

CHOC

Growth in Precocious Puberty and Benign Pubertal Variants

April 20, 2022

Lien Trinh, MD

Pediatric Endocrinology



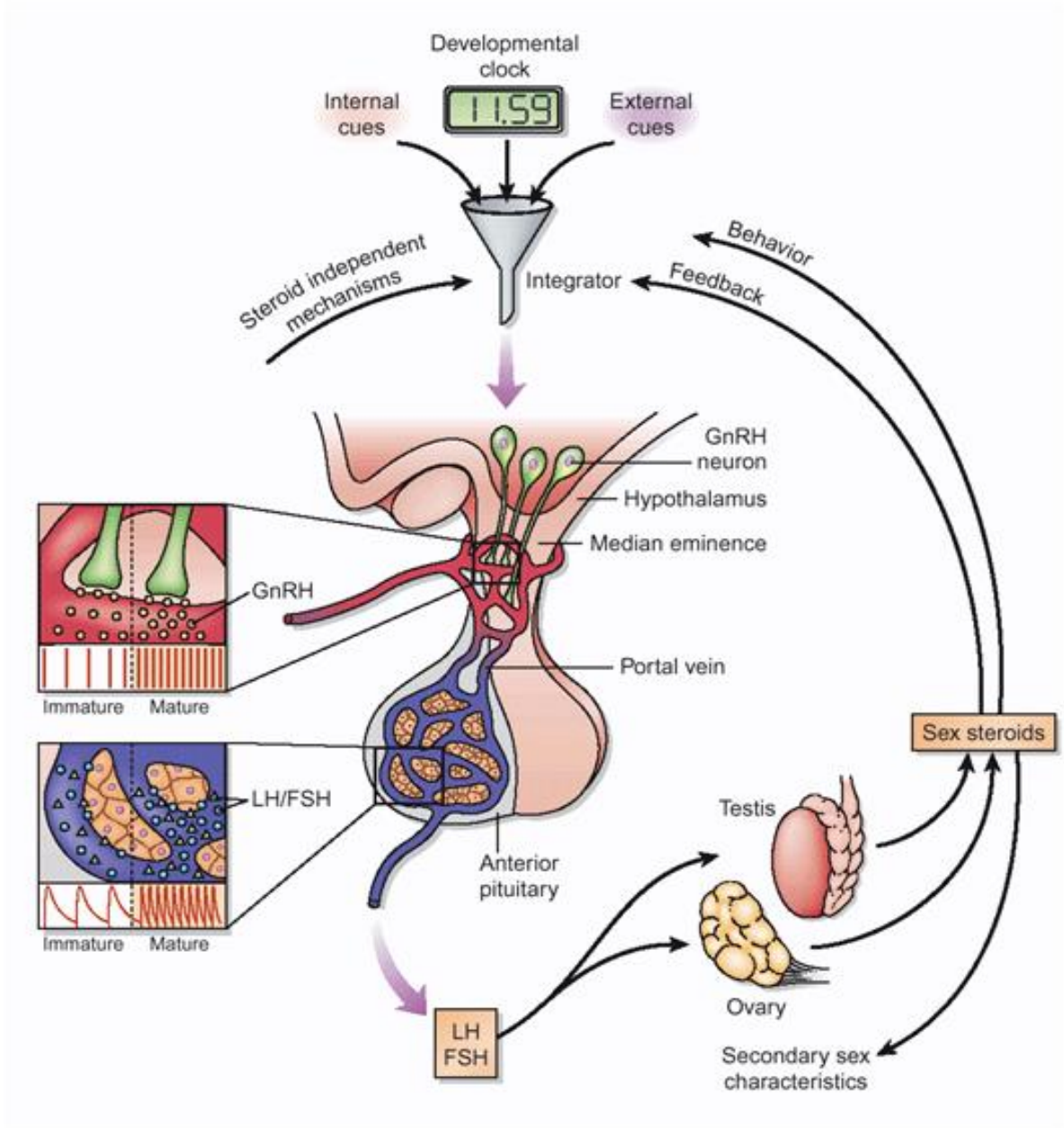
Disclosures

- None

Outline

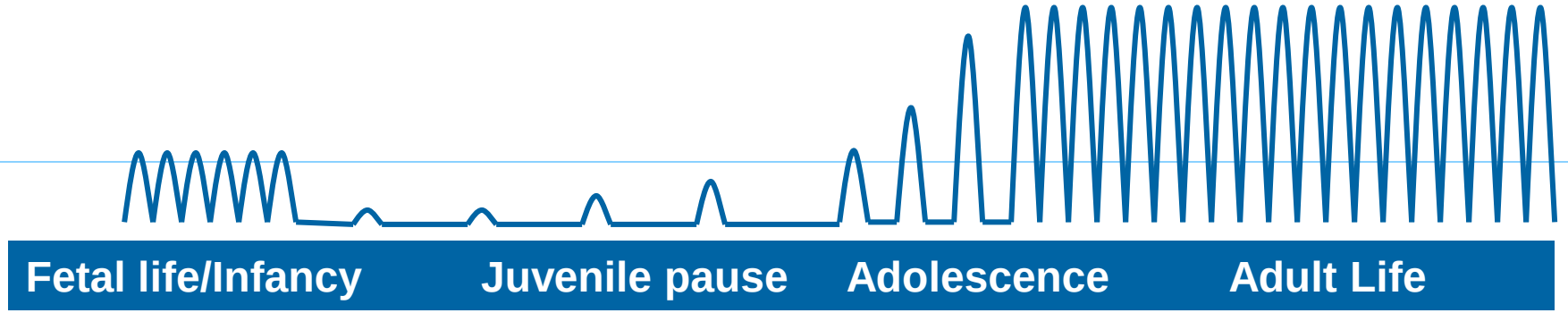
- Normal pubertal development
- Normal pubertal growth
- Age Definition of precocious puberty
- Risk factors influenced timing of puberty
- Factors influenced pubertal growth
- Height loss in precocious puberty
- Height outcome in children treated with GnRH agonists
- Benign and non-progressive pubertal variants

