Mass General Brigham

An Endocrinologist's Approach to Puberty

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MassGeneral for Children

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Learning Objectives

1. Understand the work-up of early puberty relating to both precocious adrenache and precocious central puberty

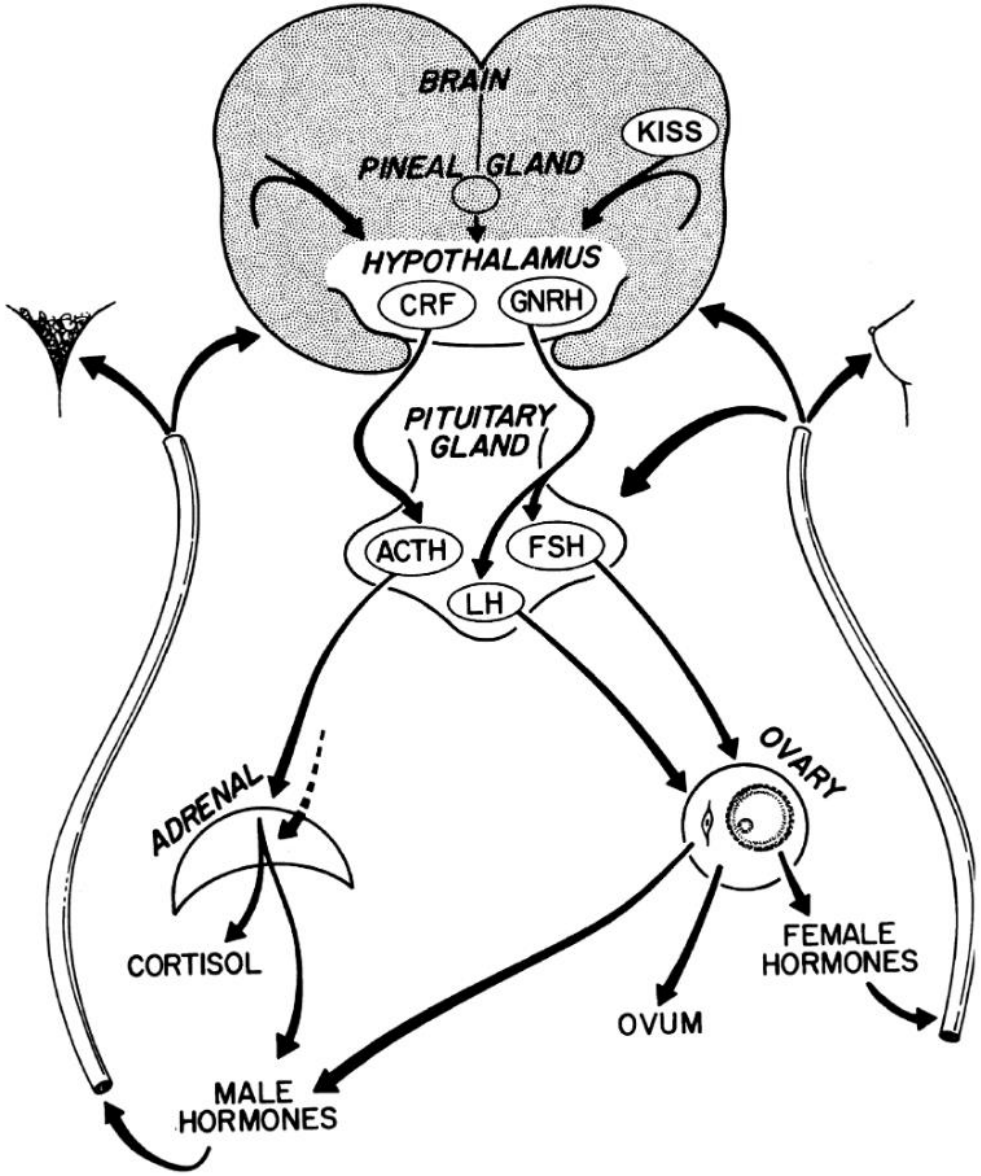
2. Identify considerations when thinking about initiating therapy for central precocious puberty

3. Identify active areas for future research related to pubertal progression

Physiology of Normal Puberty

Sexual Maturation: Puberty and Adrenarche

Figure from 1965



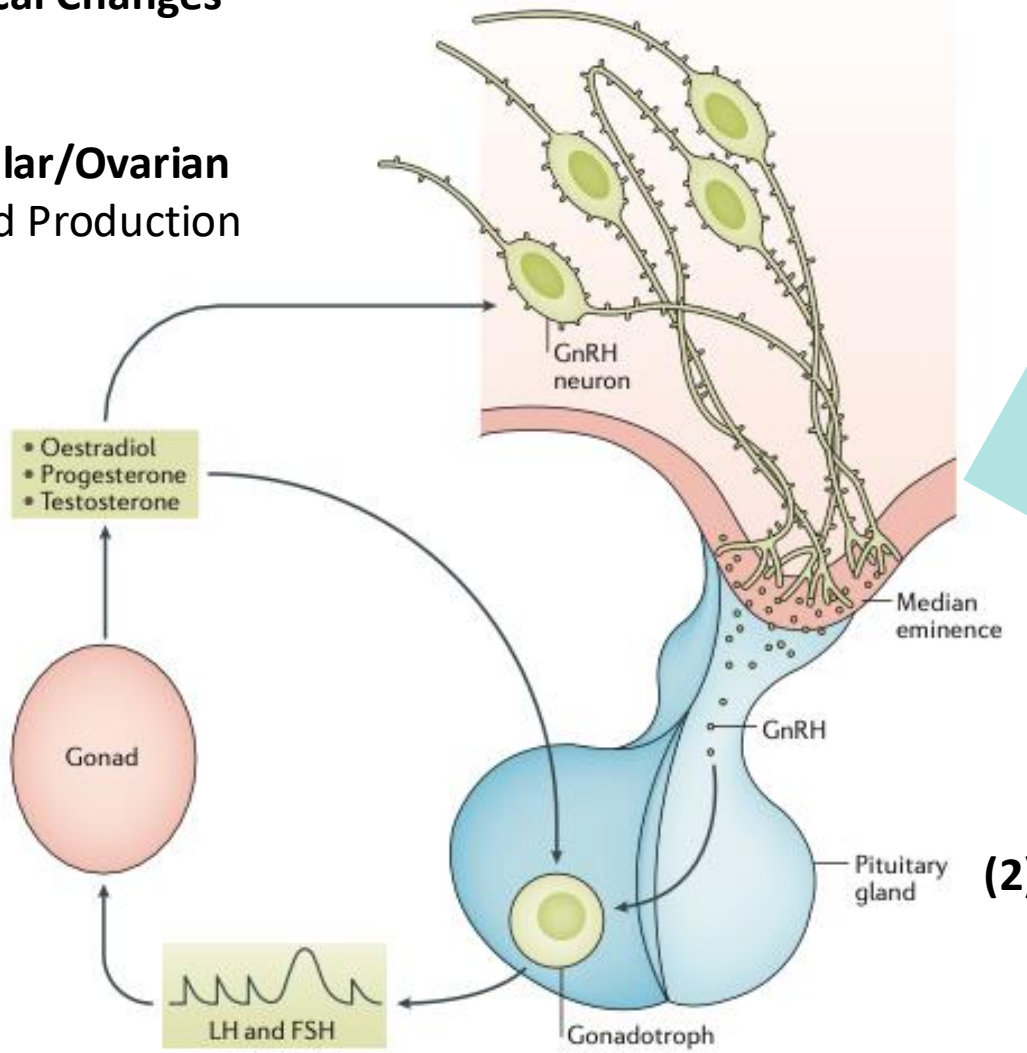
Adrenarche

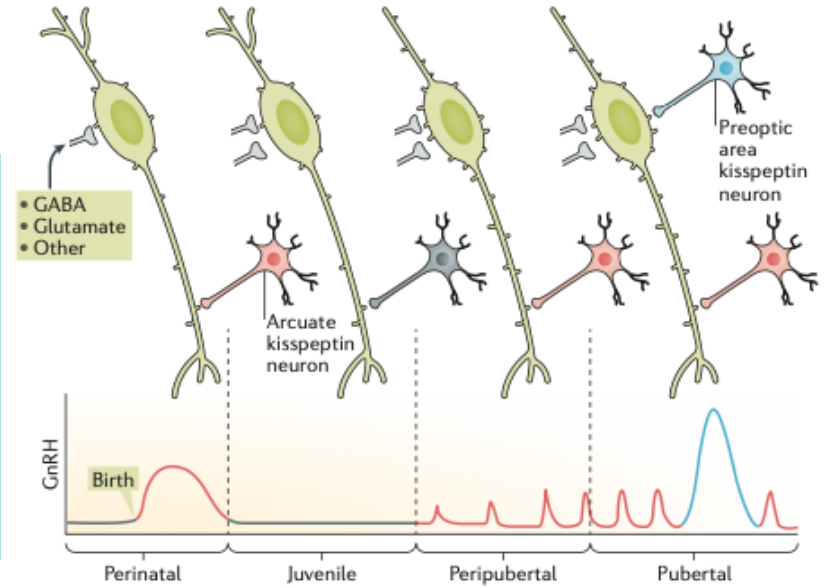
Puberty

Hypothalamic-Pituitary-Gonadal Axis

(4) Physical Changes

(3) Testicular/Ovarian
Sex Steroid Production





(1) Hypothalamic GnRH pulsatility

(2) Pituitary Gonadotropin Production

Herbison, A. Control of puberty onset and fertility by gonadotropin-releasing hormone neurons. *Nat Rev Endocrinol* **12**, 452–466 (2016). https://doi.org/10.1038/nrendo.2016.70

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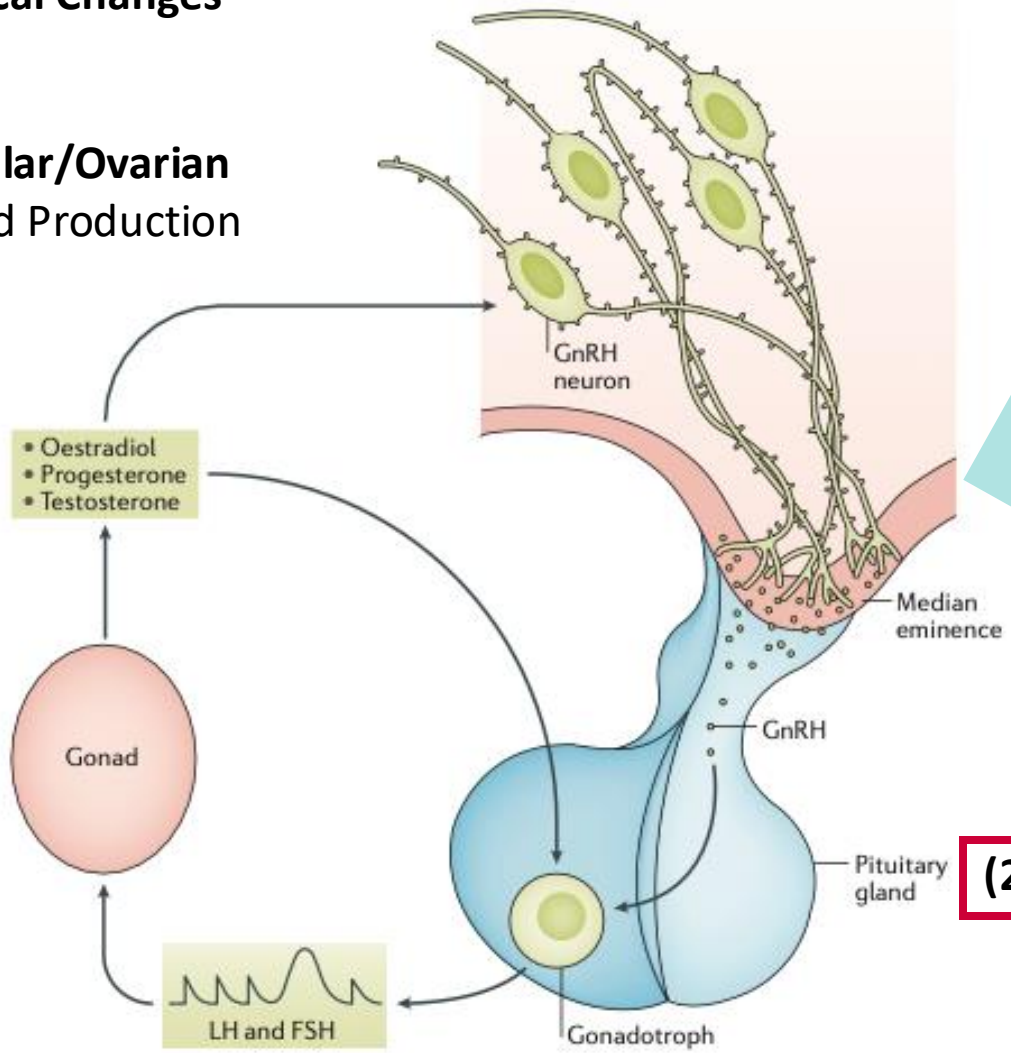

