HORMONAL ASPECTS IN ADOLESECENTS

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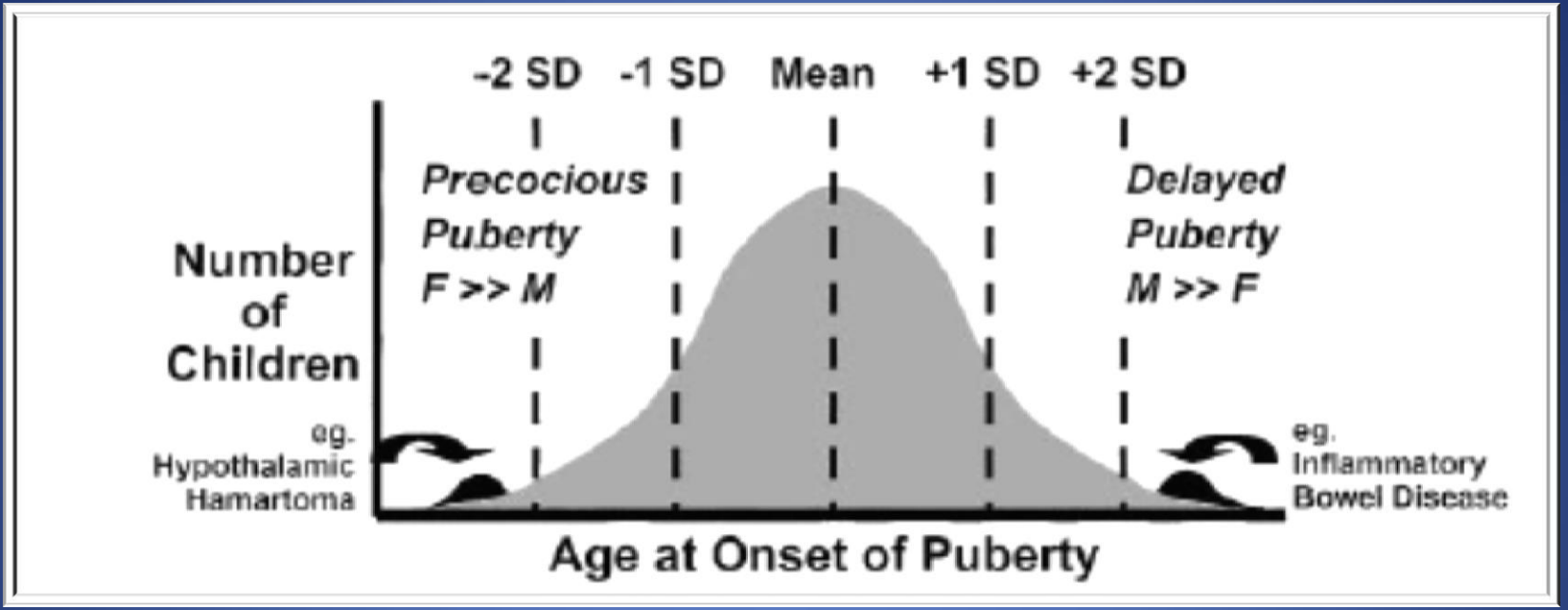
Advancing Children's Health Through Pediatric Laboratory Medicine. 29 July 2017

- I have nothing to declare

Topic outline

- Basic puberty
  - Adrenarche: Prepubertal & Peripubertal
  - Gonadarche: Pubertal
- Hormonal values by age
- Pitfalls
  - GH examination
    - Prepubertal dip
    - Diagnosis of GH deficiency
  - Sex steroid examination
    - Ontogeny of Gonadotrophin levels
    - Diagnosis of delayed or precocious puberty

