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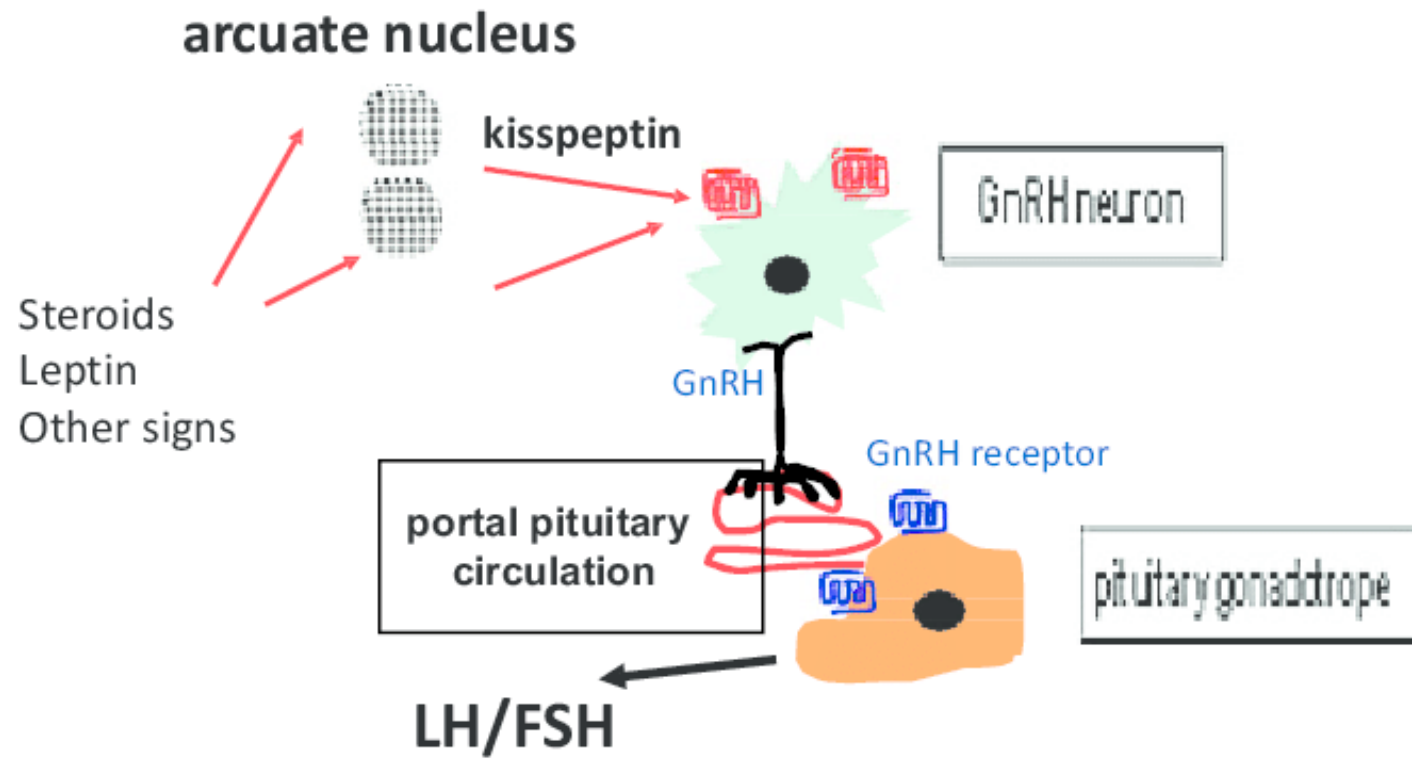
Rita Santos Silva

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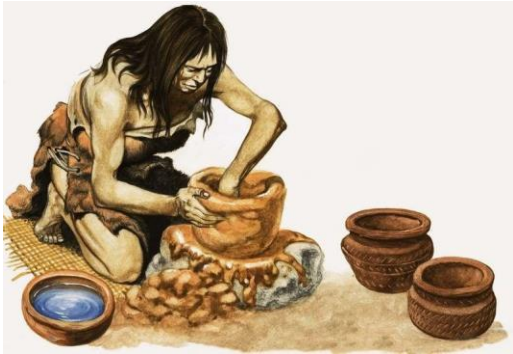
Coordenador da Unidade: Prof. Dr. Manuel Fontoura

Faculdade de Medicina da Universidade do Porto

Puberty



Secular trends in pubertal development



Paleolithic woman
7-13 years



In the classical
14 years (12-15)



After the industrial
revolution: 15-16 years

Second half of the
20th century: 12-
13 years



Modern girls:
sexual
development
5 months to a
year earlier than
those of 30 to
50 years ago

Has there been a secular advance in pubertal timing?