CHOC

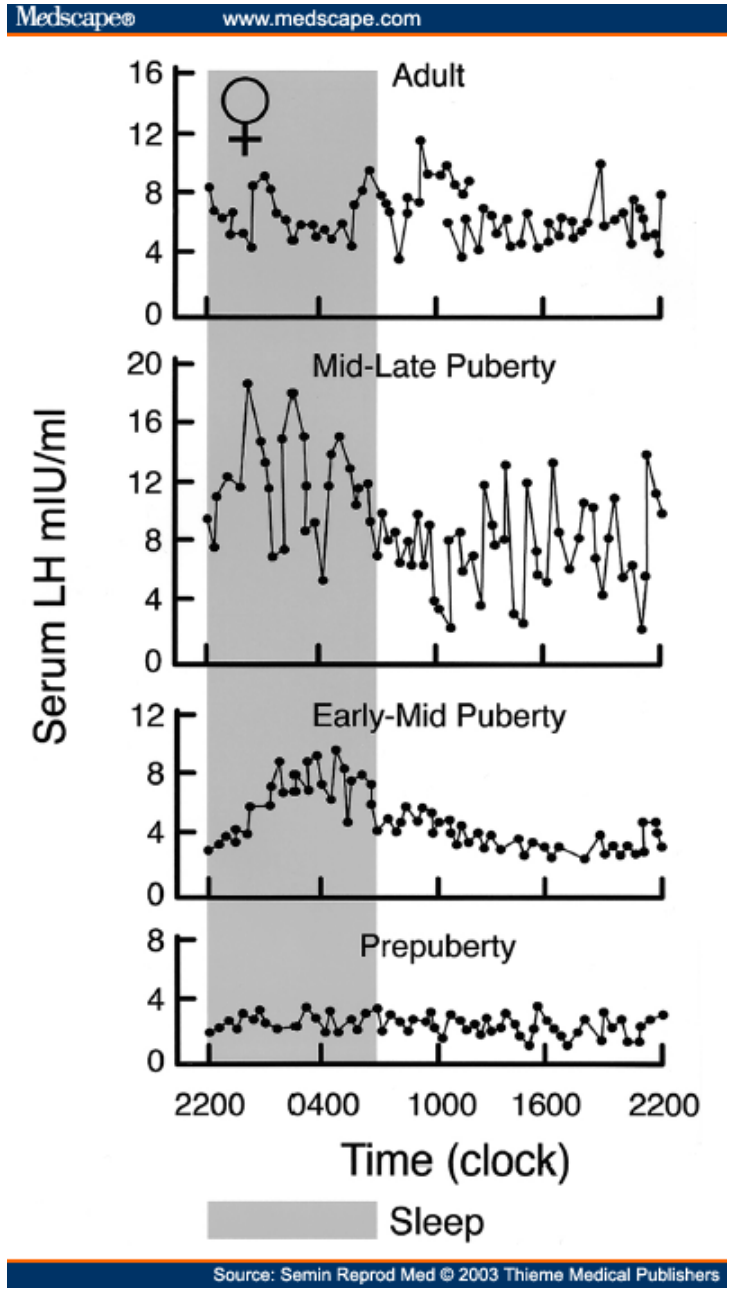

Developmental clock
11.59
Internal cues
External cues
Steroid independent mechanisms
Integrator
Behavior
Feedback
GnRH neuron
Hypothalamus
Median eminence
GnRH
Portal vein
Immature
Mature
LH/FSH
Immature
Mature
Anterior pituitary
Sex steroids
Testis
Ovary
LH
FSH
Secondary sex characteristics

GnRH Pulse Generator

- Increase in the pulse frequency and amplitude of GnRH
- Increase in FSH and LH pulses



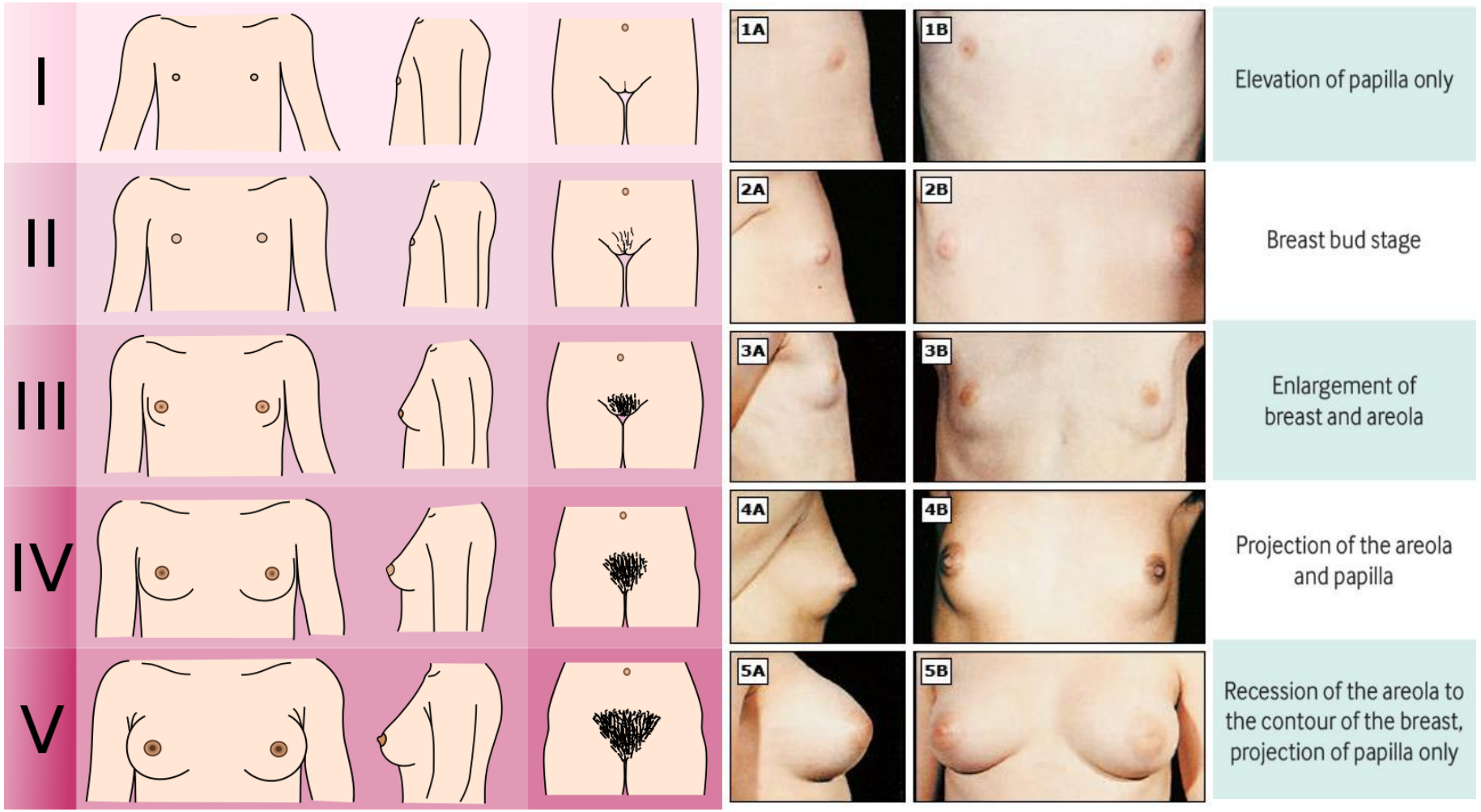
Minimal GnRH release


Medscape®
www.medscape.com
Adult
Mid-Late Puberty
Early-Mid Puberty
Prepuberty
Serum LH mIU/ml
16
12
8
4
0
20
16
12
8
4
0
12
8
4
0
8
4
0
2200
0400
1000
1600
2200
Time (clock)
Sleep
Source: Semin Reprod Med © 2003 Thieme Medical Publishers