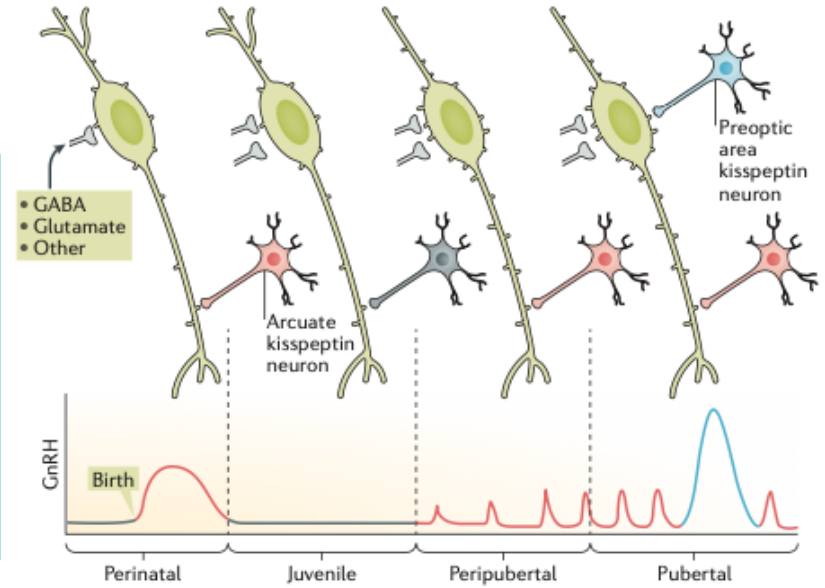

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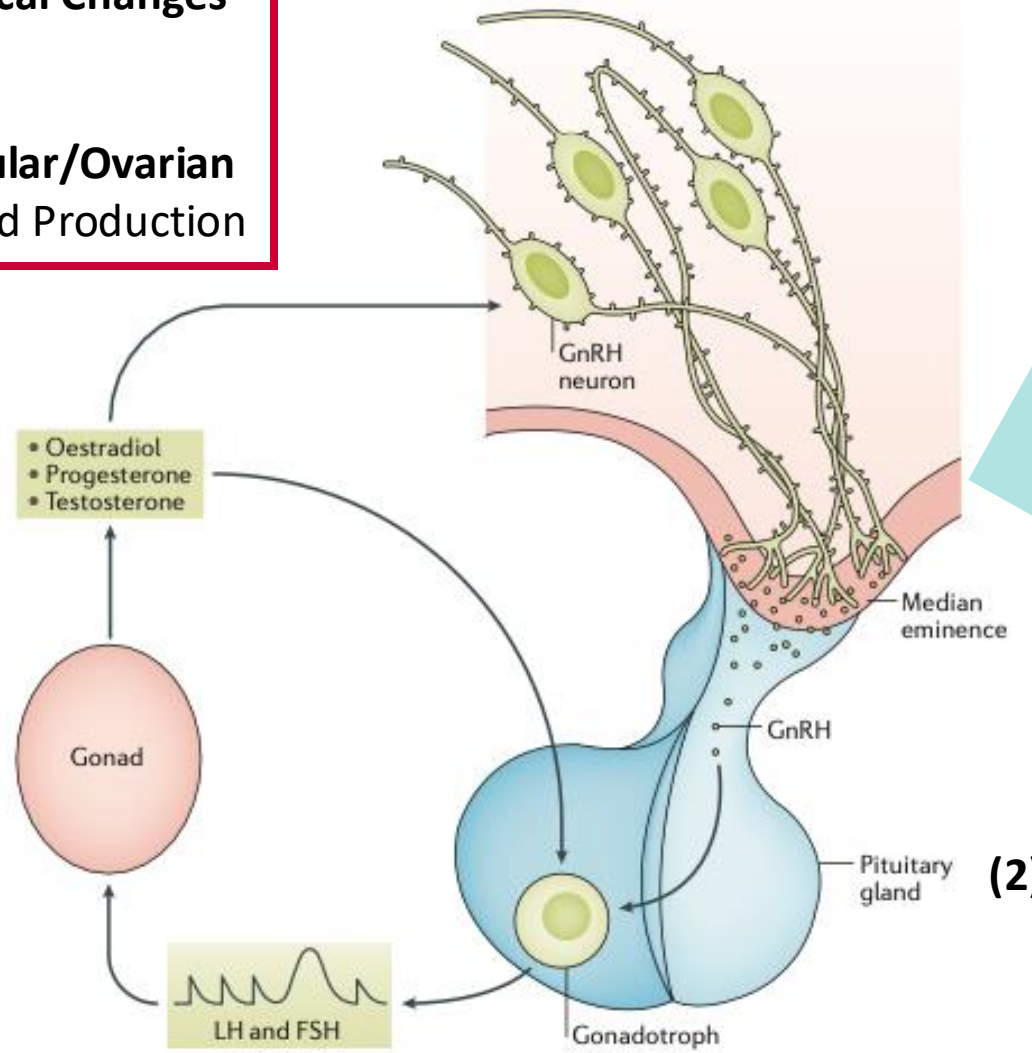

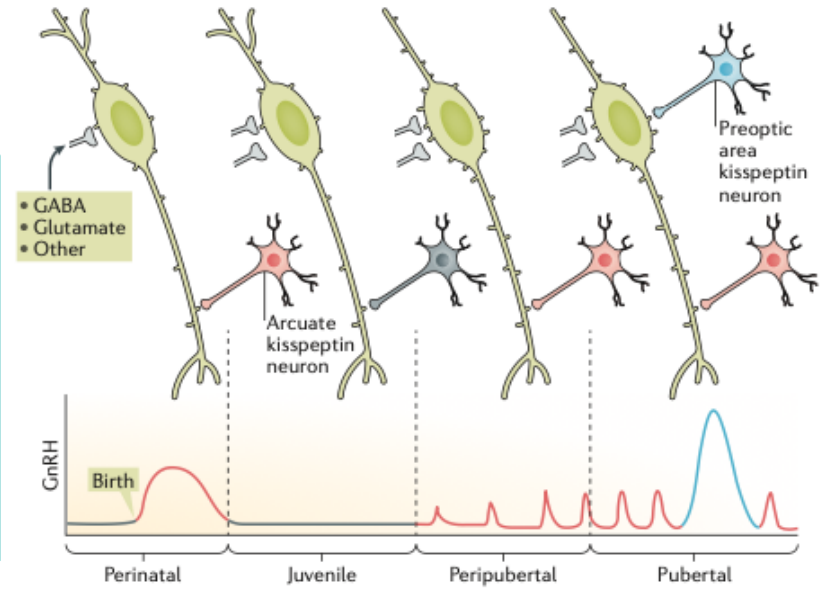

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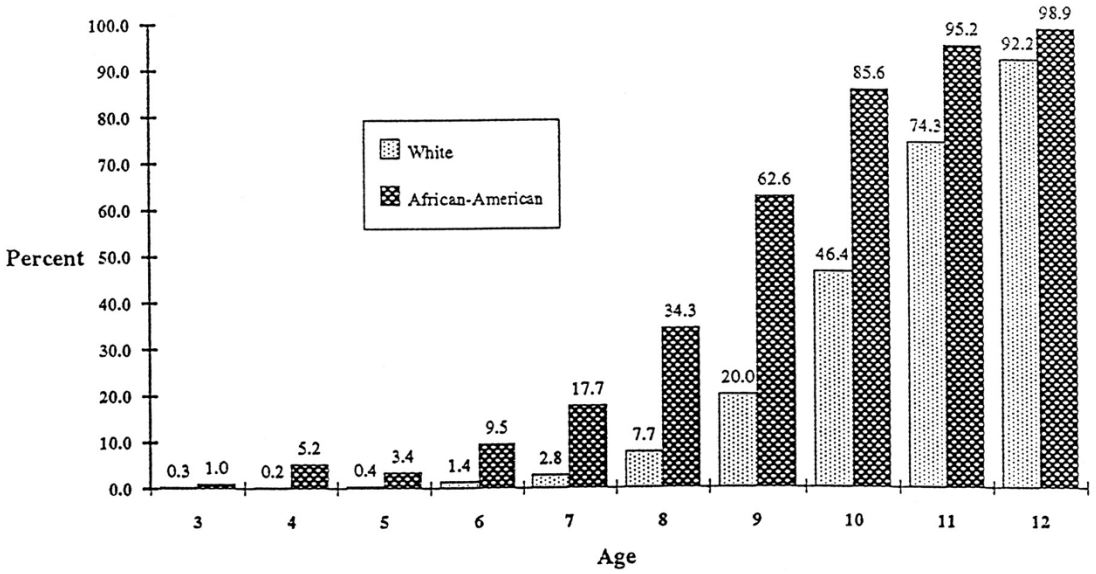
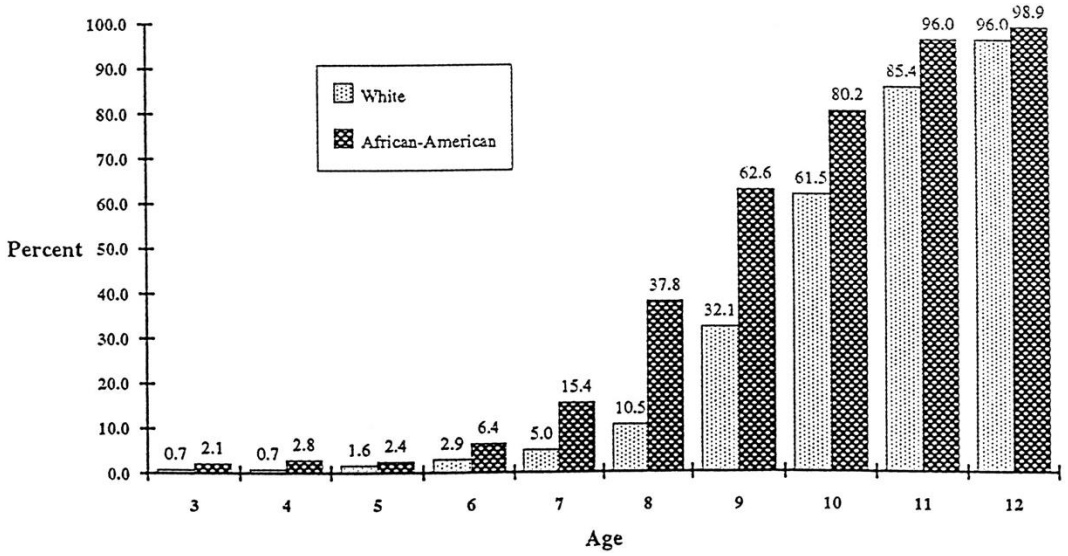
Puberty Timing (Females)

Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network



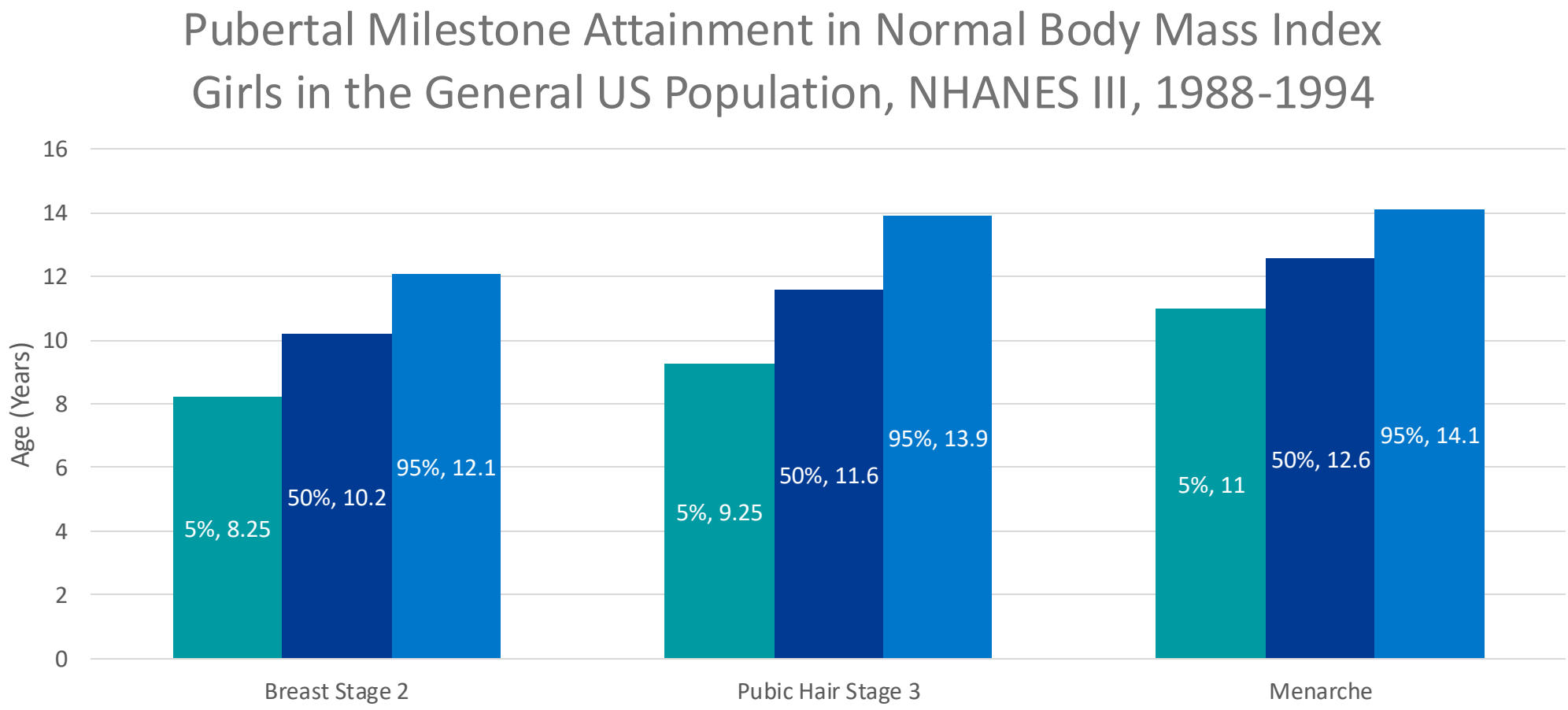
Prevalence of pubic hair development at Tanner stage 2 or greater by age and race



Prevalence of breast development at Tanner stage 2 or greater by age and race

Herman-Giddens ME, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics. 1997 Apr;99(4):505-12.