Table 1. Reported mean ages $\pm$ SD (years) for female sexual maturation in the UK and the USA

	Number of subjects (age range in years)	Breasts at Tanner stage 2	Menarche	Pubic hair at Tanner stage 2	Comments
Marshall and Tanner (UK) (1969) ⁶	192 (8 up)	11.15 $\pm$ 1.10	13.47 $\pm$ 1.02		Photographs. Whites
Reynolds and Wines (USA) (1948) ⁹	49 (8–18)	10.8 $\pm$ 1.1	12.9 $\pm$ 1.4	11.0 $\pm$ 1.1	Direct examination + photographs. Race not stated
Nicolson and Hanley (USA) (1953) ⁸	252	10.6	12.8	11.6	
Lee (USA) (1980) ⁷	18 (8.6–17.8)	11.2 $\pm$ 1.6	13.3 $\pm$ 1.3	11.9 $\pm$ 1.5	Direct examination. Almost all whites
Billwitz <i>et al.</i> (UK) (1981) ²⁵	788 (9–17)	10.8 $\pm$ 1.6	13.4 $\pm$ 1.1		Direct examination. Whites
Roche <i>et al.</i> (USA) (1995) ²⁴	67 (9.5–17)	11.2 $\pm$ 0.7		11.0 $\pm$ 0.5	Whites. Assisted self-examination
Herman-Giddens <i>et al.</i> (USA) (1997) ¹	17 077 (3–12)	African-Americans 8.87 $\pm$ 1.93 Whites 9.96 $\pm$ 1.82	African-Americans 12.16 $\pm$ 1.21 Whites 12.88 $\pm$ 1.20	African-Americans 8.78 $\pm$ 2.0 Whites 10.51 $\pm$ 1.67	Only 9.6% African-Americans Breast development assessed by palpation in 39% of girls. Otherwise by inspection
Sun <i>et al.</i> (USA) (2002) ¹⁰	1215 (8–19)	African-Americans 9.48 Whites 10.38		African-Americans 9.43 Whites 10.57	Direct examination
Wu <i>et al.</i> (USA) (2002) ¹¹	1623–1168 (8–16)	African-Americans 9.5 Whites 10.3	African-Americans 12.2 Whites 12.6	African-American 9.5 Whites 10.6	Direct examination
Freedman <i>et al.</i> (USA) (2002) ¹²					
Data collected 1973–1974	1398 (7–16)		African-Americans 12.9 Whites 12.7		
Data collected 1992–1994	1230 (7–16)		African-American 12.1 Whites 12.5		
Chumlea <i>et al.</i> (USA) (2003) ¹⁶	2510 (8–20)		African-American 12.06 Whites 12.55		
Anderson <i>et al.</i> (USA) (2003) ¹⁸					
Data collected 1963–1970	1760 (10–15)		African-Americans 12.48 Whites 12.8		
Data collected 1988–1994	767 (10–15)		African-American 12.14 Whites 12.60		

Slyper AH, The pubertal timing controversy in the USA, and a review of possible causative factors for the advance in timing of onset of puberty. Clin Endocrinol 2006

Has there been a secular advance in pubertal timing?

- No general consensus regarding breasts at T2
- Pubarche has advanced at least 6 months
- Less change with respect to menarche
- Slowing in the overall tempo of female pubertal development

Secular trend toward an increased final height at adulthood

Secular trend of final height and puberty in Korea and Netherlands

	Female				Male			
Korea (34)								
Year	1965	1984	1997	2005	1965	1984	1997	2005
Mean final height (cm)	155.9	157.1	160.4	161.3	168.7	170.2	173.4	174.2
Mean height (cm) at 2 years of age	81.5	84.6	87.0	89.0	82.7	85.5	87.9	90.4
Netherlands (2, 17)								
Year	1965	1980	1997		1965	1980	1997	
Mean final height (cm)	166.3	168.3	170.6		178.0	182.0	184.0	
BII or GII age (yr)	11.0	10.54	10.72		11.0	11.33	11.45	
BV-BII or GV-GII (yr)	4.2	3.7	3.6		4.9	4.0	3.8	
Menarcheal age (yr)	13.40	13.28	13.15					

Role of obesity and leptin on pubertal development



- Leptin receptors have been identified in the hypothalamus, gonadotrope cells, ovarian follicular cells and Leydig cells
- Obese children present increased leptin and androgen levels
- Early maturing girls are more likely to become obese in adolescence and adulthood
- Early maturing caucasian girls are heavier at the onset of puberty (NOT true for african-americans)
- No proved association in boys

Slyper AH, The pubertal timing controversy in the USA, and a review of possible causative factors for the advance in timing of onset of puberty. Clin Endocrinol 2006

Shalitin S, Putative Effects of Obesity on Linear Growth and Puberty, Hormone Research in Pediatrics 2017

Hyperinsulinemia and secular shift in onset of puberty

- Association between early pubarche, hyperandrogenaemia and hyperinsulinaemia
- Levels of insulin and HOMA-IR are higher in earlier maturing girls
- Early menarche is associated with metabolic syndrome
- Early menarche is associated to PCOS
- Lifestyle, nutrition...

