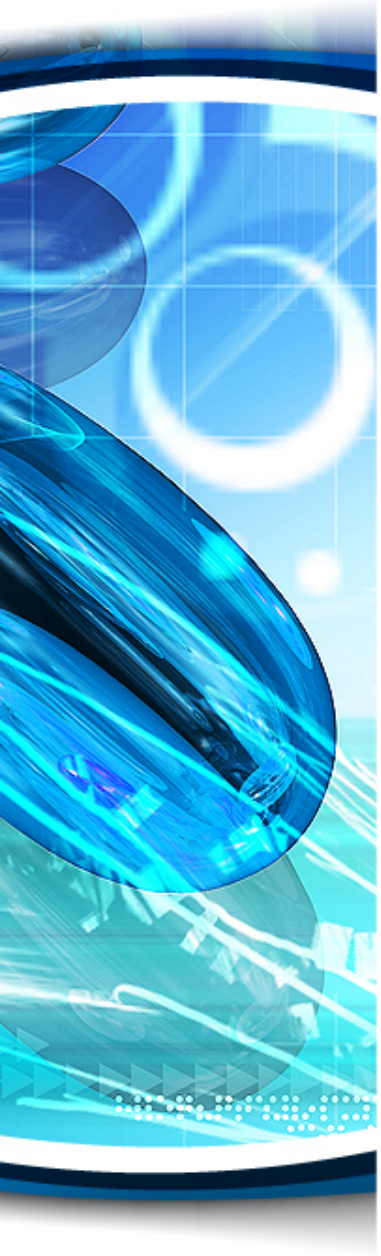
Lazar L, Pertzelan A, Weintrob N, et al. Sexual precocity in boys: accelerated versus slowly progressive puberty gonadotropin-suppressive therapy and final height. J Clin Endocrinol Metab 2001; 86:4127.

Nonprogressive or intermittently progressive PP

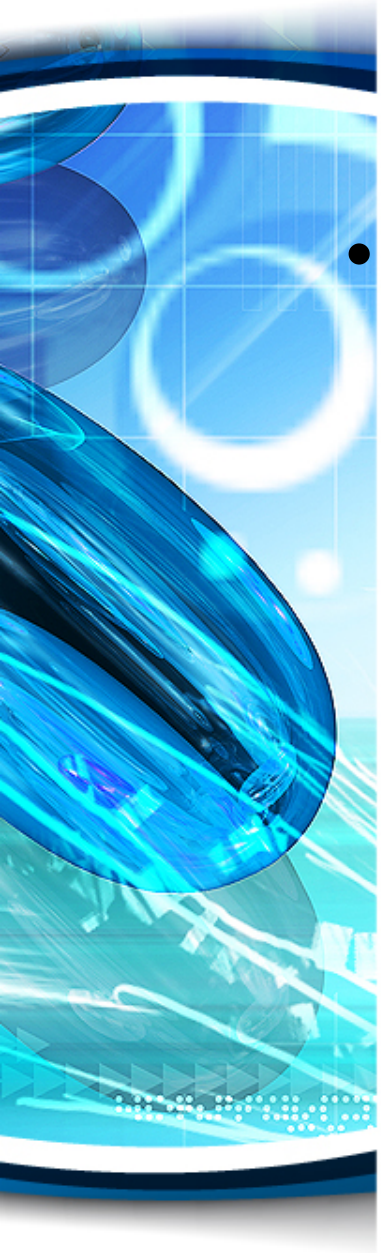


- The bone age is typically not as advanced compared with children with true CPP,
- LH concentrations are within the pre- or early-pubertal range, indicating that the HPG axis is not fully activated
- FSH-predominant response is typically seen if GnRH agonist stim test.

Nonprogressive or intermittently progressive PP



- Monitoring for evidence of pubertal progression is important to distinguish these children from those with true CPP.
- In children with non-progressive PP, treatment with a GnRH agonist is **not** needed.