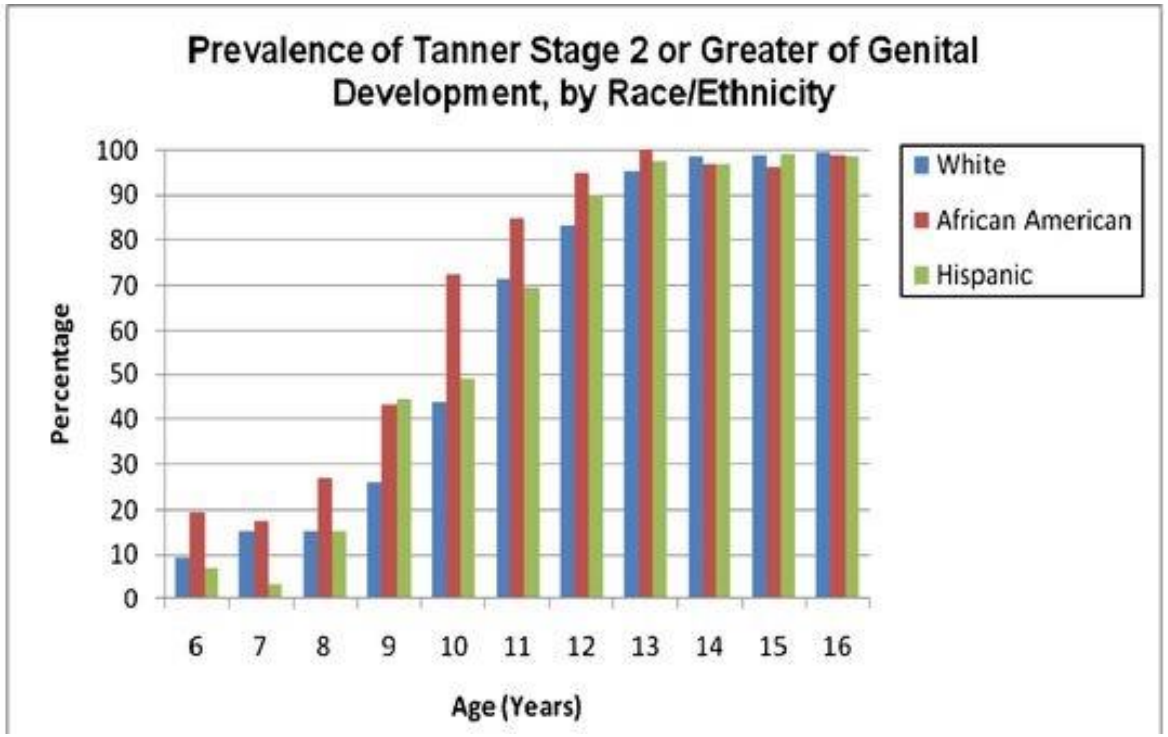
Pubertal Timing (Females)

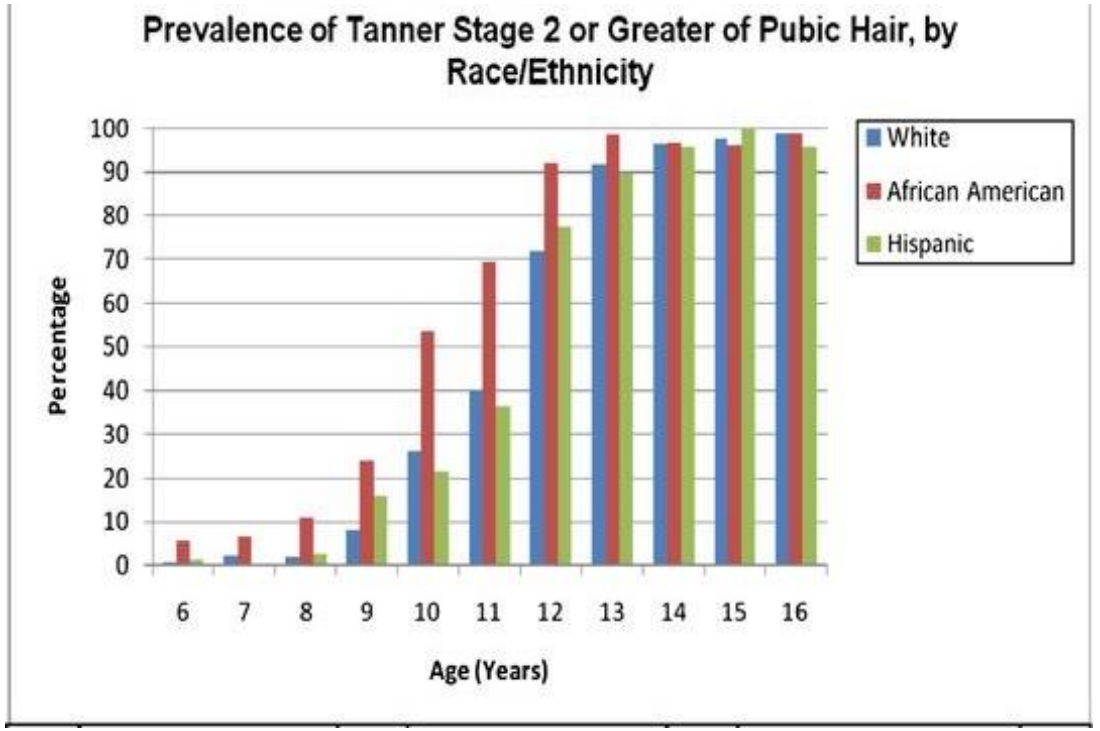


Rosenfield, R.L., Lipton, R.B., Drum, M.L. (2009). Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. *Pediatrics* , 123, 84–88.

Pubertal Timing (Males)

Secondary sexual characteristics in boys: data from the Pediatric Research in Office Settings Network.





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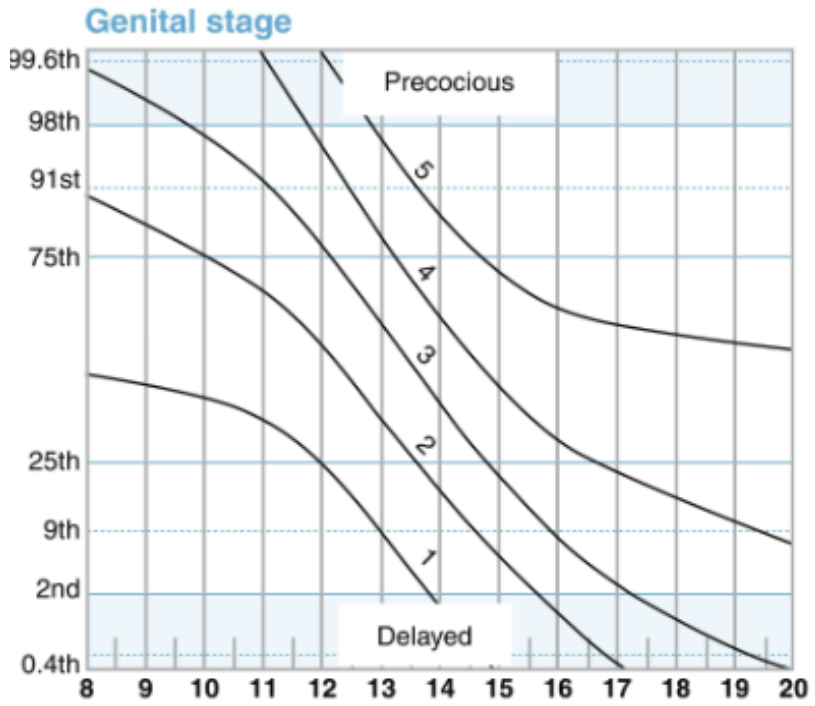
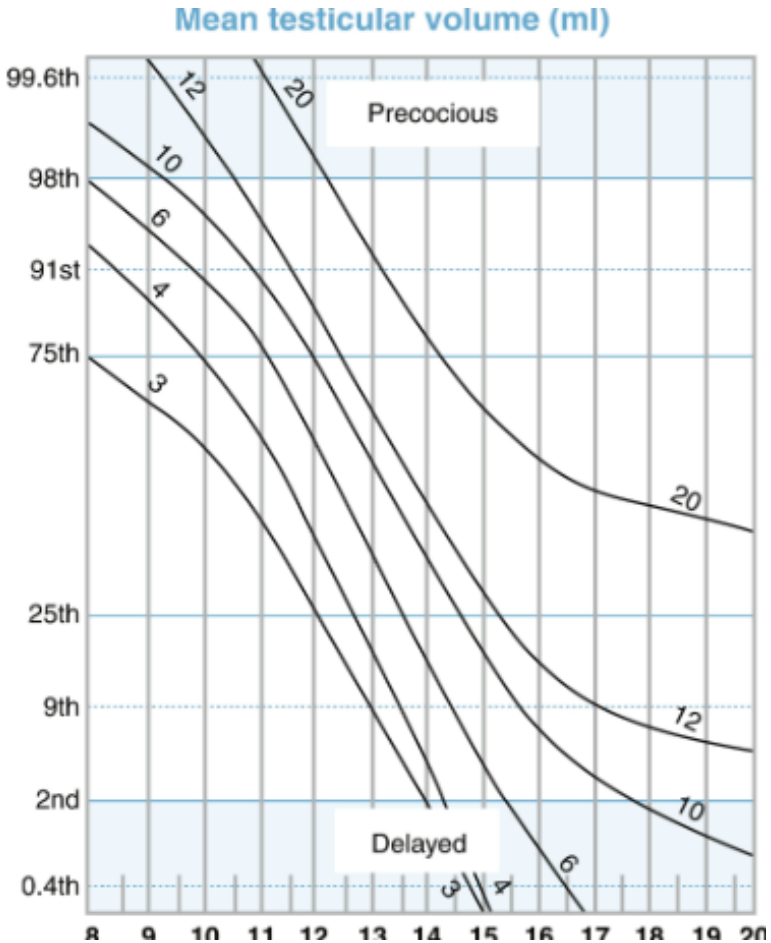
Pubertal Timing (Males)