Frontini MG, Longitudinal changes in risk variables underlying metabolic Syndrome X from childhood to young adulthood in female subjects with a history of early menarche: the Bogalusa Heart Study. Int J Obes Relat Metab Disord 2003

Lazar L, Early polycystic ovary-like syndrome in girls with central precocious puberty and exaggerated adrenal response. Eur J Endocrinol 1995

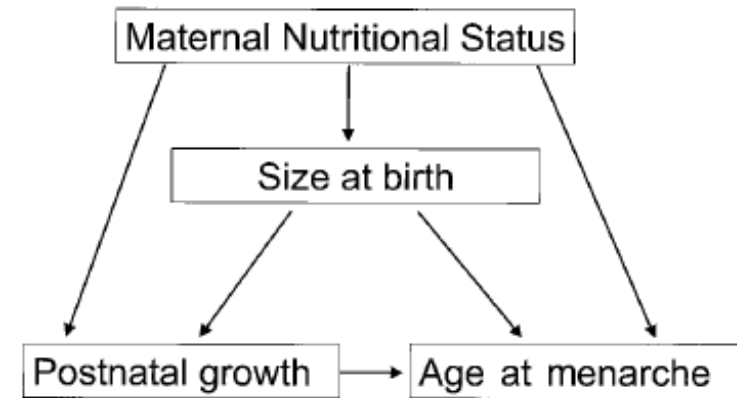
Birth weight and puberty



Size at Birth Predicts Age at Menarche
Linda S. Adair
Pediatrics 2001;107:e59



- Low size at birth
- Faster growth rates in early infancy
- Higher mother's postpartum BMI



earlier menarche

Premature adrenarche

Premature adrenarche

Pubic and axillary hair
Adult type body odor
Oily skin and hair
Acne
Transient growth acceleration
Bone maturation

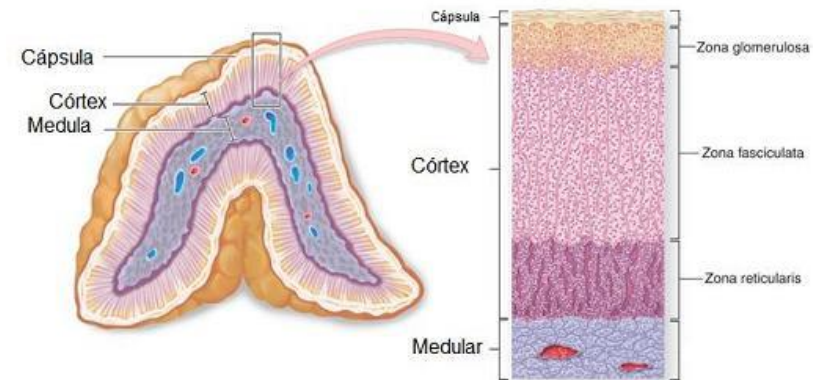
< 8 yr ♀
< 9 yr ♂

Ø breast or testicular enlargement

PREMATURE PUBARCHÉ

DHEAS concentration $\geq 40 \mu\text{g/dl}$
(Rosenfield RL, Pediatrics 2009)

PREMATURE ADRENARCHE



Premature adrenarche

- Prevalence
 - Finnish children: 8.6% in girls and 1.8% in boys (Mantyselka A, J Clin Endocrinol Metab 2014)
 - Turkish girls: 4.3% (Atay Z, Acta Paediatrica 2012)
 - American girls: $\leq 3\%$ (Rosenfield RL, Pediatrics 2009)
- Physiopathology?
- Consequences?

Premature adrenarche

Clinical Endocrinology (2000) 53, 523–527

Adrenal hyperandrogenism in adolescent girls with a history of low birthweight and precocious pubarche

Lourdes Ibáñez*, Neus Potauf, Maria Victoria Marcos† and Francis de Zegher§

high baseline and post-ACTH concentrations of most adrenal androgens, low SHBG levels and tended to

In conclusion, these longitudinal findings in girls with PP point to the possibility of an endocrine sequence of prenatal onset: low weight at birth, PP in childhood and adrenal hyperandrogenism in adolescence. The pathophysiological mechanisms underpinning this sequence remain to be identified.