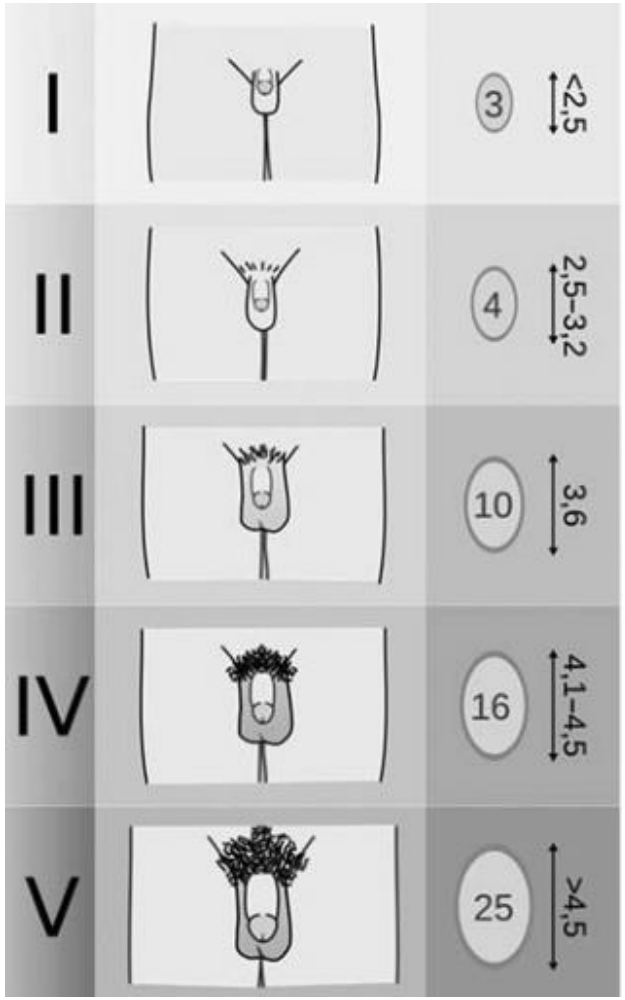
Onset of Pubertal Development

Gender	First sign	Age of onset
Girls	Breast Development	10.5 ± 1.25 years
Boys	Testicular Enlargement (≥ 4 mL)	11.5 ± 1.25 years

Tanner Staging in girls



Tanner Staging in boys



Stage I: prepubertal; testicular size less than 4 cc in volume and 2.5 cm in longest dimension

Stage II: enlargement of scrotum and testes; scrotal skin reddens and changes in texture; growth of testes to 4 cc or greater in volume

Stage III: enlargement of penis (length at first); further growth of testes

Stage IV: increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker

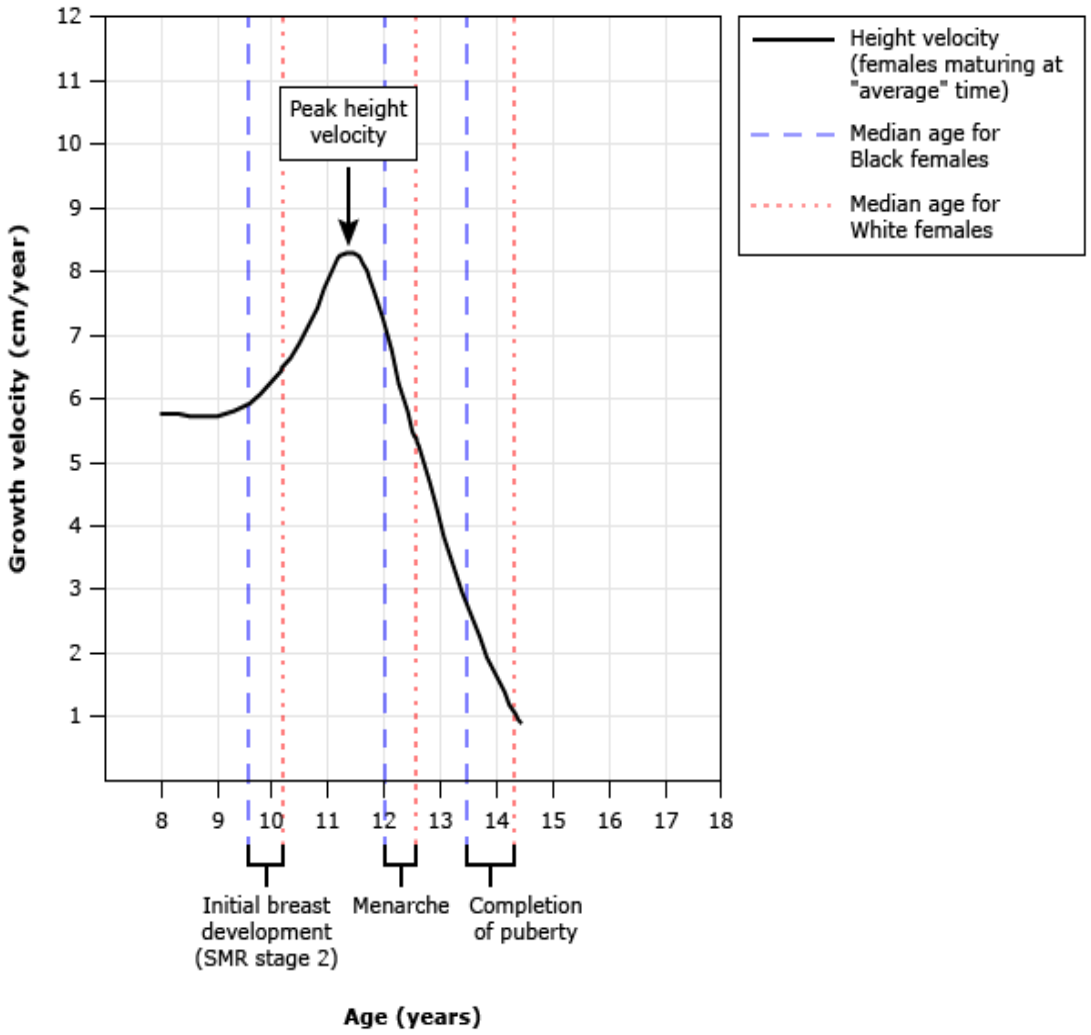
Stage V: adult genitalia

Blue (1 ml-3 ml) - prepubertal volume

Yellow (4 ml–25 ml) - pubertal volume

The onset of puberty in boys is marked by testicular enlargement and defined as **testicular volume of ≥4 ml**.