Introduction

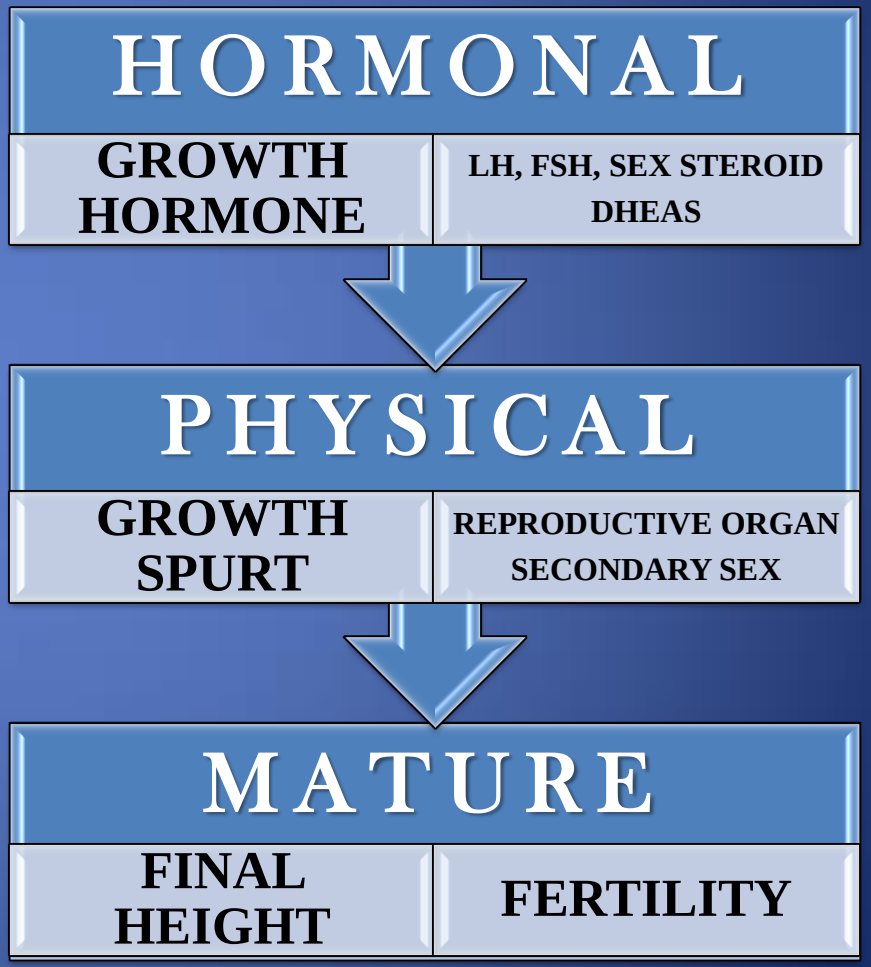


- Onset
  - Female : 8-13 years old
  - Male : 9.5-13.5 years old
- Basic changes
  - neuroendocrine : gonadotropin, sex steroid, and GH
  - biologic/physical : linear growth, body composition, reproductive organs