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Postpubertal Outcome in Girls Diagnosed of Premature Pubarche during Childhood: Increased Frequency of Functional Ovarian Hyperandrogenism

LOURDES IBÁÑEZ, NEUS POTAU, RAFFAELE VIRDIS, MARIA ZAMPOLLI, CESARE TERZI, MIQUEL GUSSINYÉ, ANTONIO CARRASCOSA, AND ENRIC VICENS-CALVET

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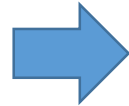
Precocious Pubarche, Hyperinsulinism, and Ovarian Hyperandrogenism in Girls: Relation to Reduced Fetal Growth

LOURDES IBÁÑEZ, NEUS POTAU, INGE FRANCOIS, AND FRANCIS DE ZEGHER

Premature adrenarche



Prenatal growth restriction in girls



Premature pubarche



Polycystic ovarian syndrome,
hyperandrogenism, insulin
resistance and metabolic syndrome

Premature adrenarche

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Hyperinsulinemia and Decreased Insulin-Like Growth Factor-Binding Protein-1 Are Common Features in Prepubertal and Pubertal Girls with a History of Premature Pubarche*

LOURDES IBÁÑEZ, NEUS POTAU, MARIA ZAMPOLLI, SUSANNA RIQUE,
PAUL SAENDER, AND ANTONIO CARRASCOSA

Adolescent and Endocrine Unit (L.I., A.C.) and Hormonal Laboratory (N.P., S.R.), Hospital Universitario Materno-Infantil Vall d'Hebron, Barcelona, Spain; Clinica Pediatrica, University of Parma (M.Z.), Parma, Italy; and the Department of Pediatrics, Albert Einstein College of Medicine / Montefiore Medical Center (P.S.), Bronx, New York 10467



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Metabolism Clinical and Experimental 57 (2008) 733–740

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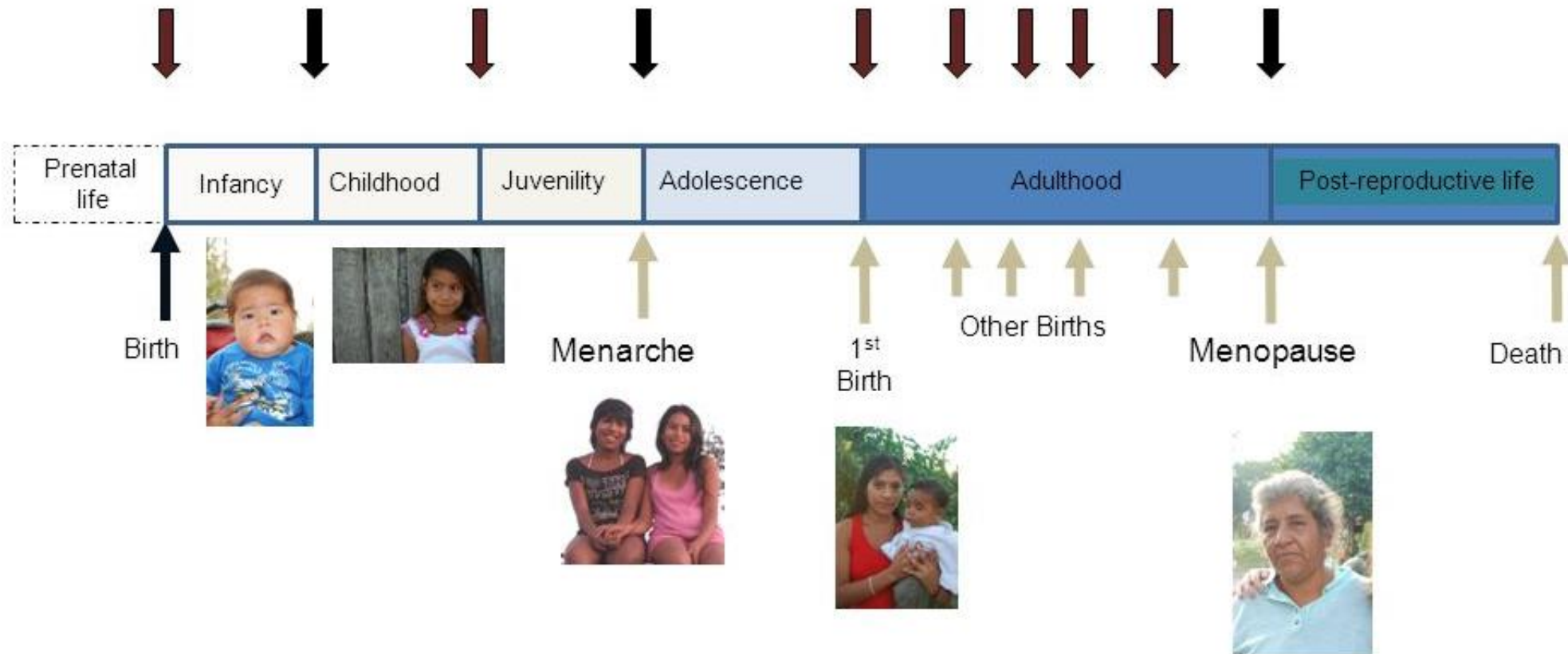
Evidence of metabolic syndrome in lean children with premature pubarche at diagnosis