Pubertal Development in Girls



Mean age for onset of

- breast development:
9.5 y for African American girls
9.8 y for Hispanic girls
10.3 y for Caucasian girls

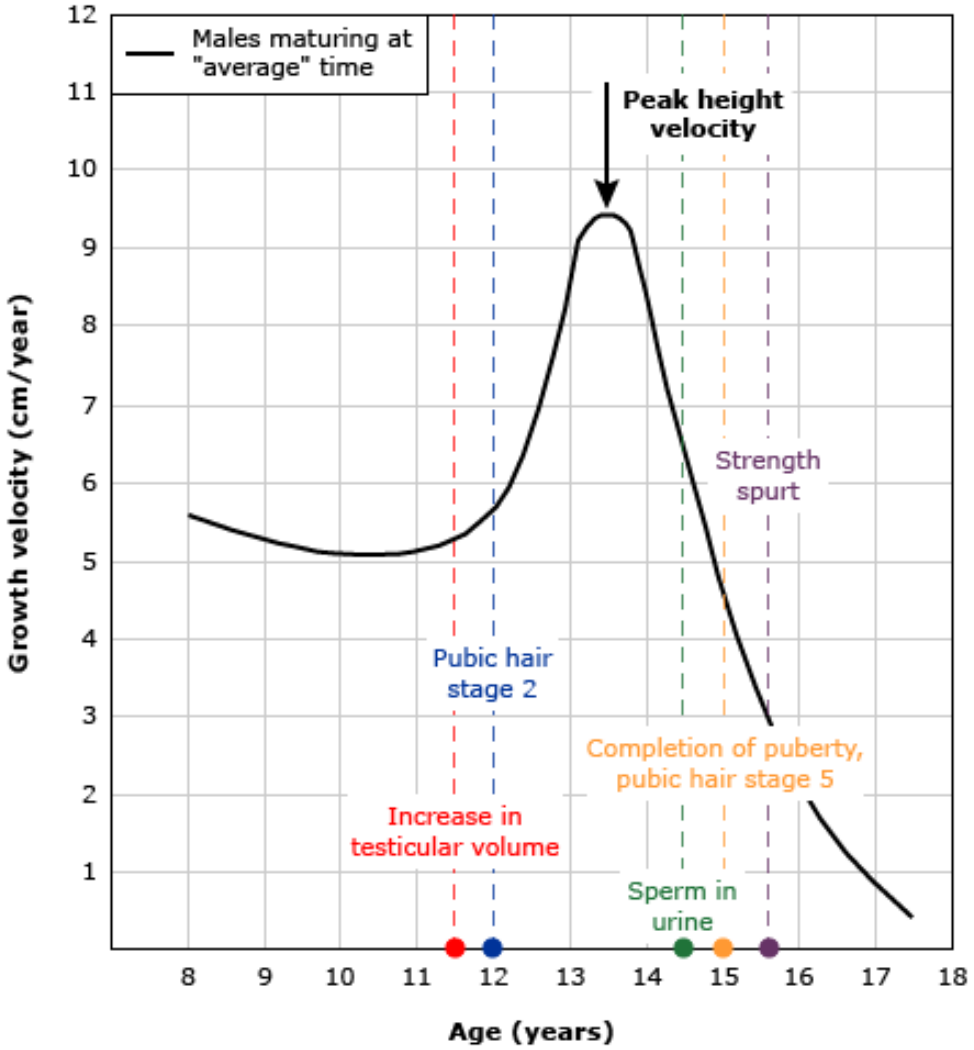
- PH development:
9.5 y for African American girls
10.3 y for Hispanic girls
10.5 y for Caucasian girls

- Menarche:
12.1 y for African American girls
12.2 y for Hispanic girls
12.7 y for Caucasian girls

NHANES III
Wu et al. Pediatrics, October 2002, Vol 110/Issue 4

CHOC

Pubertal Development in Boys



Mean age for onset of genital development stage 2:

- 9.14 years for African American boys

- 10.04 years for Hispanic boys

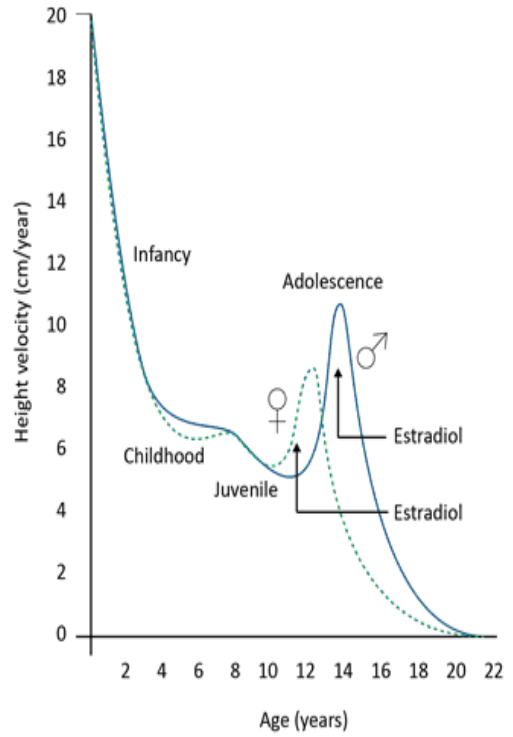
- 10.14 years for Caucasian boys

CHOC

Normal adolescent puberty

The adolescent growth spurt starts sooner in girls, at about 9.8 years. In boys the growth spurt begins at about 11.5 years.[1]