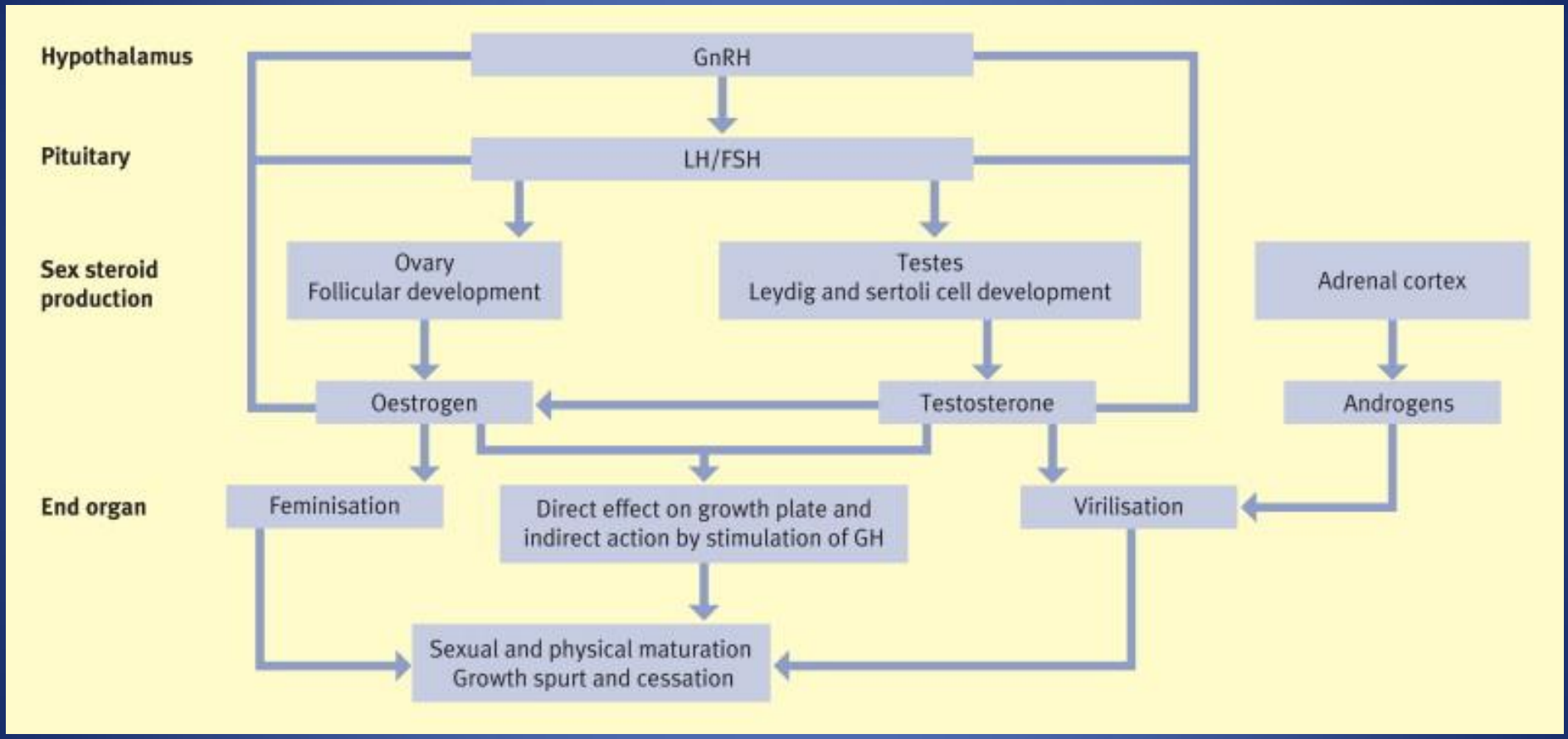
Introduction

Puberty

- ❑ Transition period between childhood to adult
- Maturation of reproductive organs and attainment of fertility“
- Termination of linear growth through estrogen