Revi P. Mathew^{a,*}, Daniel W. Byrne^b, MacRae F. Linton^c, Douglas E. Vaughan^c,
Sergio Fazio^c, William E. Russell^{a,d}

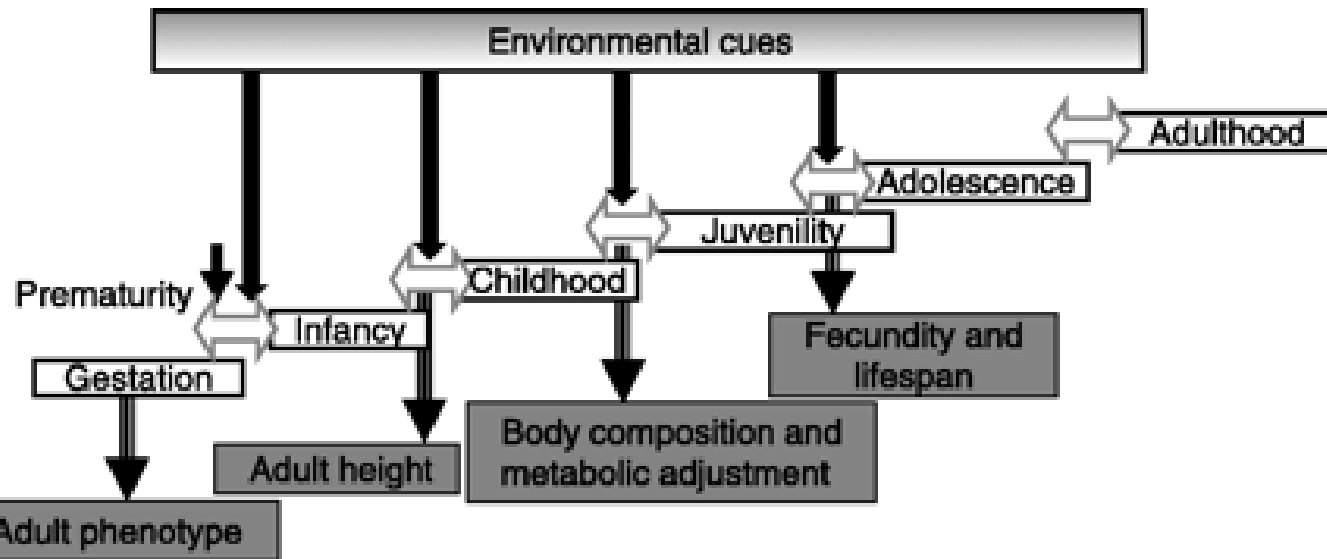
- Hyperinsulinism is present at prepubertal diagnosis of PP and increases markedly in late puberty
- The regulation of the insulin/IGF system in girls with PA seems to be altered (↑ IGF1, ↑ IGFBP3, ↓ IGFBP1, ↑ IGF1/IGFBP1 ratio)
- Girls with PA display early findings of atherosclerosis, subclinical inflammation and fibrinolytic abnormalities