Range of timing for pubertal development

Variation between genital stage and testicular volume

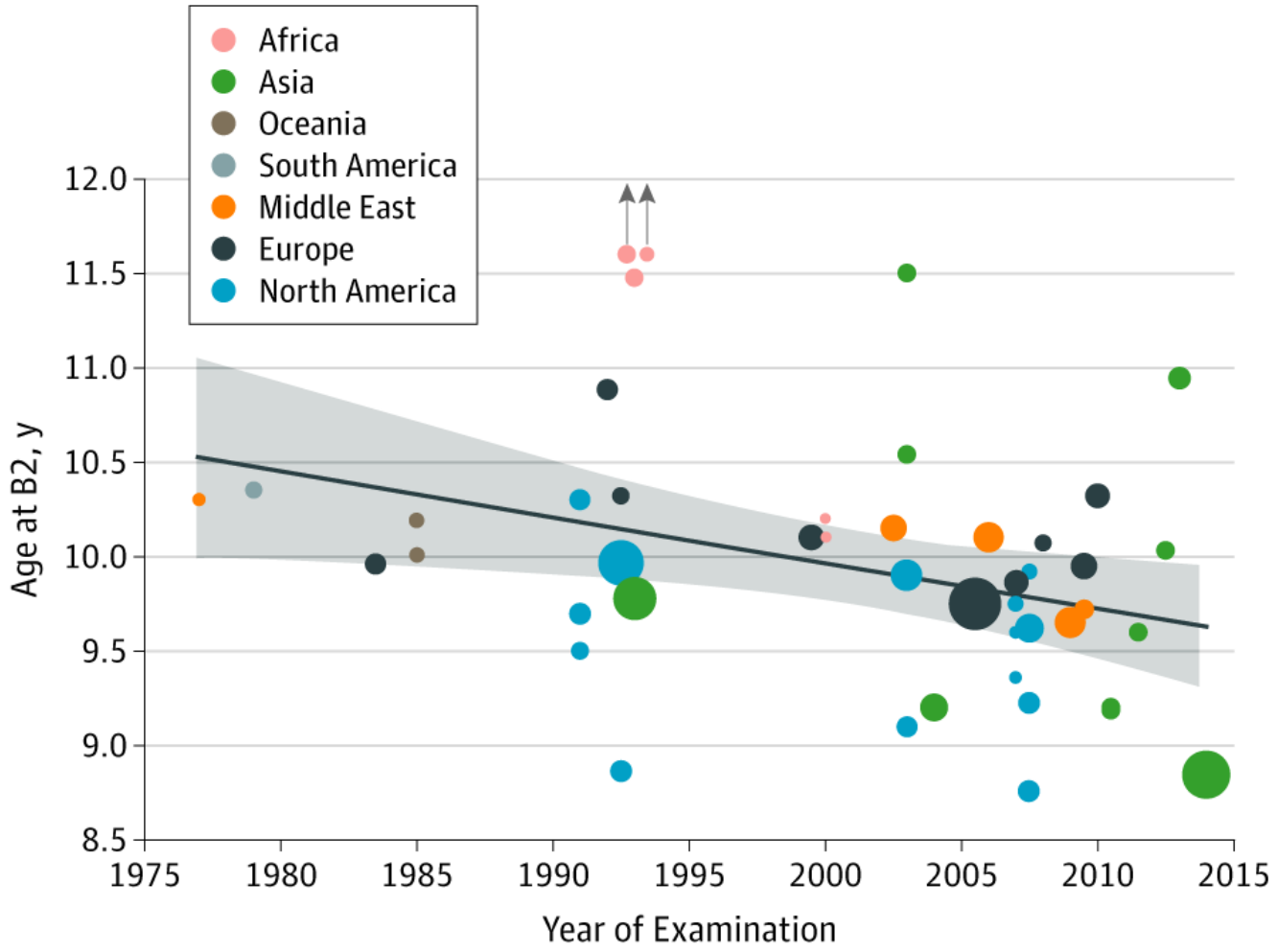




van Buuren, S. (2014). Growth charts of human development. *Stat Methods Med Res* , 23, 346–368.

Trends in Timing of Puberty

Secular Changes in Age at Onset of Tanner Breast Stage 2 From 1977 to 2013 Around the World According to Year of Study



Eckert-Lind C, Busch AS, Petersen JH, et al. Worldwide Secular Trends in Age at Pubertal Onset Assessed by Breast Development Among Girls: A Systematic Review and Meta-analysis. *JAMA Pediatr.* 2020;174(4):e195881.

Pubertal Timing – what is **early (precocious)** puberty?

Premature Puberty	
Boys	Girls
Before age of **9**	Before age of **8**
Less often Idiopathic	Most often Idiopathic *(>90% in central precocious puberty)*
Greater Chance Pathologic	Lesser Chance Pathologic

Case 1

Case 1
HPI

6 year 2 month old female

- Has always had appearance of “breasts”, more prominent in past year
- Pubic hair began to appear about 1 year ago
- Significant weight gain during COVID

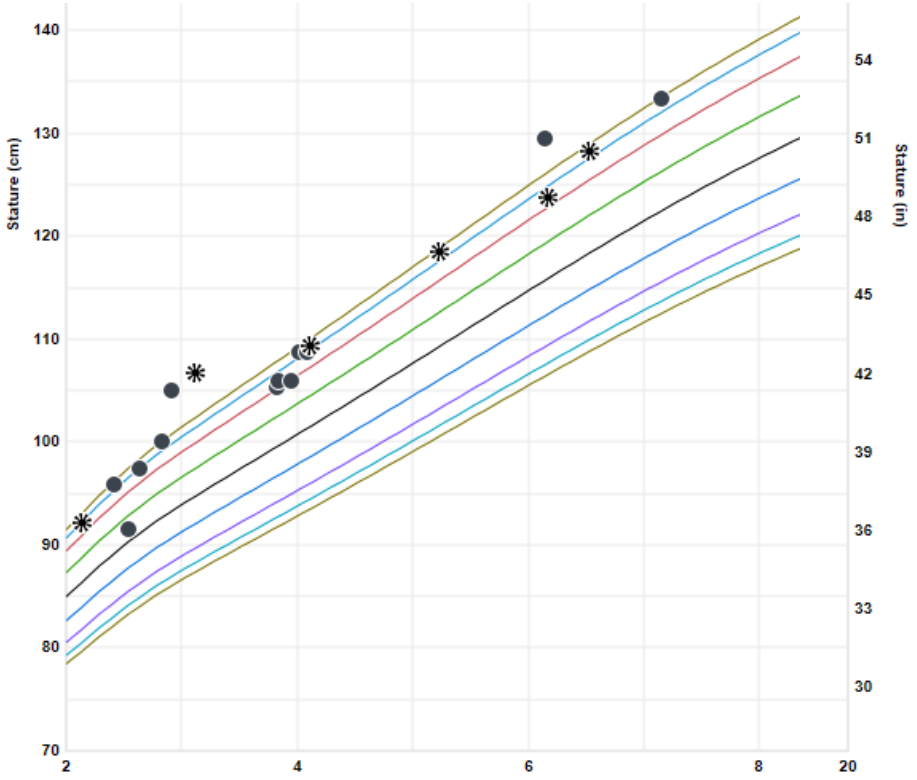
No medications

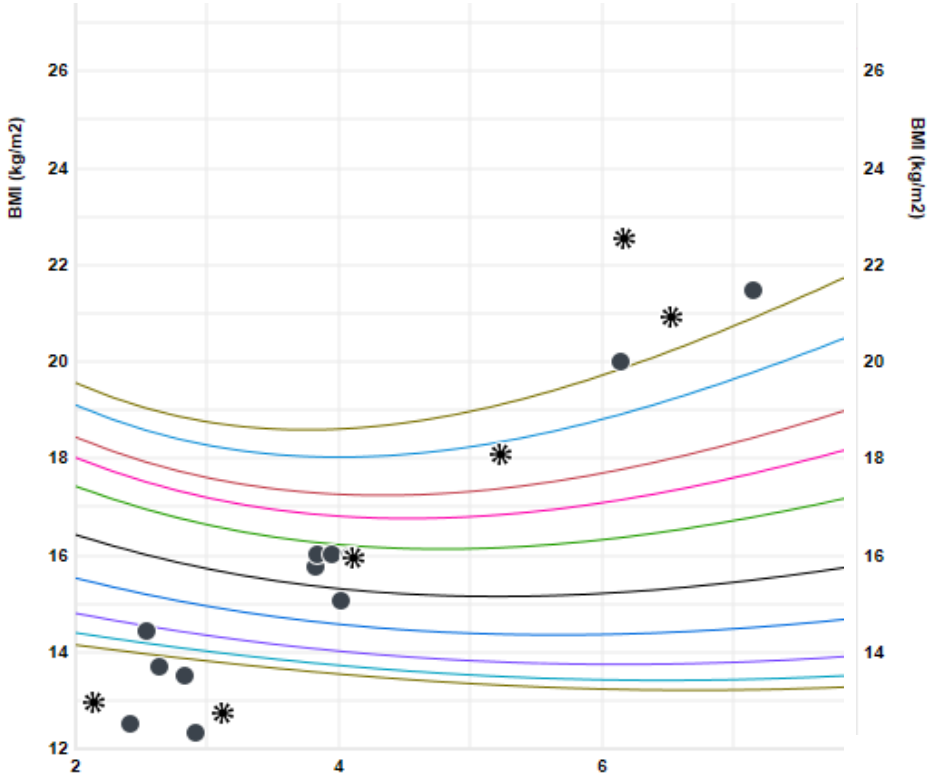
Family History:

- Maternal Height 66”, Paternal Height 68”;
- No early puberty
- Mother age 16 at menarche

Case 1
Exam and Growth Data

Lipomastia/adipomastia but **no breast tissue**
Tanner 2 pubic hair, no axillary hair, no clitoromegaly





Case 1
Differential Diagnosis

Most likely: Premature Adrenarche

- Most likely benign/idopathic

Other *potential* diagnoses:

- Non-classic congenital adrenal hyperplasia
- **Worst Case Scenarios**
  - Cushing's Disease
  - Androgen secreting tumor

Red Flag Signs:

Fast progression
Significant acne
Virilization
Hirsutism

Case 1
Additional Work-Up and Evaluation

Lack of Red-Flag Symptoms

- Clinical monitoring, return in ~6 months to evaluate for pubertal advancement
- Could also consider bone age at this time

Increased Clinical Concern

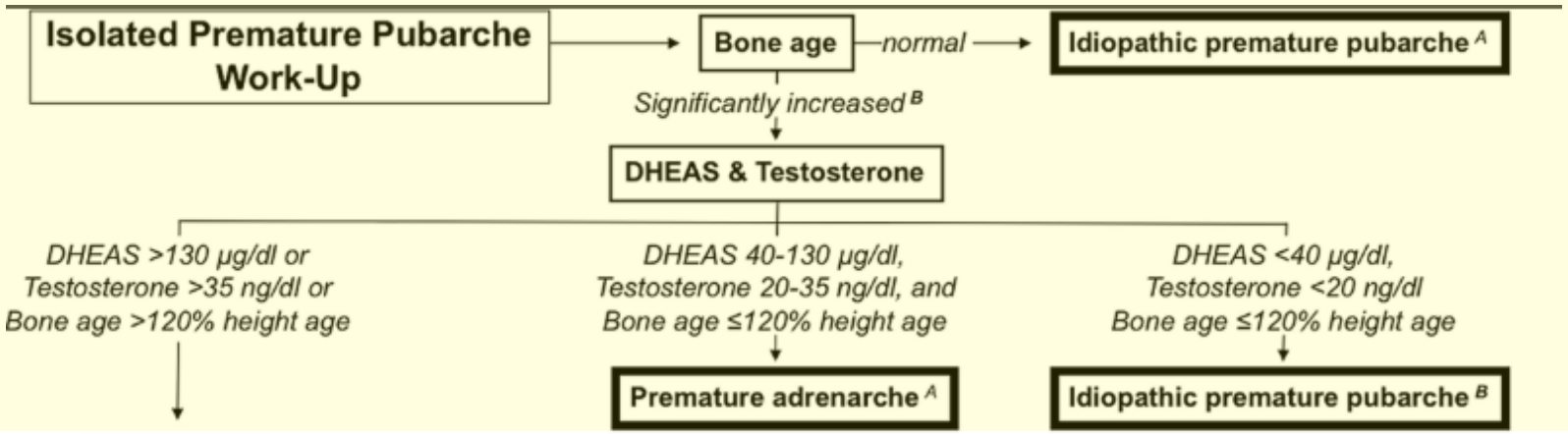
Assessment of adrenal hormones

- DHEA-S, Testosterone, 17-Hydroxyprogesterone (17OHP)*
  - **Best obtained before 9AM*
- *No need to obtain FSH, LH, Estradiol given lack of breast development*