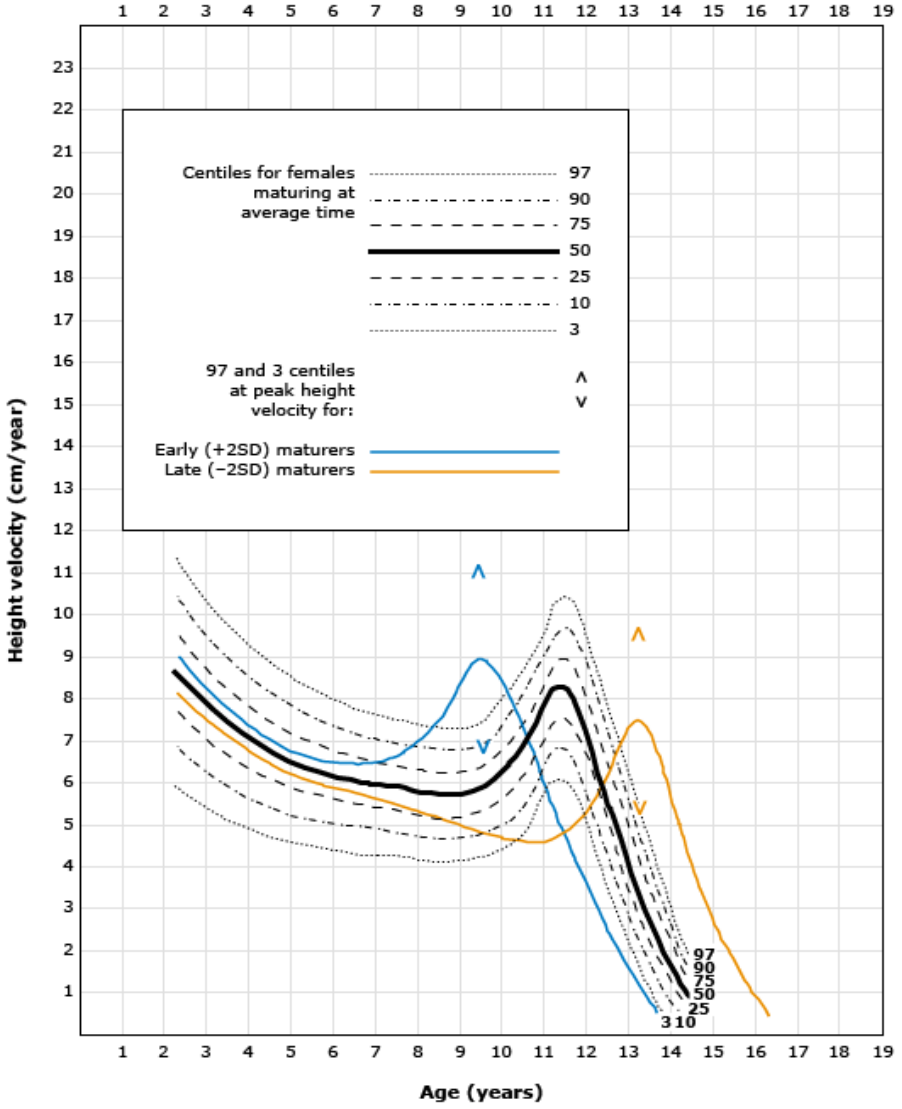
GROWTH VELOCITY IN NORMAL PUBERTY[2]



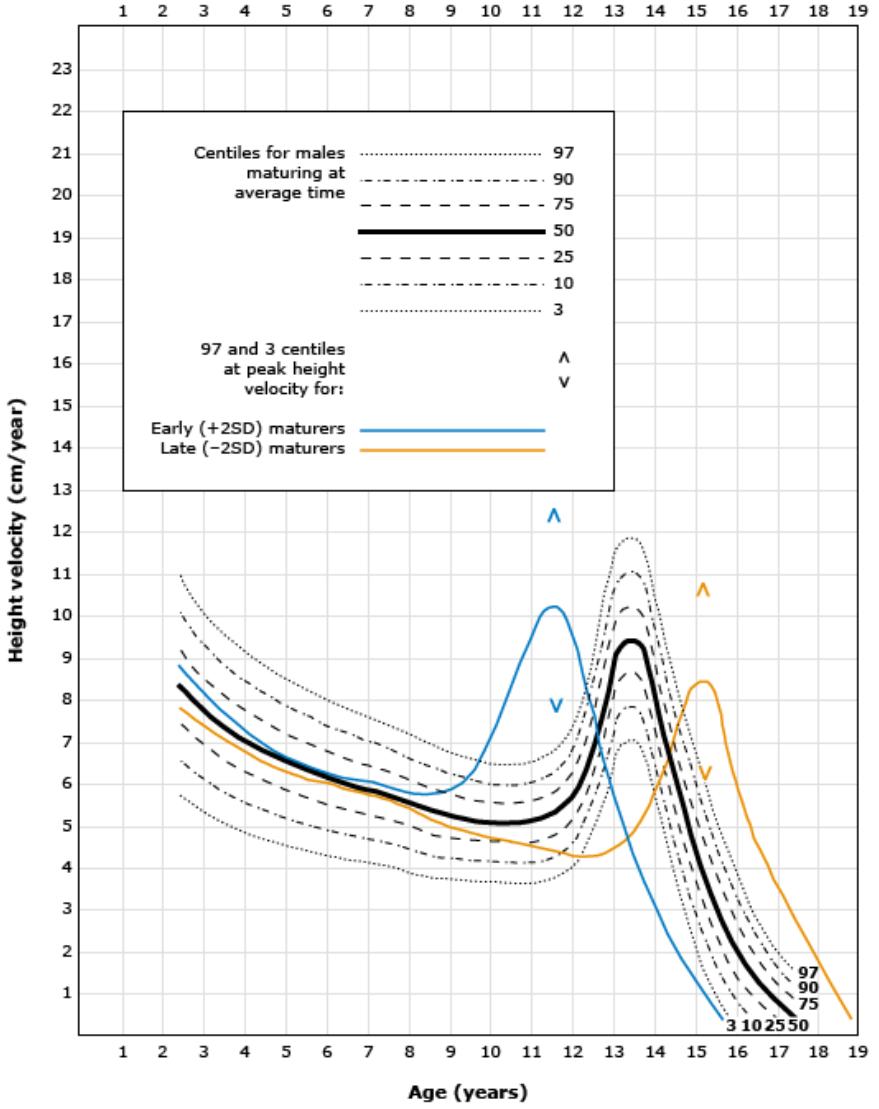
References

1. Muir A. *Pediatr Rev*. 2006;27:373-381.
2. Styne DM, et al. *Williams Textbook of Endocrinology*. 12th Ed. Philadelphia, PA. Elsevier Saunders;2011.

HEIGHT VELOCITY IN FEMALES



HEIGHT VELOCITY IN MALES



Age limit for defining when puberty is precocious

- Girls: breast development (Tanner 2) before age 8 years

- Boys: testicular enlargement (≥ 4mL) before age 9 years

CHOC

Age limit for defining when puberty is precocious

- The current recommendation that breast development before age 8 is precocious is based on outdated studies *(Marshall and Tanner 1969)*

- A meta-analysis examined the trend in onset of breast development and noted a decrease of 0.24 years per decade over the past 36 years.

- Stage 2 of breast and pubic hair development is being achieved:

  ~1 year earlier in white girls

  ~ 2 years earlier in African-American girls

  (PROS, Herman-Giddens et al 1997)

- Data on boys, less reliable, but also suggest earlier trend of development.