Premature adrenarche

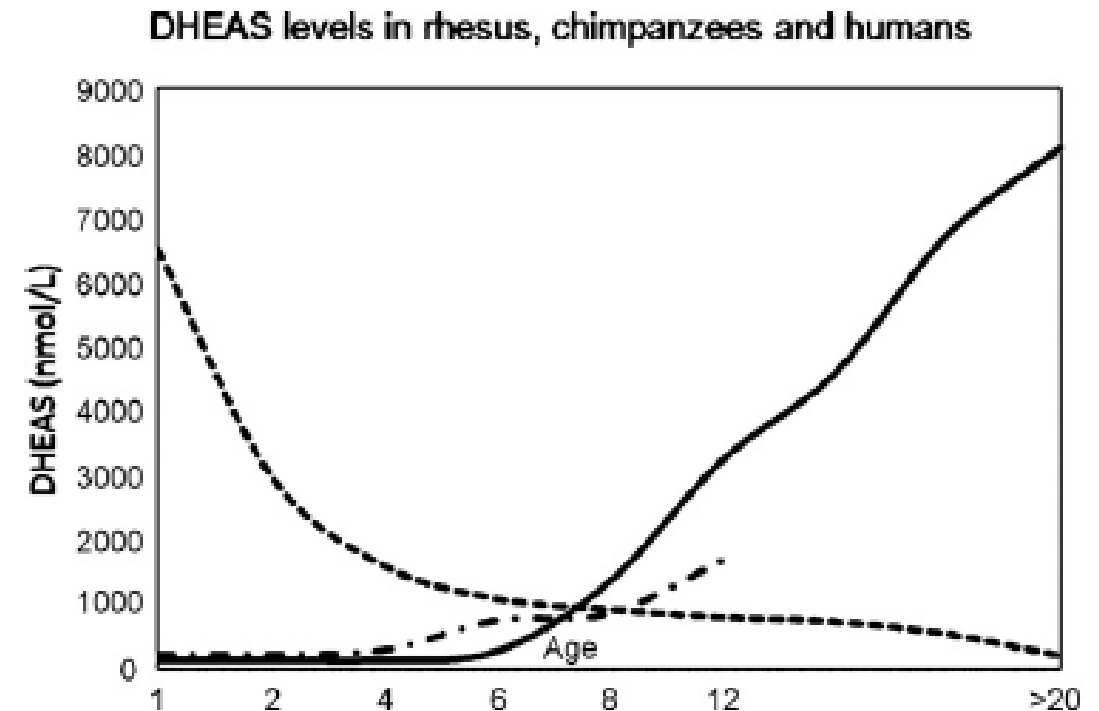
Human female life stages and major transitions



Premature adrenarche



Ze'ev Hochberg, Evo-devo of child growth II: human life history and transition between its phases, European Journal of Endocrinology (2009) 160 135–141



Flinna M, Nepomnaschyb P, Muehlenbeinc M, Ponzid D, Evolutionary functions of early social modulation of hypothalamic-pituitary-adrenal axis development in humans, Neuroscience and Biobehavioral Reviews 35 (2011) 1611–1629

Progressive *versus* non-progressive
precocious puberty

Precocious puberty

- Sexual precocity
 - < 8 yrs in girls and 9 yrs in boys (< 2.5 SD from the mean)

But...

- 15.4% african-american and 5% white girls present breast budding between 7-8
- 29.3% white, 27.3% mexican-american and 37.8% african-american boys have Tanner 2 genitalia at 8 years of age

Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997;99(4):505-12

Threshold for evaluation

SPECIAL ARTICLE

Reexamination of the Age Limit for Defining When Puberty Is Precocious in Girls in the United States: Implications for Evaluation and Treatment

Paul B. Kaplowitz, MD*; Sharon E. Oberfield, MD†; and the Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society

936 PEDIATRICS Vol. 104 No. 4 October 1999

Downloaded from <http://pediatrics.aappublications.org/> at Proquest Research on October 9, 2017

“Caucasian girls who have breast and/or pubic hair development before 7 years of age and for African-American girls who have these findings before 6 years of age”

Are Pubertal Changes in Girls Before Age 8 Benign?