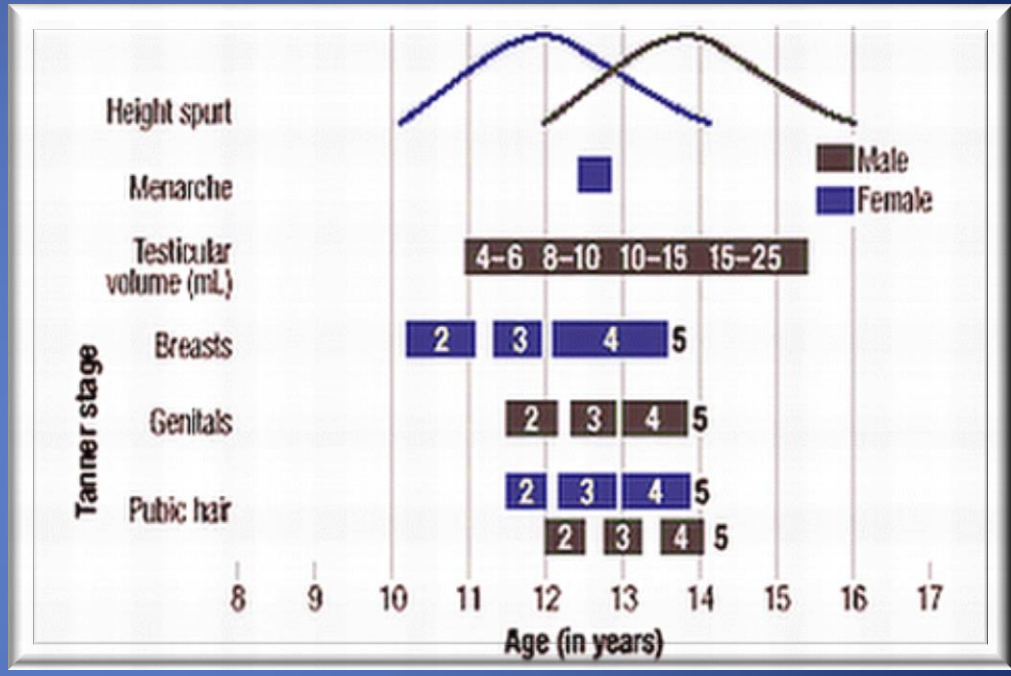


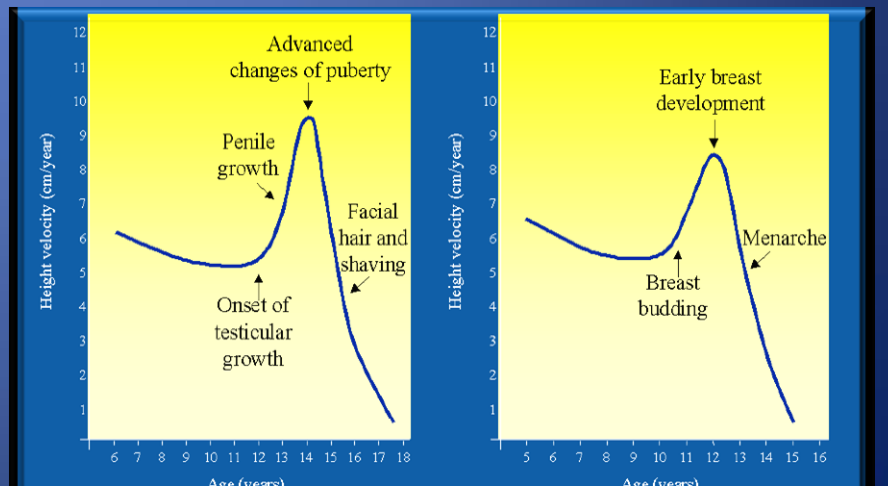
Puberty Development



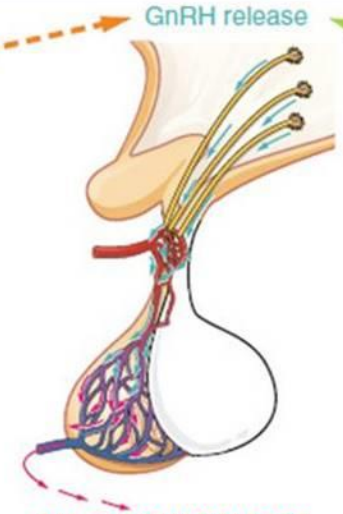
Puberty landmark

Event	Age (years)
Thelarche	10-11
Pubarche	10.5-11.5
Growth Spurt	11-12
Menarche	11.5-13
Adult Breast Development	12.5-15
Adult Sexual Hair	13.5-16





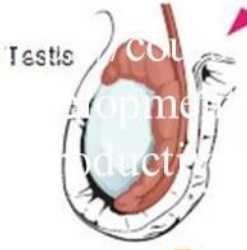
Pubertal Axis Development



① Beginning approximately age 8 yrs the hypothalamus increase its production of GnRH

② GnRH triggers anterior hypophysis to release LH and FSH

LH and FSH RELEASE



③ LH and FSH stimulates respective gonadal sex steroid

⑤ Before puberty the HHG axis threshold is high. At puberty the HHG axis threshold decreases ↓→ T & E2 secretion ↑ → 2nd ary Sexual charateristics develop

TESTOSTERONE

ESTROGEN

④ Effect of Sex steroid

Spermatogenesis

Male Secondary Sex Characteristics:
- Penis and scrotum grow
- Facial hair grows
- Larynx elongates, lowering voice
- Shoulders broaden
- Body, armpit, and pubic hair grow
- Musculature increases body-wide