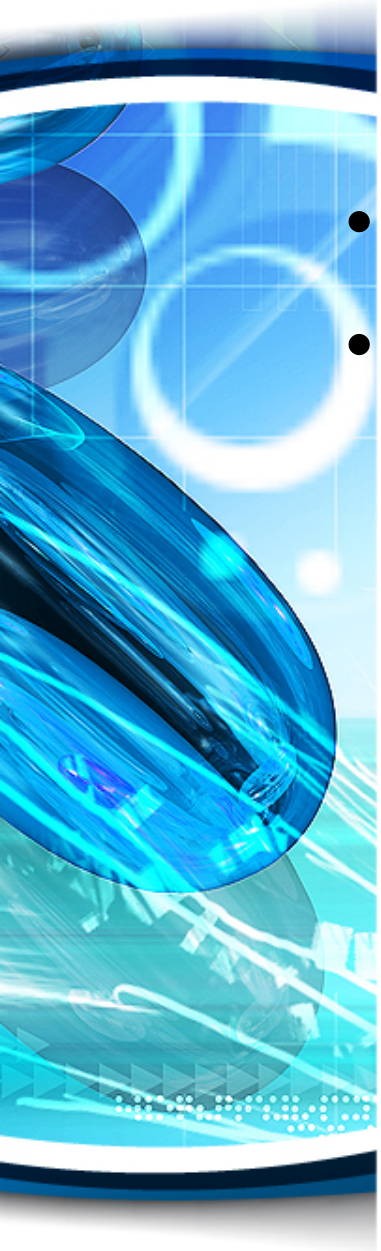


INITIAL EVALUATION PP

- **Initial laboratory evaluation**:
  - basal LH, FSH, and either E_2 and/or testosterone concentrations.
  - The results are used to differentiate between CPP and peripheral precocity, which then guides additional testing.

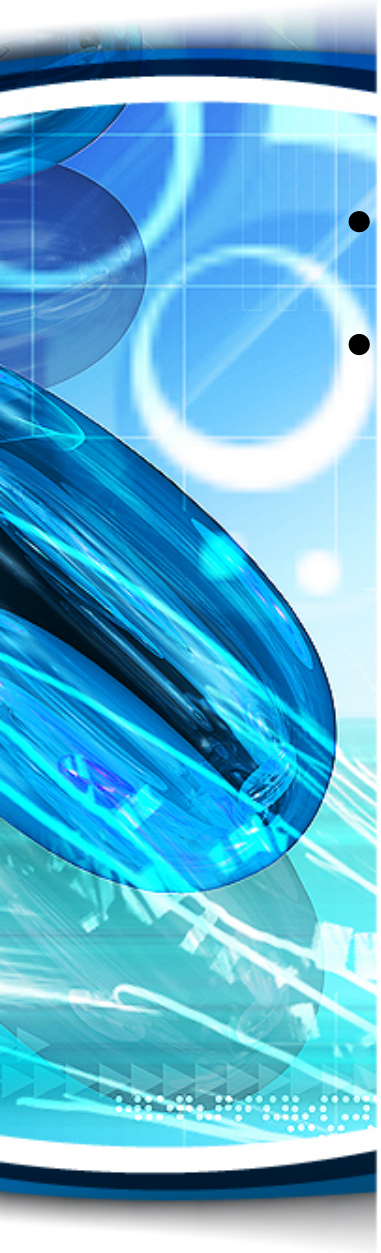
INITIAL EVALUATION PP

- **Initial laboratory evaluation**:
  - LH <0.2 mIU/mL are consistent w/ either peripheral precocity or a benign pubertal variant such as premature thelarche.
  - LH > 0.2 - 0.3 mIU/mL can identify children w/ progressive CPP.



INITIAL EVALUATION PP

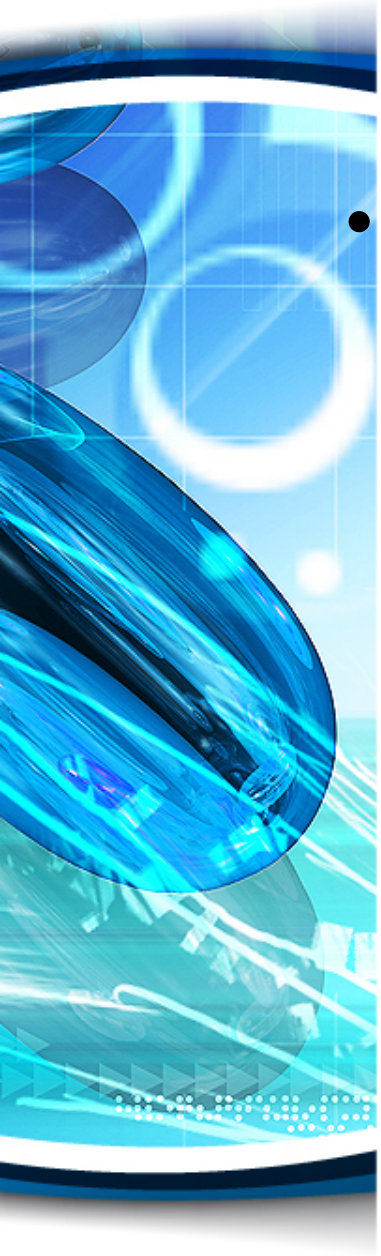
- **Initial laboratory evaluation**:
- **Serum E_2**:
  - Very ↑ concentrations, w/ associated suppression of gonadotropins, are generally indicative of peripheral precocity.
  - Most E_2 immunoassays, have poor ability to discriminate at the lower limits between prepubertal and early pubertal concen-trations.