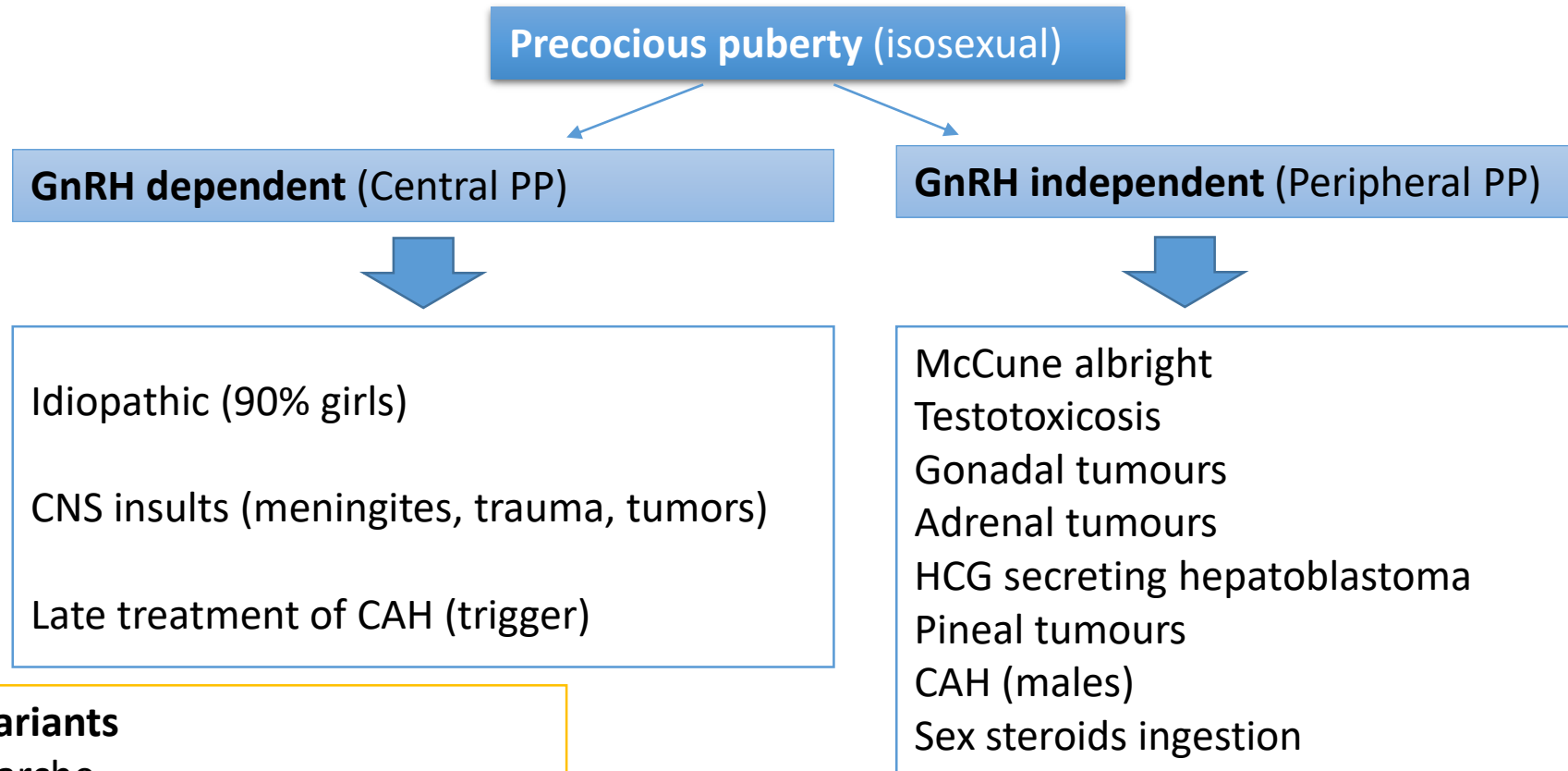
L. Kurt Midyett, MD; Wayne V. Moore, MD, PhD; and Jill D. Jacobson, MD

PEDIATRICS Vol. 111 No. 1 January 2003 47

Downloaded from <http://pediatrics.aappublications.org/> at Proquest Research on October 9, 2017

223 girls aged 7-8 years for whites and 6-8 years for african-americans – 12.3% had a pathological cause for their sexual precocity