Female Secondary Sex Characteristics:
- Breasts develop and mature
- Hips broaden
- Pubic hair grows

Folliculogenesis

https://courses.lumenlearning.com/ap2/chapter/development-of-the-male-and-female-reproductive-systems/

ADRENARCHE

Role of adrenarche

- Adrenarche is the prepubertal onset of increased adrenal secretion of DHEA, DHEA-S, and androstenedione and occurs in children at about age 6-8 years
- The hypothesis presented in the present paper proposes that adrenarche is a harbinger or promoter of gonadarche, an evolutionary safeguard, ensuring that gonadarche occurs earlier and perhaps with greater certainty than it would otherwise.
- The hypothesis proposed here is that adrenarche, which precedes gonadarche, provides the initial source of androgens, leading to the disinhibition of GnRH, and hence gonadarche

Nader. J Pediatr Adolesc Gynecol. 2007;20:353e360

Clinical signs

- Development of body odor, pubic and axillary hair
- occur after 8 years in both boys and girls
- onset is subject to wide individual variations.
- Progressive increase in the secretion of weak androgens by the adrenal glands, in particular dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), occurs until adult values are reached at about 15 years of age or in the mid- to late pubertal years.
- Precocious adrenarche will occur before the age of 8 years, usually between 5 and 7 years and is a common reason for referral to a pediatric endocrinology clinic. It is thought to be a normal variant of development as long as the growth velocity is in the pre pubertalrange, the bone age is at most only mildly advanced

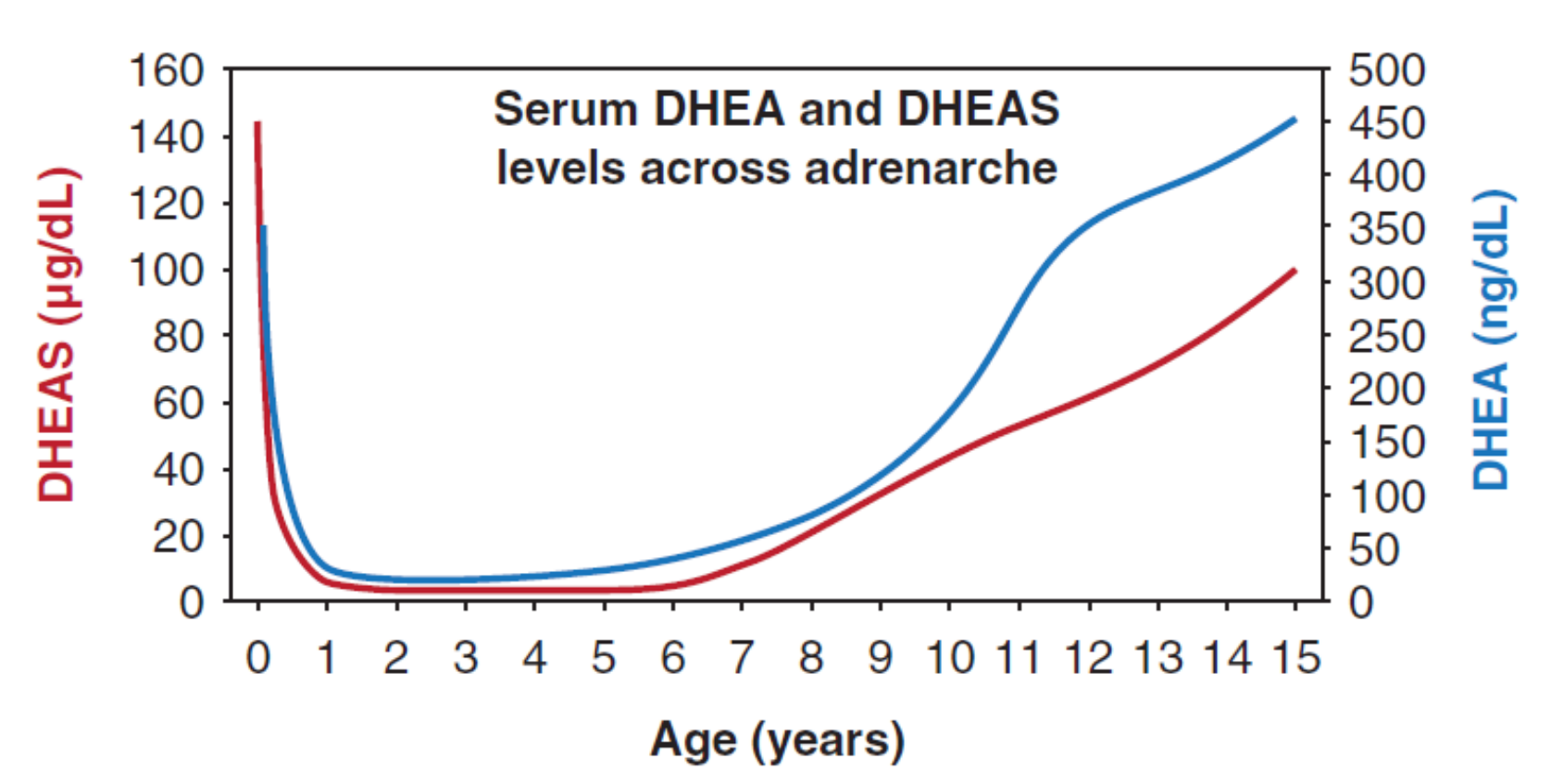
Granados A,Kasa-Vubu JZ. Pediatrics (Newsletter).2014;23:3-9