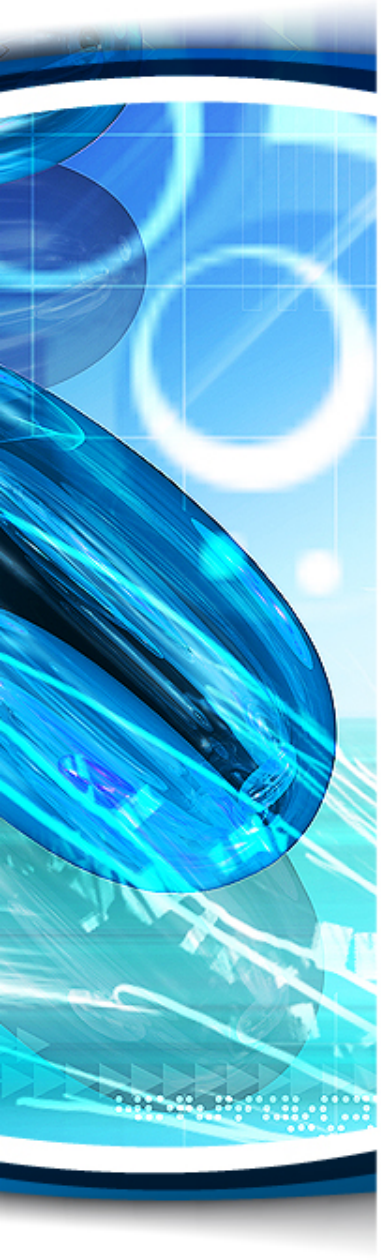
INITIAL EVALUATION PP

- **Initial laboratory evaluation**:
- **Serum testosterone (T):**
  - Elevated **T** concentrations are indicative of testicular production in boys, or of adrenal **T** production or exogenous exposure in both sexes.
  - Very high concentrations, w/ associated suppression of gonadotropins, are generally indicative of peripheral precocity.

GnRH stimulation test



- Peak stimulated LH:
  - Cutoff value of peak stimulated LH for identifying children w/ CPP has not been established.
  - For most LH assays, a value of 3.3 to 5 mIU/mL defines the upper limit of normal for stimulated LH values in prepubertal children.
  - Stimulated LH concentrations > this normal range suggest CPP.



INITIAL EVALUATION PP

- **Pelvic ultrasound (US):**
  - May be a useful adjunct investigation to help differentiate between CPP & benign pubertal variants, especially when the evaluation remains equivocal.
  - Girls w/ CPP have greater uterine & ovarian volumes compared with girls who are prepubertal or those with premature thelarche.

Eksioglu AS, Yilmaz S, Cetinkaya S, et al. Value of pelvic sonography in the diagnosis of various forms of precocious puberty in girls. J Clin Ultrasound 2013; 41:84.

SUMMARY

Who should be evaluated?

- Children w/ 2^{ry} sex characteristics
- <8 girls, < 9 boys
- Concern w/ less age

Is PP central *vs* peripheral?

- CPP recapitulates normal puberty
- Peripheral puberty does <u>not</u>

How fast PP is progressing?

- Rapid growth & bone maturation → CPP
- Normal growth & bone maturation → Benign PP

It's due to E_2 *vs* Androgens?

- Are 2^{ry} sex Sx's virilizing *vs* feminizing?
- Isosexual *vs* contrasexual (no CPP)