CHOC

Table 4 Ages of pubertal events in US females from the 1940s on

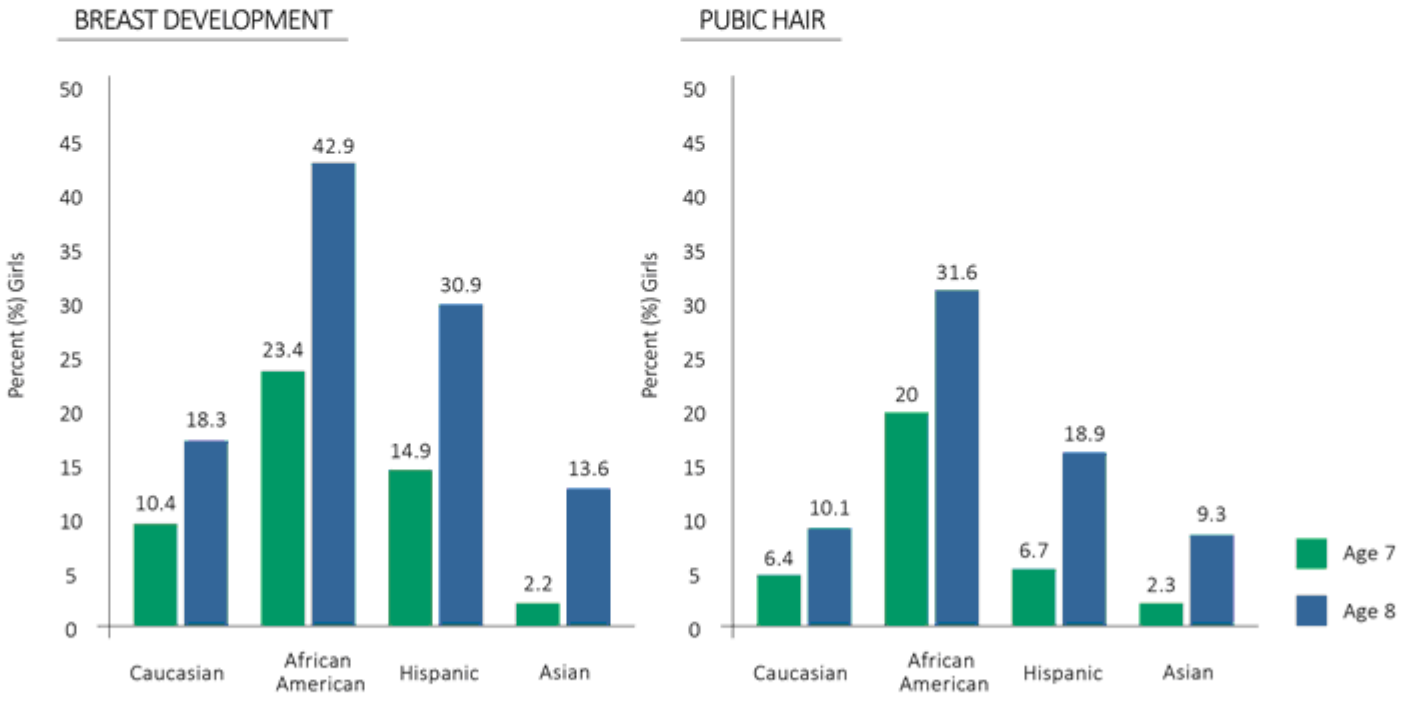
Country	Years data collected	*N*, type	Age in years				Menarche
			B2	B5	PH2	PH5	
England (Marshall & Tanner, 1969)	1969	192 M	11.2	15.3	11.7	14.4	13.5 W
USA (Reynolds & Wines, 1948)	1948	49 L	10.8	13.7	11.0	13.9	12.9 W
USA, NHES (MacMahon, 1974)	1963–1970	6710 C-S	–	–	–	–	12.8 W 12.5 B
USA (Lee, 1980)	1969–1974	18 L	11.2	14.5	11.9	14.6	13.3
USA (Foster *et al.*, 1977)	1973–1974	C-S 1059 W 621 B	10.4 W 10.2 B	– –	10.9 W 10.1 B	–	12.7 W 12.8 B
USA (Herman-Giddens *et al.*, 1997)	1992–1993	17 077 C–S	10.0 W 8.9 B	– –	10.5 W 8.8 B	–	12.9 W 12.2 B
USA, NHANES (Sun *et al.*, 2002; Chumlea *et al.*, 2003)	1988–1994	*c.* 2000 C–S	10.4 W 9.5 B	15.5 W 13.9 B	10.6 W 9.4 B	16.3 W 14.7 B	12.6 W 12.1 B

Marcia E. Herman-Giddens. International Journal of Andrology. Feb 2006; Vol 29 (1): 241-246

CHOC

Onset of pubertal signs can vary by race

Variations among racial groups should be noted when considering normal age at onset of pubertal signs.[1]



Reference
1. Biro FM, et al. *Pediatrics*. 2010;126: e583-590.

Onset of menarche

According to the National Longitudinal Study of Adolescent Health:

Menarche onset before age 11:

- African American girls 1.55 times more likely than Caucasian girls
- Hispanic American girls 1.76 times more likely than Caucasian girls