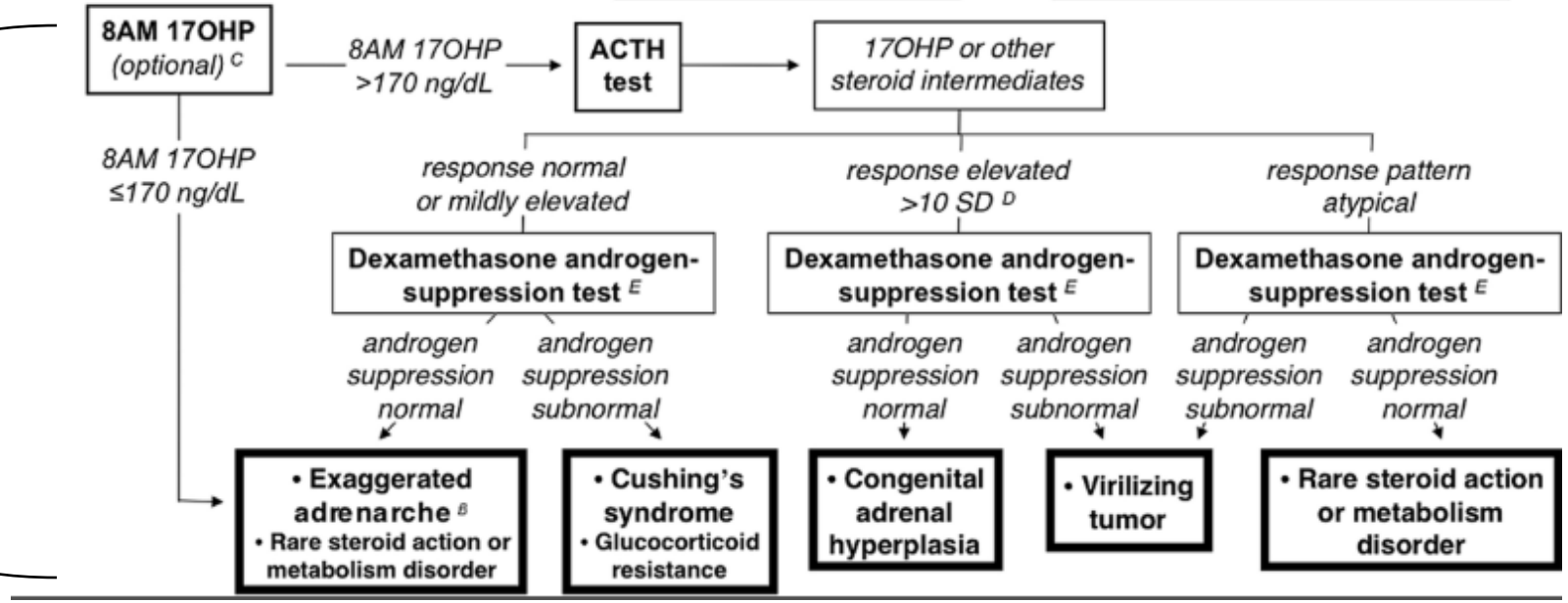
Premature Adrenarche: Algorithm

DHEA-S
Testosterone
Bone Age
+/- 17OHP

Primary Care



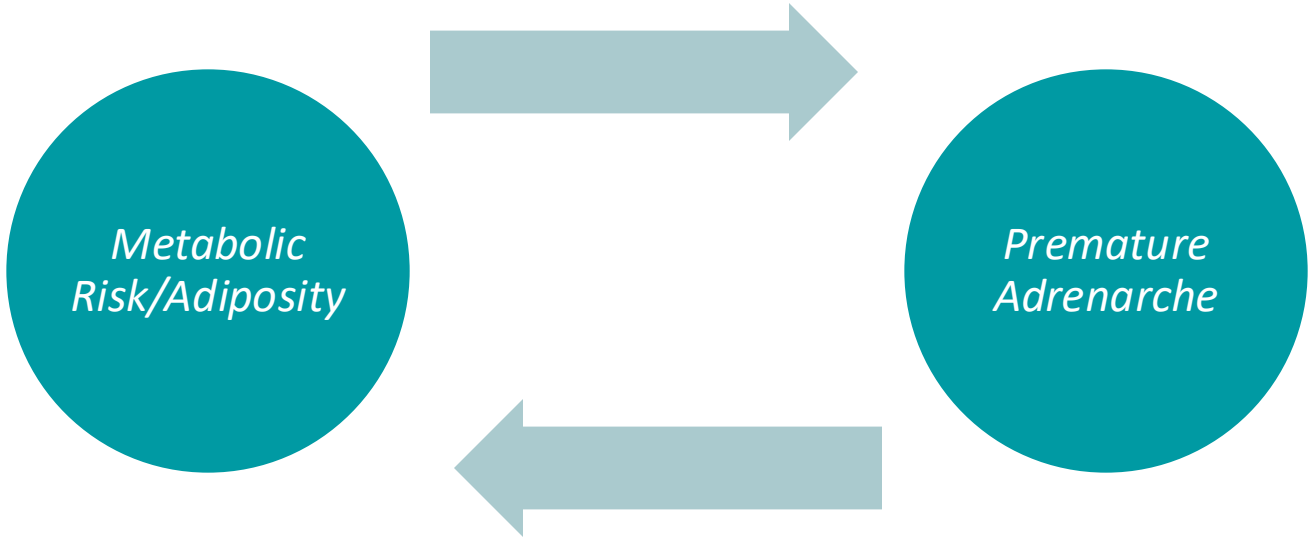
Sub-specialty Evaluation



Sperling Textbook of Pediatric Endocrinology: 5th Edition (2021)

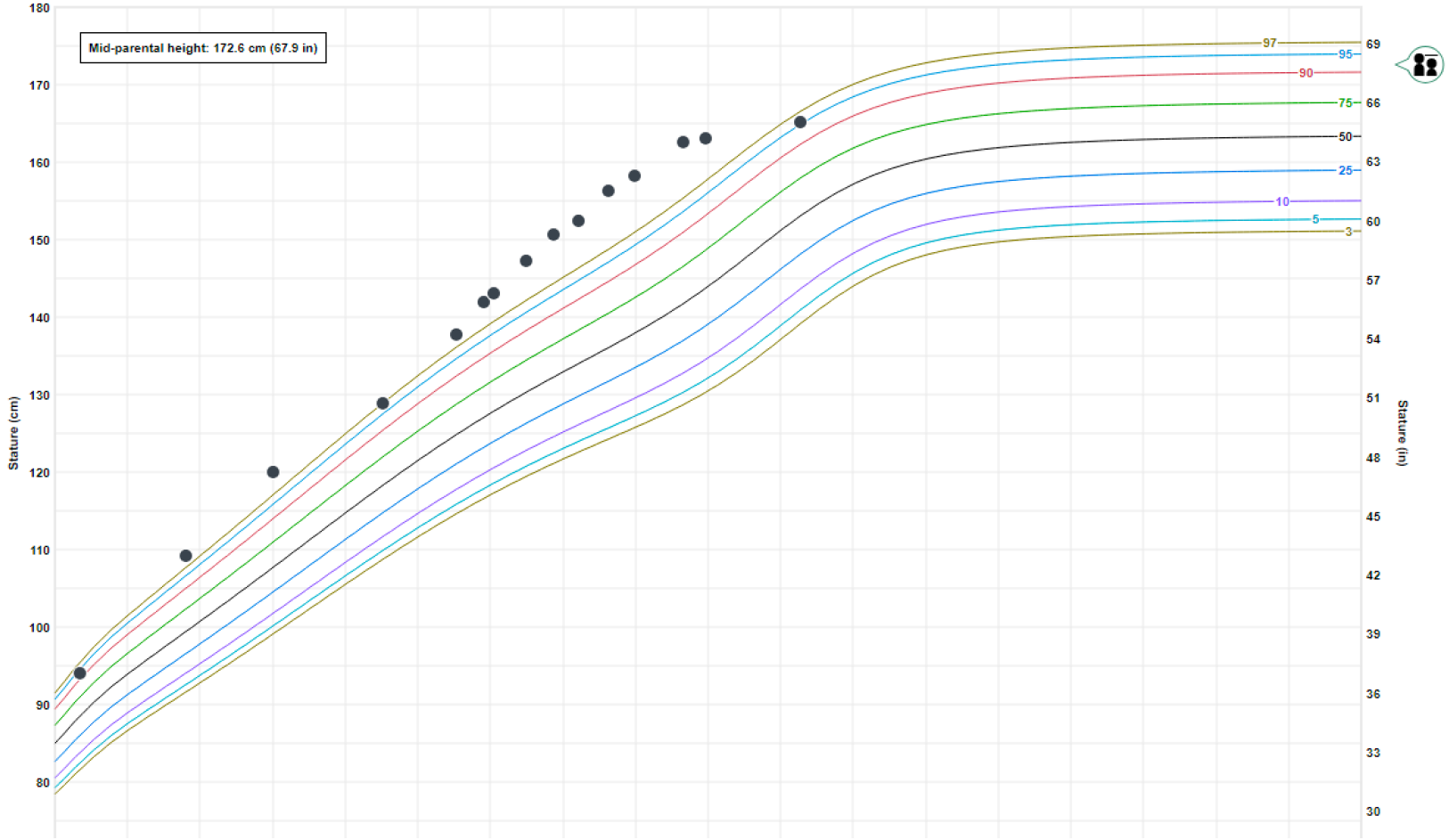
Premature Adrenarche
Clinical Pearls

- Importance of recognizing impact of bone age advancement on height potential
  - *Growing at top of growth chart –or– lower mid-parental height = less significant*
  - *Example next slide*
- Lack of effective therapy for isolated idiopathic adrenarche
  - Most important thing is ruling out any other concerning conditions
- Connection between earlier adrenarche with later cardiometabolic risk
  - *Bidirectional!*



Premature Adrenarche Clinical Pearls

Growth chart with earlier acceleration but ultimate height within mid-parental range



Premature Adrenarche
Summary of Approach

Premature Adrenarche:
Obtain Bone Age or follow-up in clinic in 6 months

Bone Age <u>normal</u>
- *Follow-up in 6 month*
  - *Ensure no rapid progression*
- *Counsel regarding metabolic risk*

Bone Age <u>advanced</u>
- *Adrenal labs*
  - *17-OHP*
  - *DHEA-S*
  - *Testosterone*
- *± endo consult*

Case 2

Case 2
HPI and Exam

6 year 11 month old female with breast development 2 months ago

No meds
PMH: asthma
Fam Hx:

- Mother menarche age 9; maternal aunt menarche age 9
- Mother hypothyroidism
- Mom 63 inches, Dad 71 inches

Exam

- Normal vital signs, Ht 56th %, BMI 80th %; no clear acceleration in growth velocity
- **T2 breast tissue b/l**
- Fine thin hair on mons, T1 pubic hair, no axillary hair

Case 2
Differential Diagnosis

First Step: Central versus Peripheral

	Central	Peripheral
	COMMON	*LESS COMMON*
LH and FSH	Pubertal	**Suppressed**
Estradiol or Testosterone	Pubertal	Pubertal
Differential Diagnosis	***Worst Case: sellar tumor*** **Most likely: idiopathic** Hypothalamic hamartoma h/o CNS radiation Other CNS (cysts, hydrocephalus, etc.) Known genetic causes (KISS1, MKRN3) CAH (because of androgen exposure)	***Worst case: Tumor making estrogen or testosterone*** **Most likely: exogenous** McCune Albright Ovarian cyst LH receptor activating mutation

Case 2
Additional Work-Up and Evaluation

Lack of Red-Flag Symptoms

- Follow-up in clinic in 3 months
  - Can assess tempo of pubertal progression
- *Consider laboratory evaluation*

Red Flag Signs:
Fast progression
Signs of increased intracranial pressure

Increased Clinical Concern

- *Family preference if treating puberty might be a consideration*
- Evaluate **gonadotropins** and **end gonadal hormone** (ideally in AM)
  - LH
  - FSH
  - Estradiol **OR** Testosterone

Note: without any signs of adrenarche– no need to send adrenal hormones

Case 2
Lab Results

8am Labs:
LH 0.17 U/L
FSH 4.91 U/L
High sensitivity estradiol 12 pg/mL
TSH 3.14 uU/mL, Free T4 1.1 ng/dL

Interpretation:

LH is prepubertal; FSH is a little higher than usual

- *Most likely* is central precocious puberty (gonadotropins are not suppressed as would be in peripheral precocity) – but not diagnostic

Options: observation x 6 months versus leuprolide stimulation test

Case 2
Lab Results

Pubertal: AM > 0.3

Later in the day: any presence

8am Labs:

LH 0.17 U/L

FSH 4.91 U/L

High sensitivity estradiol 12 pg/mL

TSH 3.14 uU/mL, Free T4 1.1 ng/dL

Alternative Example: 3 pm labs

LH 1.2

FSH 5.1

Estradiol 15

= Consistent with Central Puberty

Interpretation:

LH is prepubertal; FSH is a little higher than usual

- *Most likely* is central precocious puberty (gonadotropins are not suppressed as would be in peripheral precocity) – but not diagnostic

Options: observation x 6 months versus leuprolide stimulation test

Case 2
Leuprolide Stimulation Test

Leuprolide stimulation test

- Leuprolide 500mcg SC x 1
- Measure LH at 0, 60, 120, 180)

Principle: if the gonadotrophs in the pituitary have already "seen" GnRH, they will secrete more LH in response to leuprolide than if puberty has not yet begun. (Usual LH cutoff ~5 U/L)