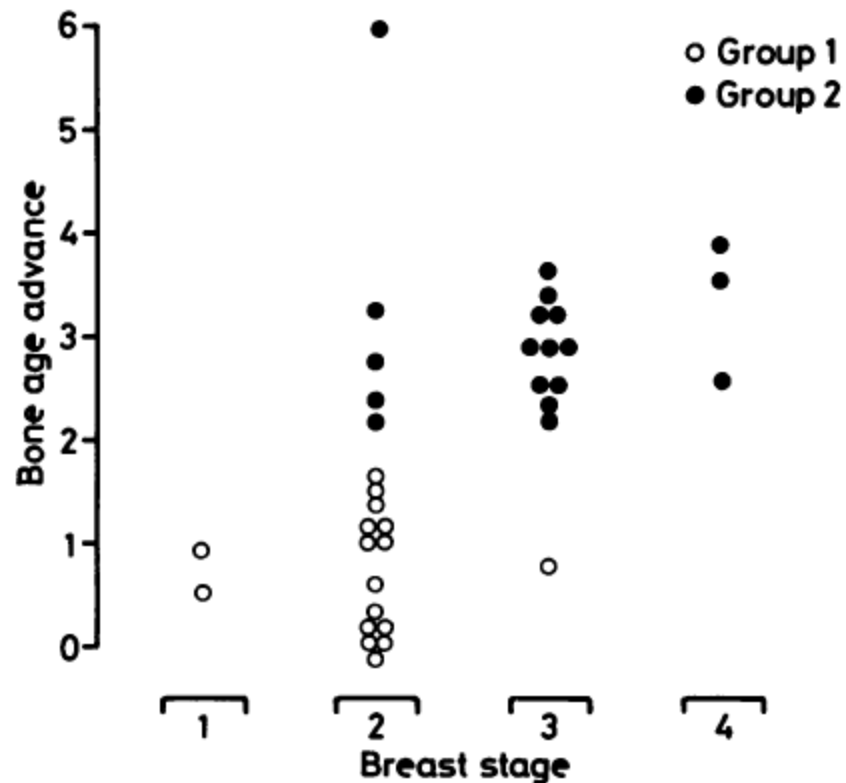
Etiology



Benign pubertal variants

- Premature thelarche
- Premature adrenarche
- Pubic hair of infancy
- Benign prepubertal vaginal bleeding

Non-progressive/intermittently progressive/slowly progressive/unsustained precocious puberty



- Bone age not as advanced
- Fewer clinical signs of excessive oestrogen production
- Normal growth hormone secretion
- Lack of excessive progression of bone age 9 to 12 months after the onset of puberty are good indicators of moderate oestrogen activity

Figure Distribution of the breast development stage in relation to bone age advance (bone age—chronological age) in girls with precocious puberty.

Fontoura M, Brauner R, Prevot C, Rappaport R, Precocious puberty in girls: early diagnosis of a slowly progressing variant. Arch Dis Child 1989;64(8):1170-6

Non-progressive/intermittently progressive/slowly progressive/unsustained precocious puberty

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Unsustained or Slowly Progressive Puberty in Young Girls: Initial Presentation and Long-Term Follow-Up of 20 Untreated Patients*

MARK R. PALMERT, HOLLY V. MALIN, AND PAUL A. BOEPPLE

- Serum LH concentrations are within the pre- or early-pubertal range
- FSH-predominant response is seen in GnRH α stimulation testing
- Adult height is not affected
- Monitoring for evidence of pubertal progression
- Treatment with a GnRH α is not needed

Non-progressive/intermittently progressive/slowly progressive/unsustained precocious puberty

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Clinical characteristics of forms of early pubertal development

	Nonprogressive precocious puberty	Central precocious puberty (CPP)	Peripheral precocity
Physical examination: Advancement through pubertal stages (Tanner stage)	No progression in Tanner staging during 3 to 6 months of observation	Progression to next pubertal stage in 3 to 6 months	Progression
Growth velocity	Normal for bone age	Accelerated (>6 cm per year)*	Accelerated*
Bone age	Normal to mildly advanced	Advanced for height age	Advanced for height age
Serum estradiol concentration (girls)[†]	Prepubertal ^Δ	Prepubertal to pubertal	Increased in ovarian causes of peripheral precocity, or with exogenous estrogen exposure
Serum testosterone concentration (boys, or girls with virilization)[†]	Prepubertal ^Δ	Prepubertal to pubertal	Pubertal and increasing
Basal (unstimulated) serum LH concentration[†]	Prepubertal ^{Δ◇}	Pubertal [◇]	Suppressed or prepubertal [◇]
GnRH (or GnRHa) stimulation test[†]	LH peak in the prepubertal range ^{Δ§} Lower stimulated LH to FSH ratio [‡]	LH peak elevated (in the pubertal range) [§] Higher stimulated LH to FSH ratio [‡]	No change from baseline, or LH peak in the prepubertal range

Brain magnetic resonance imaging



All boys with CPP and girls < 6 yrs



Girls 7-8 yrs if:

- no clinical evidence of CNS pathology
 - family history of earlier pubertal onset
 - Increased BMI
-
- Younger age of onset of pubertal signs and higher basal LH and estradiol concentrations – predictive features for intracranial pathology

Pedicelli S, Alessio P, Scirè G, Cappa M, Cianfarani S, 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(12):4455-61.

Treatment in central precocious puberty

- Goals of treatment
- Decision to treat



Indications for treatment in central precocious puberty

Decision to treat

Age

Onset of CPP < 6 yrs - 9 to 10 cm

Onset of CPP > 6 yrs – 4 to 7 cm

Rate of pubertal progression

Slow if no change in stage of breast, pubic hair, or genital development during 6 or more months of observation

Height velocity

Accelerated if more than 6 cm per year

Bone age advancement

Estimated adult height



Puberdade precoce ou avançada – que implicações

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