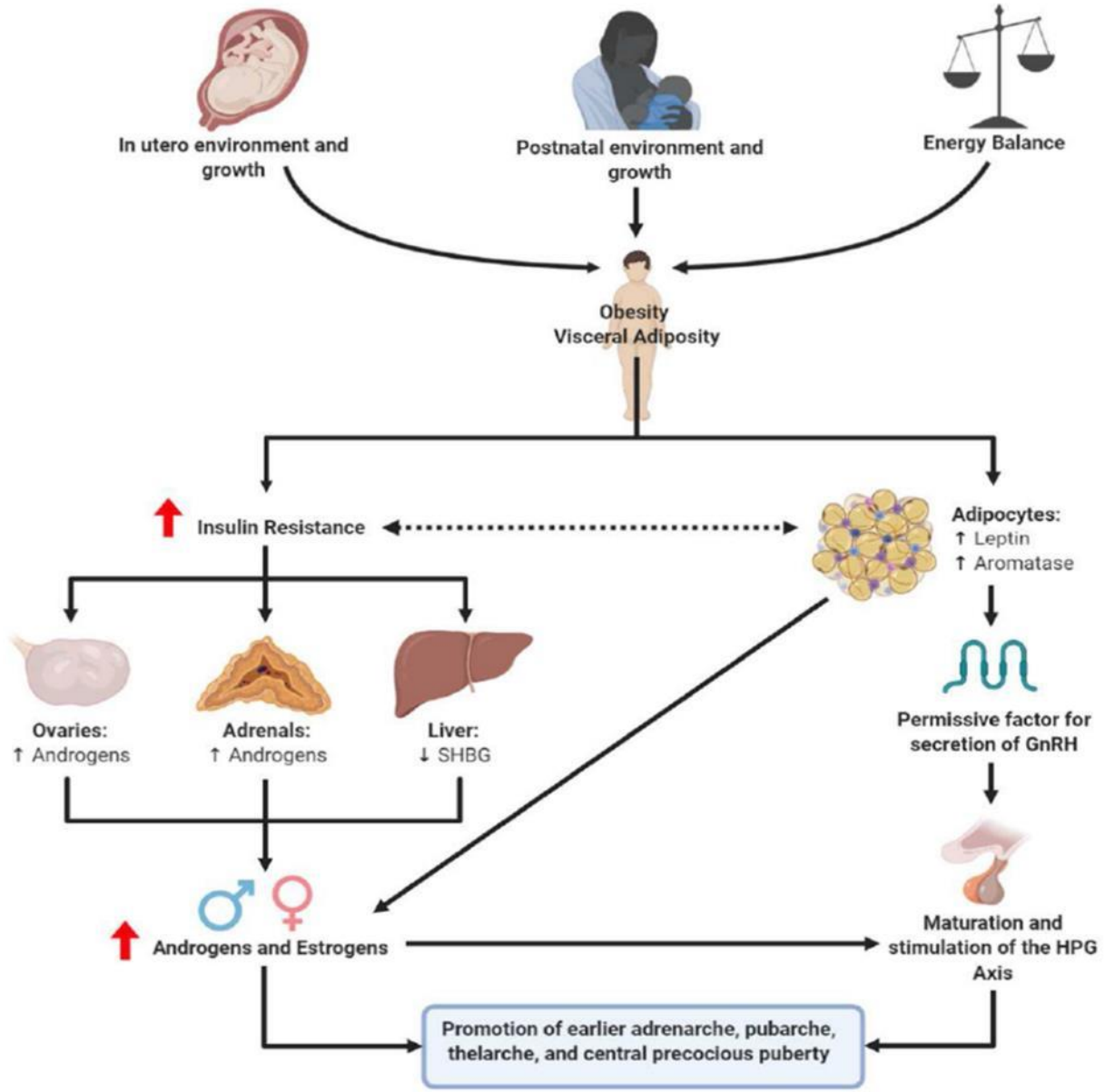
Styne DM et al, Williams Textbook of Endocrinology, 12th Ed, Philadelphia, PA. Elsevier Saunders, 2011

Risk factors associated with early puberty

- The genetic factors remain the dominant determinant of pubertal timing.
- The shifts in pubertal timing observed in the recent decades have been attributed to obesity and endocrine disrupting compounds (EDCs).

Obesity

- Recent data suggest that excess adiposity during childhood may influence pubertal development.
- It may advance puberty in girls, but it is controversial in boys, possibly delay puberty.
- Obesity in peripubertal girls may also be associated with hyperandrogenemia and a high risk of adolescent polycystic ovary syndrome.



Huang A. et al. Current Opinion in Endocrine and Metabolic Research. Vol 14, Oct 2020, 160-168

Endocrine Disrupting Compounds (EDCs)

Specific compounds that have weak estrogenic and anti-androgenic properties:

- Phenols and phthalates: Bisphenol A (BPA)

  Plasticizers used in both medical products and consumer good such as medical tubing, plastic bottles and toys, dental sealants, and linings of metal container

- Flame retardants: Polybrominated Diphenyl Ethers (PBDEs)

  Used in carpeting, clothing, and furniture

- Pesticides: 3-Phenoxybenzoic Acid (3-PBA)

CHOC

Lavender and Tea Tree Oils

- Essential-oil components have not previously been classified as EDCs but recent reports show evidence that these components have the estrogenic and anti-androgenic effects.
- Several case reports demonstrated premature thelarche in girls and prepubertal gynecomastia in boys was associated with exposure to lavender or tea tree oil containing products (e.g., soaps, lotions, colognes, shampoos, lice treatment, essential oils).

Dietary exposures

Can dietary exposures through dairy, meat or soy intake alter the timing of puberty?

- Data from NHANES (1999-2004) suggested that greater milk intake was weakly associated with an increased risk of early menarche. (1)

- A longitudinal study of Chilean girls showed that yogurt and low-fat milk consumption was associated with later menarche by 4.6 months.(2)

- (1)Wiley A. PLoS One. 2011; 6(2): e14685.
- (2)Gaskins et al. Am J Clin Nutr. 2017; 105(5):1166-75.

CHOC

Dietary exposures

- Inconsistent findings on phytoestrogen (soy) exposures: certain metabolite associated with an increased risk of earlier menarche, but other studies showed no association or an increased risk of later menarche and later thelarche.
- A prospective study of girls in Columbia found that earlier menarche associated with higher red meat consumption. (3)

- (3) Jansen EC et al. J Nutr. 2016.

Concerns in Precocious Puberty

- The primary concern is the underlying cause- CNS or gonadal neoplasm
- The secondary concern is height
  - Accelerated bone maturation
  - Premature fusion of epiphyses
  - shortens the duration of pre-pubertal growth
  - Reduced final stature

Factors influencing pubertal growth

- Estradiol is the active hormone involved in growth plate maturation and bone metabolism in both boys and girls

  Explains the different tempo of pubertal growth

  Bone age advancement in precocious puberty

- FGFR3, the fibroblast growth factor receptors, expressed in growth plate, involved in the regulation of growth plate physiology:
  - Activating mutations lead to premature closure of growth plate
  - In a mouse model, disruption of the receptor results in tall stature
- Amount of body fat: acceleration of growth and puberty observed in obesity- thought to be related to the aromatization of androgens (from adrenals or gonads) by the adipose tissue.