Time (min)	LH (U/L)	FSH (U/L)
0	<0.1	2.2
60	7.8	
120	8.4	
180	9.5	30.1

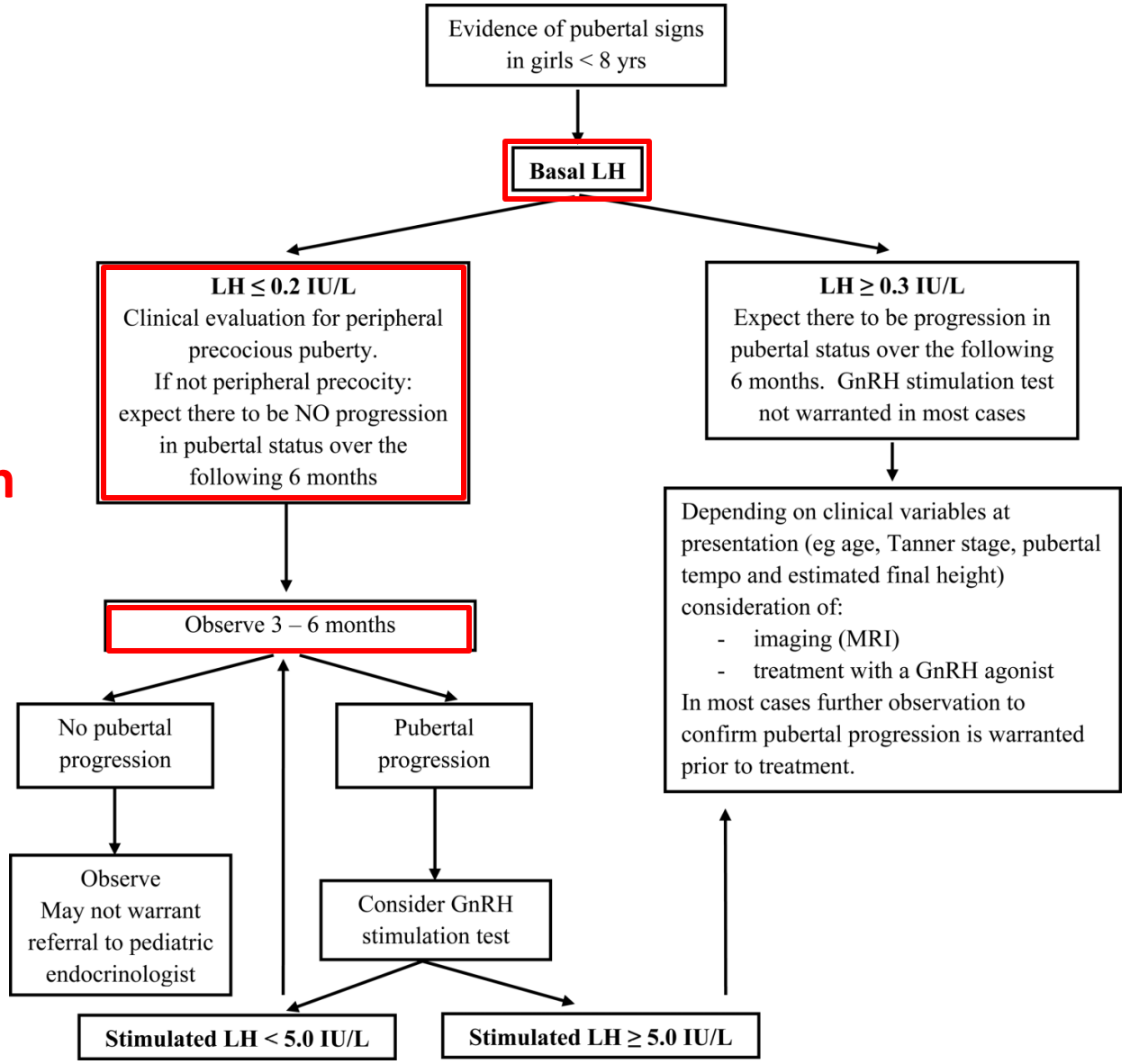
Pubertal: LH > 5

Case 2
Diagnosis = Central Precocious Puberty

Brain MRI normal

Parents chose supprelin (vs. Lupron vs. no treatment)

Algorithm for Precocious Puberty Evaluation



Observation would have been fine!

Harrington J, et al. Arch Dis Child 2014;99:15–20.

Case 2
Diagnosis: Central Precocious Puberty

Brain MRI normal

Parents chose supprelin (vs. Lupron vs. no treatment)

Treatment Options

Extended-Release Preparations of GnRH Analogs Available in the United States

Generic Name	Brand Name (Manufacturer)	Route of Administration	Available Doses (mg)	Duration of Action
3-Monthly leuprolide	Lupron Depot-PED 3 mo (AbbVie, Chicago, IL)	IM	11.25, 30	3 mo
6-Monthly triptorelin	Triptodur (Arbor Pharmaceuticals, Atlanta, GA)	IM	22.5	6 mo
Histrelin implant	Supprelin LA (Endo Pharmaceuticals, Malvern, PA)	Subcutaneous implant	50	≥2 y

Eugster EA. Treatment of Central Precocious Puberty. J Endocr Soc. 2019 Mar 28;3(5):965-972. doi: 10.1210/js.2019-00036. PMID: 31041427; PMCID: PMC6486823.

Case 3

Case 3
HPI

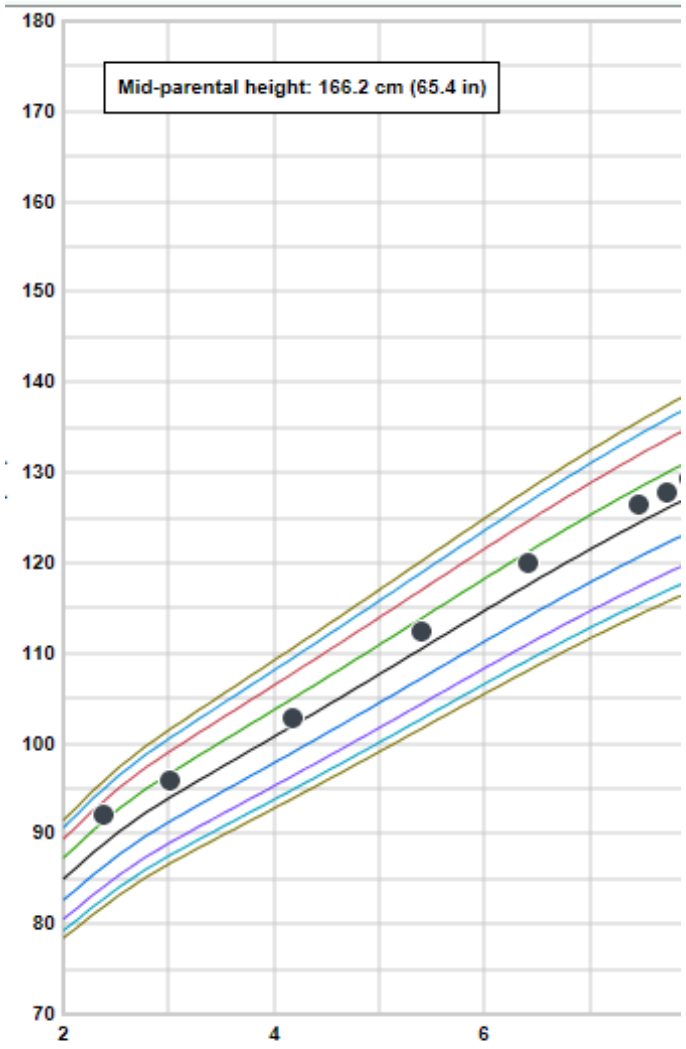
7 8/12 year old female presenting for evaluation of premature thelarche

- *First noted by her mother while bathing her several months ago*
- *Not associated with headaches, vision changes, vomiting*
- *Denies signs of adrenarche, including pubic hair, acne, body odor*
- *No family history of early puberty*
- *Otherwise healthy, no medications*
  – “Lavender bubble bath” as toddler

Case 3
Exam

Physical exam

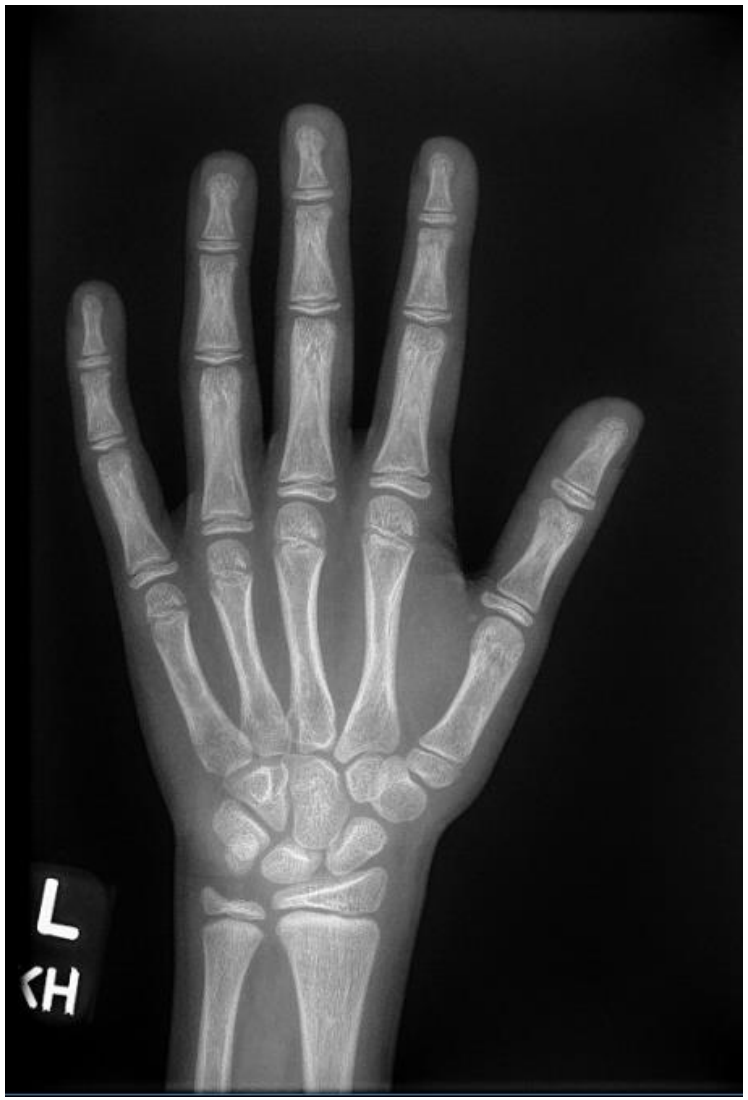
- Height 127.9 cm (62nd %ile), Weight 26.1 kg (61st %ile)
  – *BMI 16 kg/m2 (56th %ile)*
- Notable for Tanner II Breast Development
- Otherwise unremarkable



Case 3
Evaluation

FSH	5.4 IU/L	
LH (unstimulated)	**5.6 IU/L**	**Prepubertal <5.0**
Estradiol	<5 pg/mL	
DHEA-S	70 mcg/dL	

<u>Bone Age</u>
Advancement to 10 years (Chronologic Age 7 8/12 years)
Current height gives predicted adult height of 5'1" +/- 2.5"
➔*Slightly below mid-parental height of 5'5" +/- 2.5"*

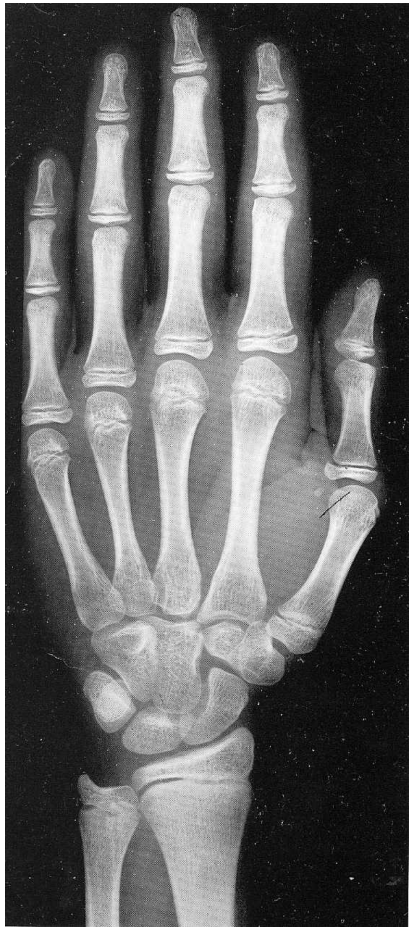


Case 3
Next Steps

Parental preference for **observation**

Follow-up in 5 months:

- Growth velocity of 3.7 cm over 5 months
- Progression to Tanner III breast tissue
- Bone age advancement to 11 years at chronologic age 8 2/12 years
    - *Height prediction decreased to 59” +/- 3”*



Who to treat for central precocious puberty?

Who to treat for Central Precocious Puberty?

	Progressive	Slowly progressive
Clinical		
Pubertal Stage	Progression to next stage <6 months	Stabilization or regression
Growth velocity	Accelerated (>6cm/year)	Normal
Bone age	Variable to Advanced	Variable
Height Prognosis	Below target height or declining	Within target height range
Biological		
LH Peak	Pubertal	Prepubertal

Carel JC et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009 Apr;123(4):e752-62.