Adrenarche

- maturation zona reticularis of the adrenal gland, resulting in increased production of adrenal androgens associated with secondary sexual characteristics such as the development of pubic hair (pubarche), axillary hair, body odor, and acne.
- Adrenarche typically begins at the age of 8 years, but can occur as early as 6 years
- the onset of adrenarche appears to be a gradual, progressive maturational process that begins in early childhood and is marked by further increases in the production of adrenal androgens (DHEA, DHEA-S, androstenedione) around the time of puberty
- Adrenarche may precede gonadarche by 1 to 2 years in boys and girls, but the timing of clinical signs can vary.

Nathan BM, Palmert MR.Endocrinol Metab Clin N Am. 2005;34: 617–641

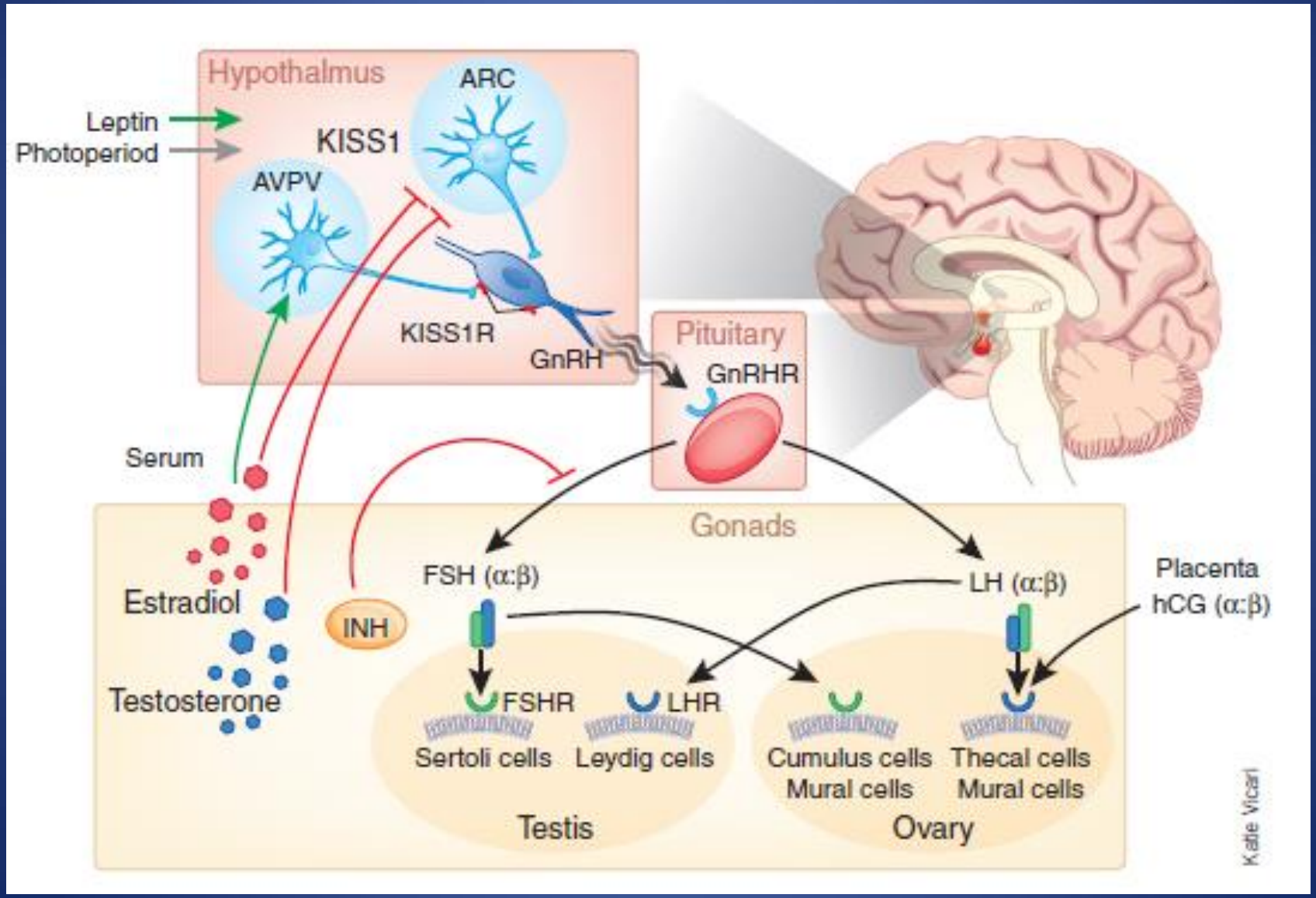
Serum DHEA and DHEAS levels before and after the onset of human adrenarche.



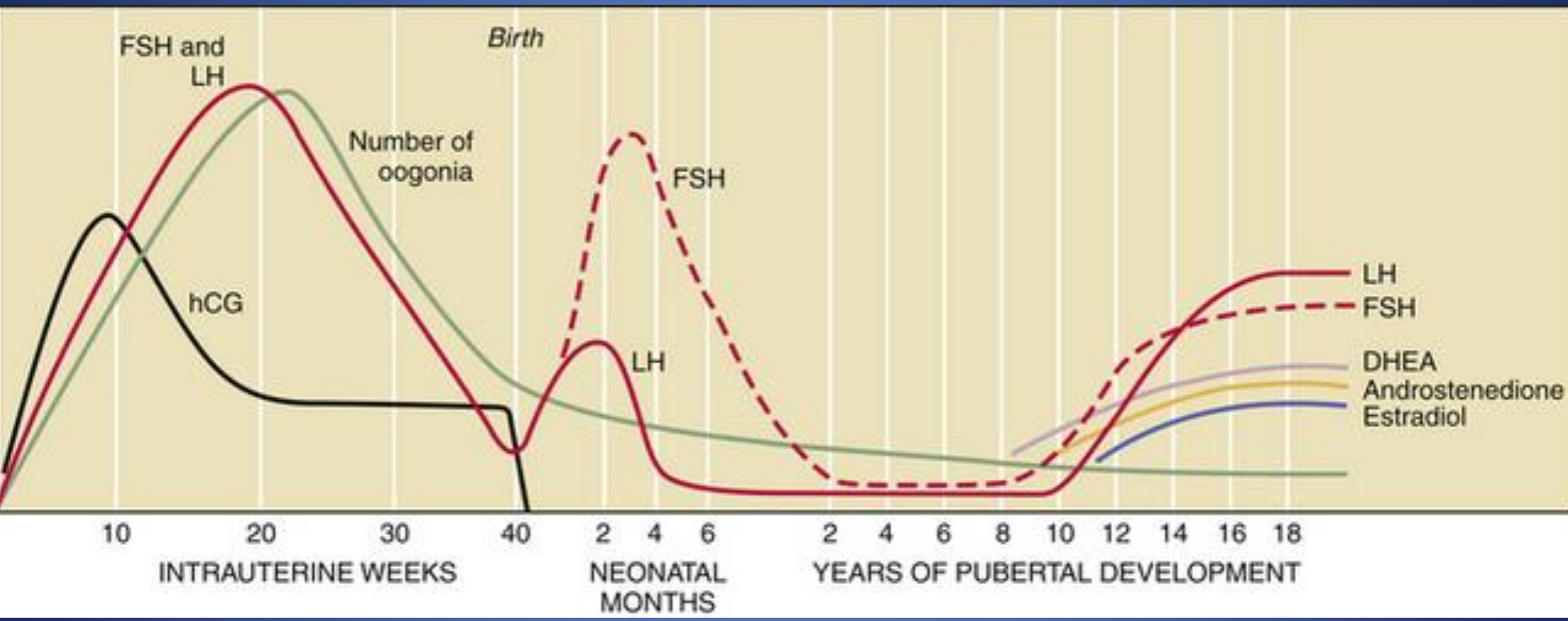
Rege, Rainey. J Endocrinol. 2012; 214:133–143