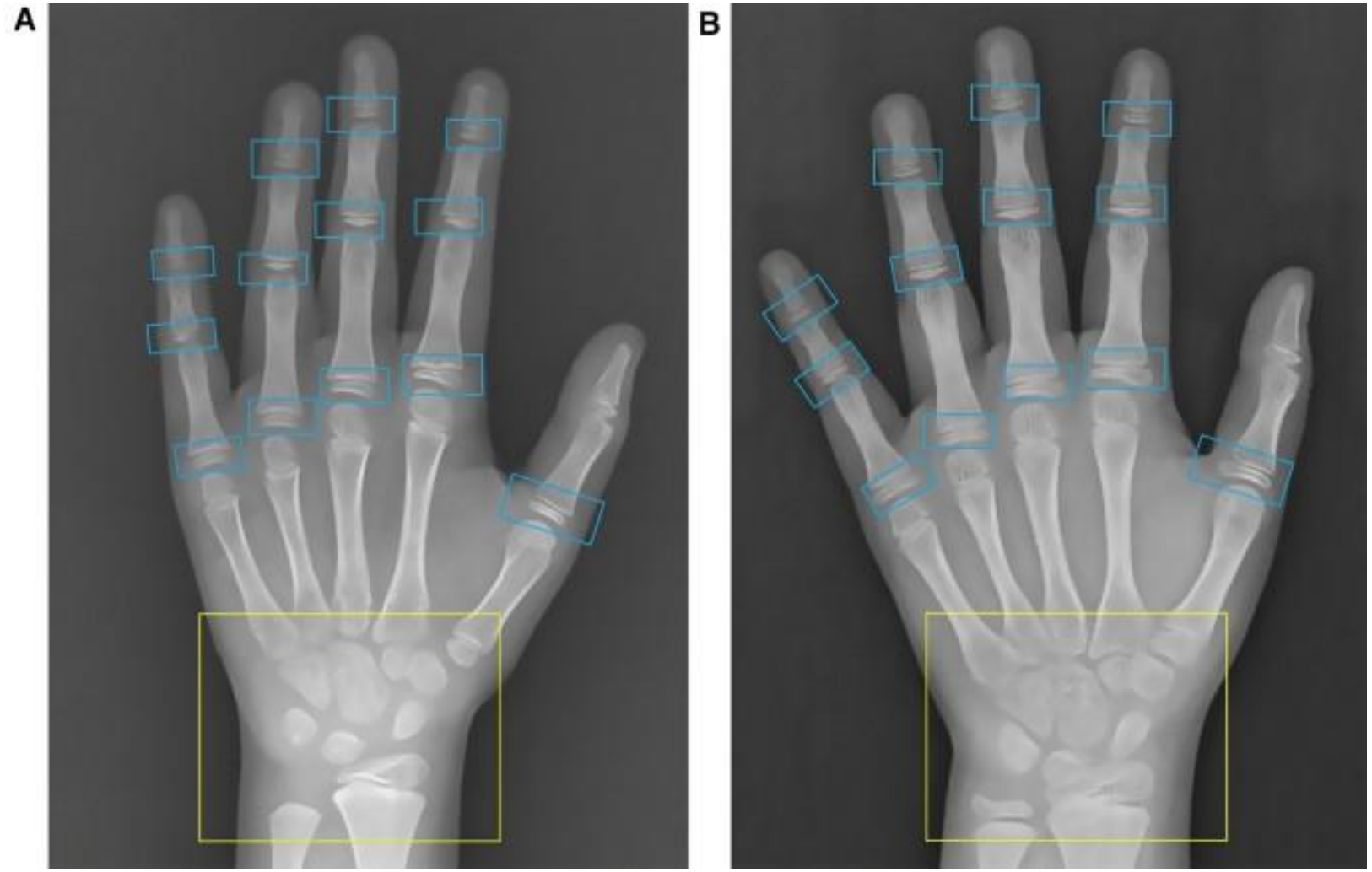
CHOC

Initial Auxology at Diagnosis of Precocious Puberty

- Height and growth velocity (GV) increased
  - Mean GV ranges 8 – 10 cm/yr
  - Increased height between 1.5-2.5 SD
- Bone age advanced
  - BA advancement 2-3 years

Girl
Bone Age: ~6 years

Girl
Bone Age: ~ 9 years



Height loss in precocious puberty

- Rapid advancement of bone age leads to premature closure of growth plates
- Early onset of puberty shortens the duration of pre-pubertal growth

Height loss in precocious puberty

- Historical data showed a loss of up to 10 cm in girls and up to 20 cm in boys.

  (Bar et al., 1995; Kauli et al, 1997)

- Negative correlation between the age of onset of precocious puberty and adult height
  - Poor height prognosis in the most severe and early cases
- Good height prognosis in slowly progressive forms of PP without treatment

CHOC

GnRH (leuprolide) stimulation test

- Gold standard test to diagnose Central Precocious Puberty
- To distinguish early CPP from isolated premature thelarche by examining gonadotropin response to GnRH
  - girls with isolated premature thelarche have a FSH-predominant response to GnRH - peak LH/FSH ratio <1
  - girls with complete sexual development have a LH-predominant response - peak LH/FSH ratio >1.
  - FSH predominant response suggests slowly progressive PP

Pescovitz *et al*, J Clin Endocrinol Metab. 1988 Sep;67(3):474-9

CHOC

Height outcome in children treated with GnRH agonists

Girls:

- Average height gain: 2.9 to 9.8 cm (mean 4.8 cm)

Boys:

- Average height gain: 6.2 ± 8.7 cm

Adult height : ~0.5 SD below target height

Factors influenced height outcome in children treated with GnRH agonists

- Age at initiation of treatment
- Degree of bone age advancement
- Age at discontinuation of treatment

CHOC

Growth Hormone treatment in precocious puberty

- Combination therapy of Growth Hormone and GnRH agonist has been used in patients with true precocious puberty who appear to have a poor adult height prognosis.
- *Pasquino et al., 1999 :* After 3 years of combined treatment (out of 5 years of GnRH agonist), patients achieved a 6 cm higher adult height than a non-randomized control group which received GnRH agonist alone.

Benign and Nonprogressive pubertal Variants

Premature thelarche:

- Isolated breast development (unilateral or bilateral) present before 2 years of age.

- Absence of other secondary sexual characteristics

- No growth acceleration

- Normal or near normal bone age (not advanced)

- Related to maternal hormones or minipuberty of infancy

- Most cases do not progress and spontaneously regress

**If there are increased growth rate, other signs of pubertal development or progression of breast development, further evaluation is required.

Benign and Nonprogressive pubertal Variants

Premature adrenarche/pubarche:

- Increase of adrenal androgens (mainly DHEAS) accompanied by development of pubic hair and/or axillary hair, body odor, or acne prior to age 8 years in girls and age 9 years in boys.

- Absence of breast development in girls or testicular enlargement in boys.

- Can associate with mild growth acceleration or mild bone age advancement.

**If >2 SD bone age advancement (>1 year advanced) or progressive virilization, and/or elevated testosterone and 17OH progesterone levels, further evaluation is required to assess for other pathological conditions such as CAH (congenital adrenal hyperplasia) or adrenal tumors.

CHOC

Benign and Nonprogressive pubertal Variants

Nonprogressive precocious puberty

- Clinical evidence of true puberty but there will be stabilization or very slow progression of pubertal signs

- Typically normal growth rate for age and minimally advanced bone age

- HPG axis is not fully activated: LH within pre-pubertal or early-pubertal range and a FSH-predominant response seen in GnRH agonist stimulation testing.

- Treatment is not needed since the adult height is not affected

PRACTICE INFORMATION

Endocrinology, CHOC Specialists

Main Office: CHOC Specialty Care Clinic
CHOC Clinic Building
1201 W. La Veta Ave., Orange, CA 92868

Scheduling: 888-770-2462
Fax: 855-246-2329

Additional Locations
Corona, Huntington Beach, Mission Viejo, Newport Beach, and Whittier

Specialty Care Physician Concierge Service: 714-509-4013.

Physicians available via Telehealth and pingmd®.

CHOC

LONG LIVE CHILDHOOD

THANK YOU!

Contact: bdinfo@choc.org

CHOC