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Parental Concerns about Precocious Puberty

Consequences of early menses?

Treatment side effects

Weight concerns

Growth

Consequences of developing earlier than peers?

Is this the right treatment for my daughter?
Or should we do nothing….

Pediatrics, 2009
Consensus Statement on the Use of GnRH Analogs in Children

Recognition that GnRH analogues have revolutionized treatment of precocious puberty **BUT** questions exist regarding optimal use

Consensus meeting of 30 participants throughout the US, Canada, and Europe

- Working groups with assigned topics and specific questions
- Review of literature with focus on long term outcomes
- Conclusions based on majority vote


SPECIAL ARTICLE

Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children

Jean-Claude Carel, MD, PhD[a], Erica A. Eugster, MD[b], Alan Rogol, MD, PhD[b,c], Lucia Ghizzoni, MD[d], Mark R. Palmert, MD, PhD[e,f], , on behalf of the members of the ESPE-LWPES GnRH Analogs Consensus Conference Group

Carel JC et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009 Apr;123(4):e752-62.

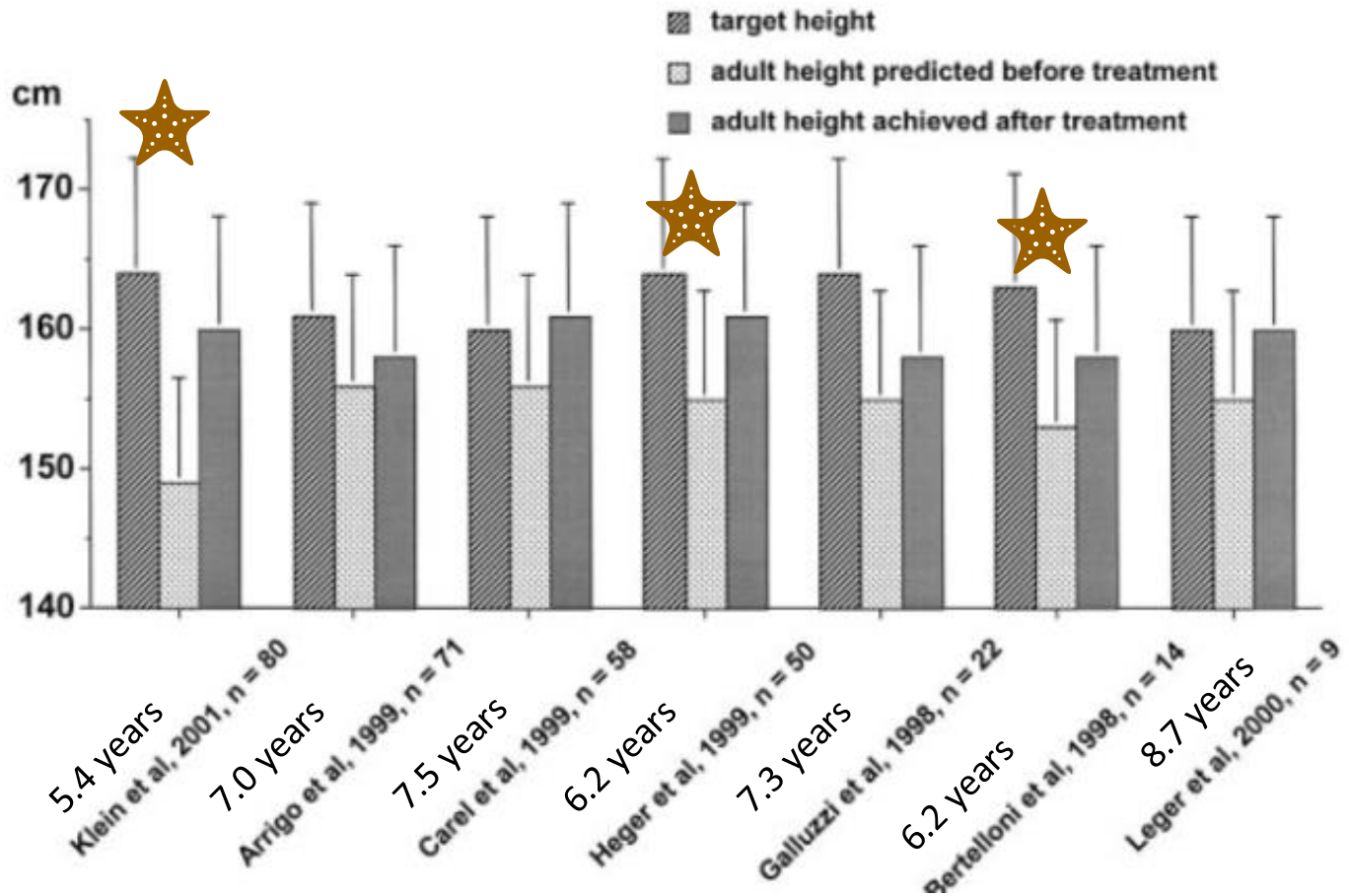
Pediatrics, 2009
Consensus Statement on the Use of GnRH Analogs in Children

Conclusions:

- **Undisputed efficacy** in increasing adult height in early onset central precocious puberty (girls < 6 years old)
- **Did not support** common concerns regarding effects on **bone** or **BMI**
- **Did not support** "off-label" use
- **Lack of evidence** regarding **psychosocial outcomes** of CPP, with or without treatment
- Overall **lack of prospective evidence**
  - *Many conclusions based on **expert opinion***

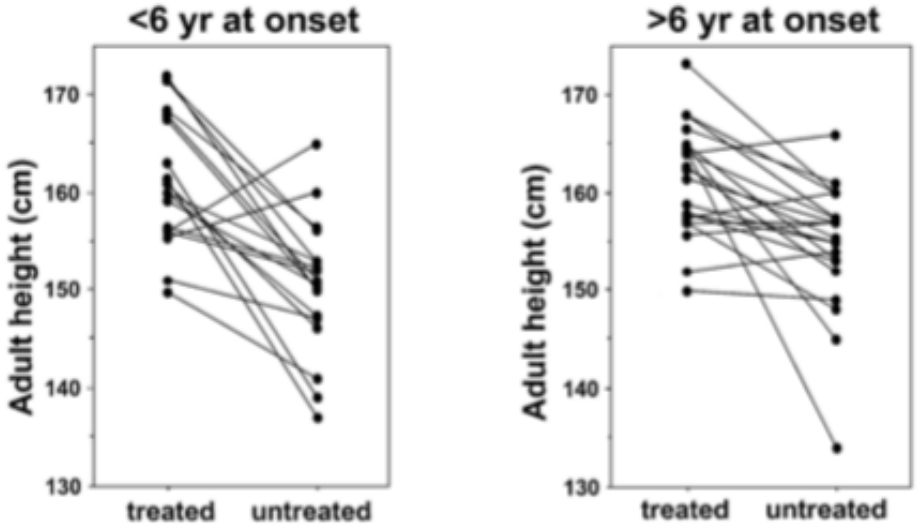
Treatment with GnRH Agonist
Impact on Height

Adult height in girls treated with GnRH agonists for precocious puberty: results of selected studies.



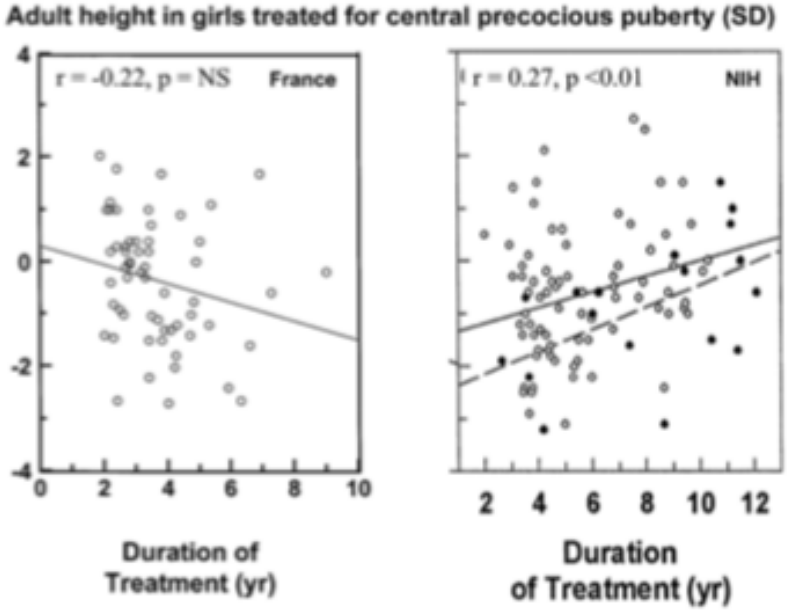
Carel, JC et al.. Precocious puberty and statural growth. Human Reproduction Update, Vol.10, No.2 pp. 135-147, 2004

Treatment with GnRH Agonist
Impact on Height



Greater increase in height if treated <6 years old

Uncertain relationship between duration of treatment and gain in adult height



Carel, JC et al.. Precocious puberty and statural growth. Human Reproduction Update, Vol.10, No.2 pp. 135-147, 2004

Treatment with GnRH Agonist
Other Questions

Bone health	"Young adults treated with GnRHas for CPP in childhood ultimately accrue BMD within the normal range for age"
BMI and Metabolic Syndrome	*"Above-average BMI is frequent at diagnosis of CPP. Long-term GnRHa treatment does not seem to cause or aggravate obesity, as judged from BMI.* ***Studies of body composition and fat distribution are needed."***
Long term fertility	*"The available data suggest that gonadal function is not impaired in girls treated with GnRHas (BII). Nevertheless, available data are limited.* ***Long-term data on fecundity and ovarian reserve of treated patients with CPP are needed."***
PCOS	*"Follow-up of treated or untreated girls with CPP into the midteenage years suggests that the development of PCOS or polycystic ovary morphology is not clearly different from that in the general population.* ***Longitudinal data through adolescence are needed."***
Emotional function	*"Little evidence to show whether CPP leads to psychological or behavioral problems or whether treatment with GnRHas are associated with improved psychological outcome. Thus, no recommendations related to psychosocial outcomes are possible.* ***Controlled studies with standardized instruments are needed."***

Carel JC et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009 Apr;123(4):e752-62.

Treatment with GnRH Agonist
Longterm Outcomes

Overall Health / Reproductive Outcomes ***(Lazar et al., 2014)***	**Metabolic Health** ***(Lazar et al., 2015)***
Single center, cross-sectional historical cohort study (1975-2005)	Case-control study of historical cohort (1984-2005)
214 women with CPP, ages 25-56 153 treated, 61 untreated, 446 age-matched controls	142 CPP women ages 27-50 (100 treated, 42 untreated) 413 age-matched controls
No difference in marital status, education, or number of children between groups *Reassuring for social-emotional impact of precocious puberty* Higher rates of clinical hyperandrogenism among **all** with CPP compared to controls *Underlying neuroendocrine dysfunction, regardless of treatment* Spontaneous pregnancy rates similar between <u>treated</u> CPP and controls Higher rates of needing fertility assistance with <u>untreated</u> CPP *Potential protective effect of treatment?*	Menses: Younger age in untreated BMI percentile: • Higher at <u>diagnosis</u> in treated, similar in late adolescence • BMI in 3rd-5th decades is similar to general population No increased rates of metabolic disease or malignancy Despite increase risk of early childhood obesity and precocious puberty: • BMI findings <u>are not</u> attributable to GnRHa treatment • High weight status at time of starting treatment does represent risk for future obesity

Lazar L, Padoa A, Phillip M. Growth pattern and final height after cessation of gonadotropin-suppressive therapy in girls with central sexual precocity. *J Clin Endocrinol Metab* 2007; **92:** 3483–89.Lazar L, Meyerovitch J, de Vries L, Phillip M, Lebenthal Y. Treated and untreated women with idiopathic precocious puberty: **long-term follow-up and reproductive outcome between the third and fifth decades**. *Clin Endocrinol (Oxf)* 2014; **80:** 570–76.

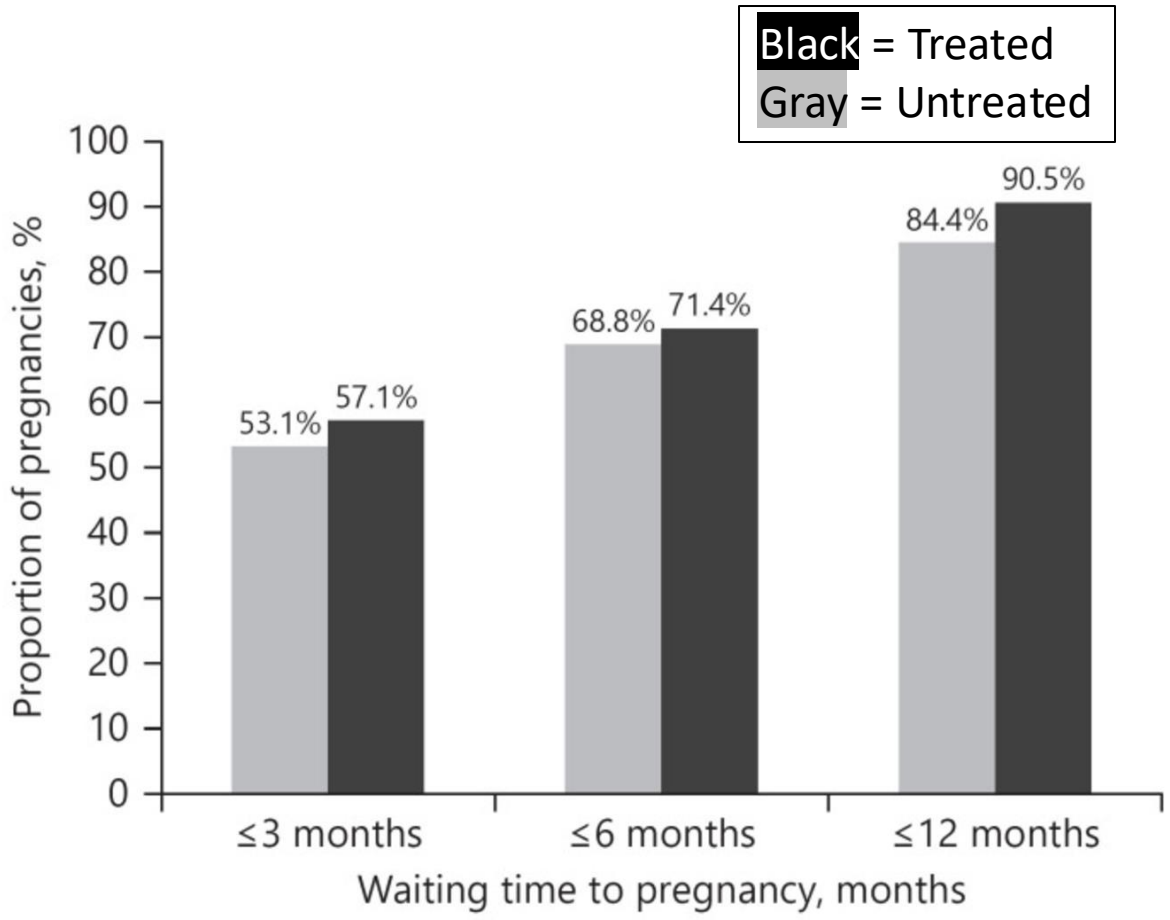
Treatment with GnRH Agonist
Updates to the Literature

PREFER Study (2021)

194 women treated with Triptorelin in childhood (1984-1996)

Follow-up at 27 centers in France from 2007-2009, 18-30 years old

No decrease in rate of successful desired pregnancy among those treated

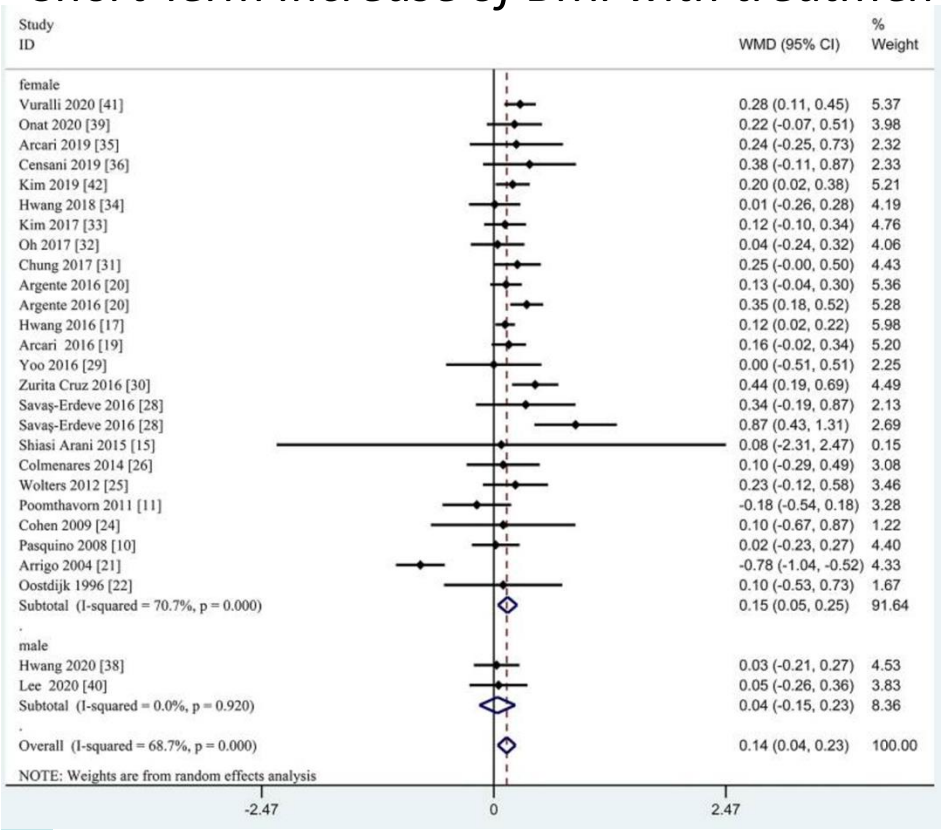


Martinerie L, de Mouzon J, Blumberg J, di Nicola L, Maisonobe P, Carel JC; PREFER study group. Fertility of Women Treated during Childhood with Triptorelin (Depot Formulation) for Central Precocious Puberty: The PREFER Study. Horm Res Paediatr. 2020;93(9-10):529-538.

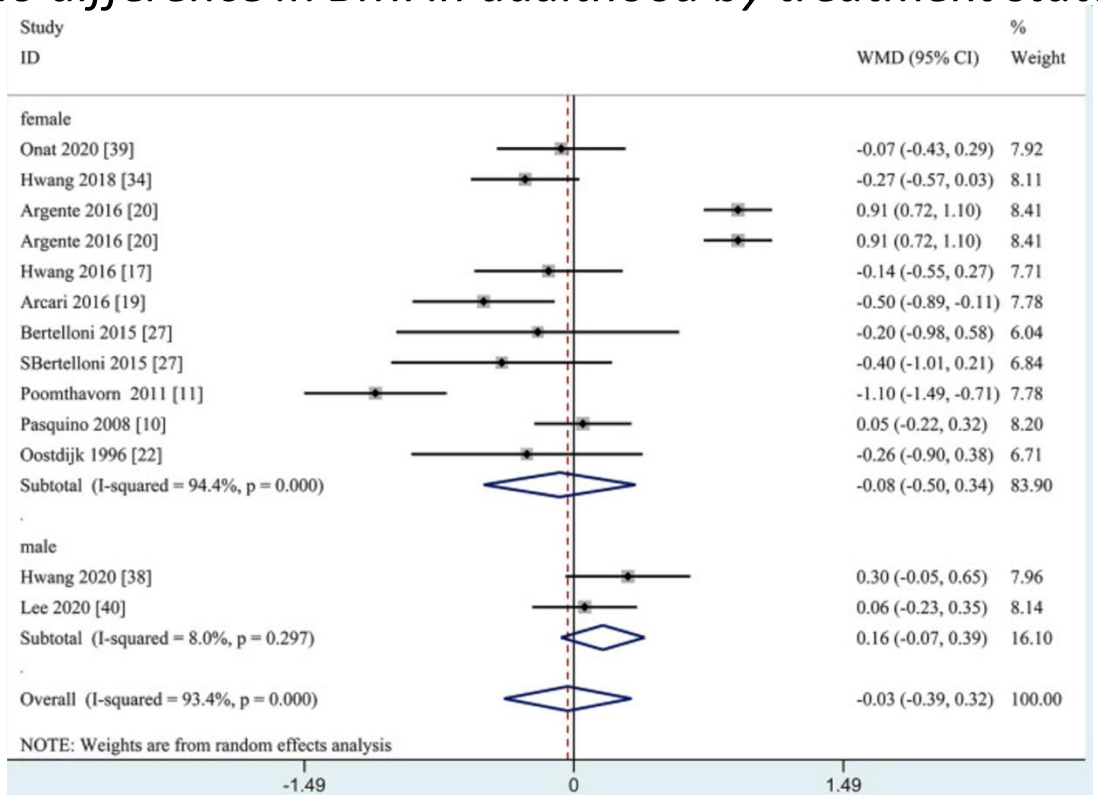
Treatment with GnRH Agonist
Updates to the Literature

Impact on BMI: Systematic Review and meta-analysis of 28 studies

Short Term Increase of BMI with treatment



No difference in BMI in adulthood by treatment status



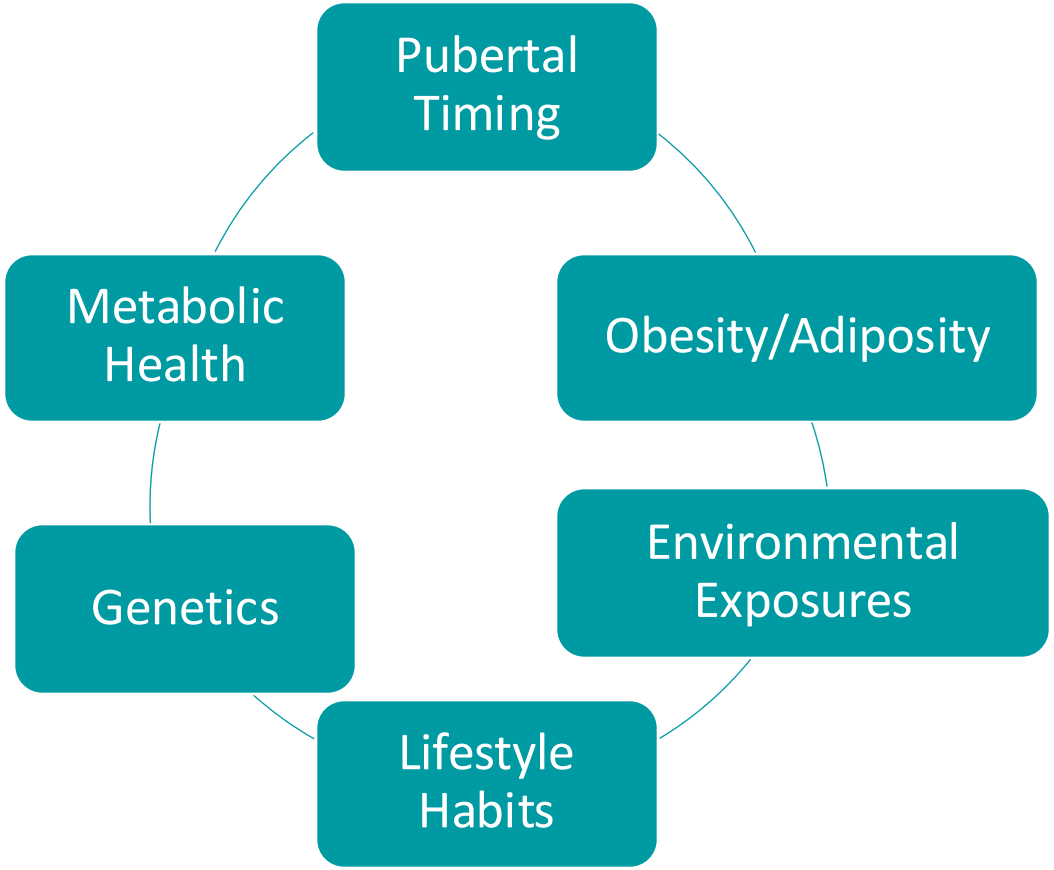
Hou L, Ying Y, Wu W, Ye F, Zhang C, Luo X. The Effect of GnRHa Treatment on Body Mass Index in Central Precocious Puberty: A Systematic Review and Meta-Analysis. Horm Res Paediatr. 2024;97(5):419-432.

Open questions relating to puberty…

Inter-relationships between each of these

Causality is unclear

Many areas for future work and research!



In Conclusion…

1. **Understand the work-up of early puberty relating to both precocious adrenache and precocious central puberty**

Working up early adrenarche (pubic hair) is different than working up early gonadarche (breast budding or enlarged testes)
On exam, palpate for breast tissue or assess testicular size (>4cc/>2cm)
Isolated adrenarche:

- Send adrenal androgens (DHEA-S, androstenedione)
- Send testosterone
- Send 17-OHP (r/o NCCAH)

Isolated gonadarche: LH, FSH, end gonadal steroid
Both – both lists above

In Conclusion…

2. **Identify considerations when thinking about initiating therapy for central precocious puberty**

    Evidence base is limited but overall suggests lack of longterm consequences for treatment of central puberty

3. **Identify active areas for future research related to pubertal progression**

    Many!

    Pubertal timing, genetic influences, environmental exposures, lifestyle habits, obesity/adiposity, metabolic health

Thank you!

Questions welcome…

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Mass General Brigham