GONADOTROPHIN

HPG Axis


Hypothalmus
ARC
Leptin
Photoperiod
KISS1
AVPV
KISS1R
GnRH
Pituitary
GnRHR
Serum
Gonads
Estradiol
Testosterone
INH
FSH (α:β)
LH (α:β)
Placenta
hCG (α:β)
FSHR
LHR
Sertoli cells
Leydig cells
Cumulus cells
Mural cells
Thecal cells
Mural cells
Testis
Ovary
Katie Vicari

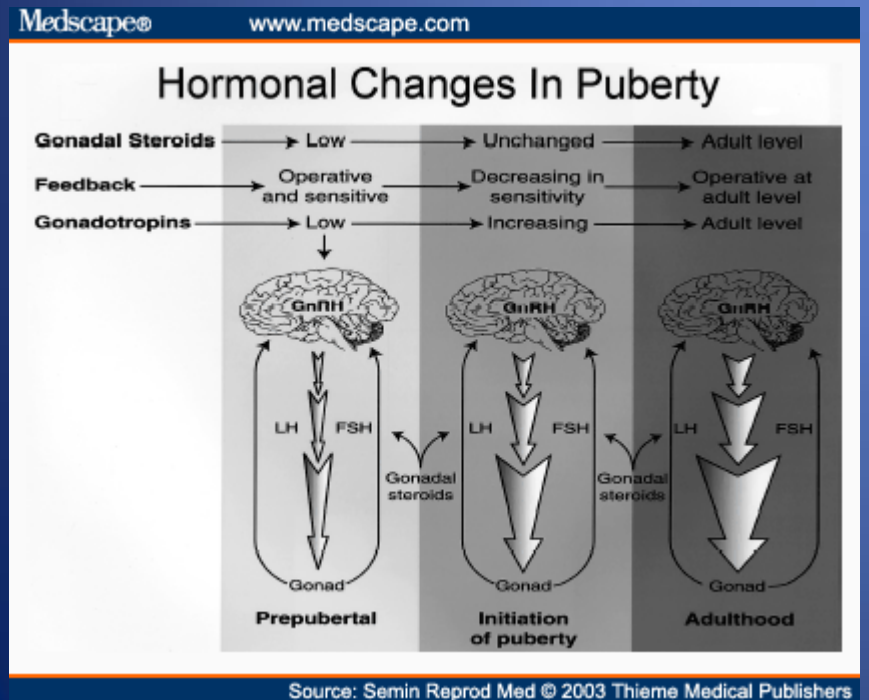
Pattern of gonadotropin secretion

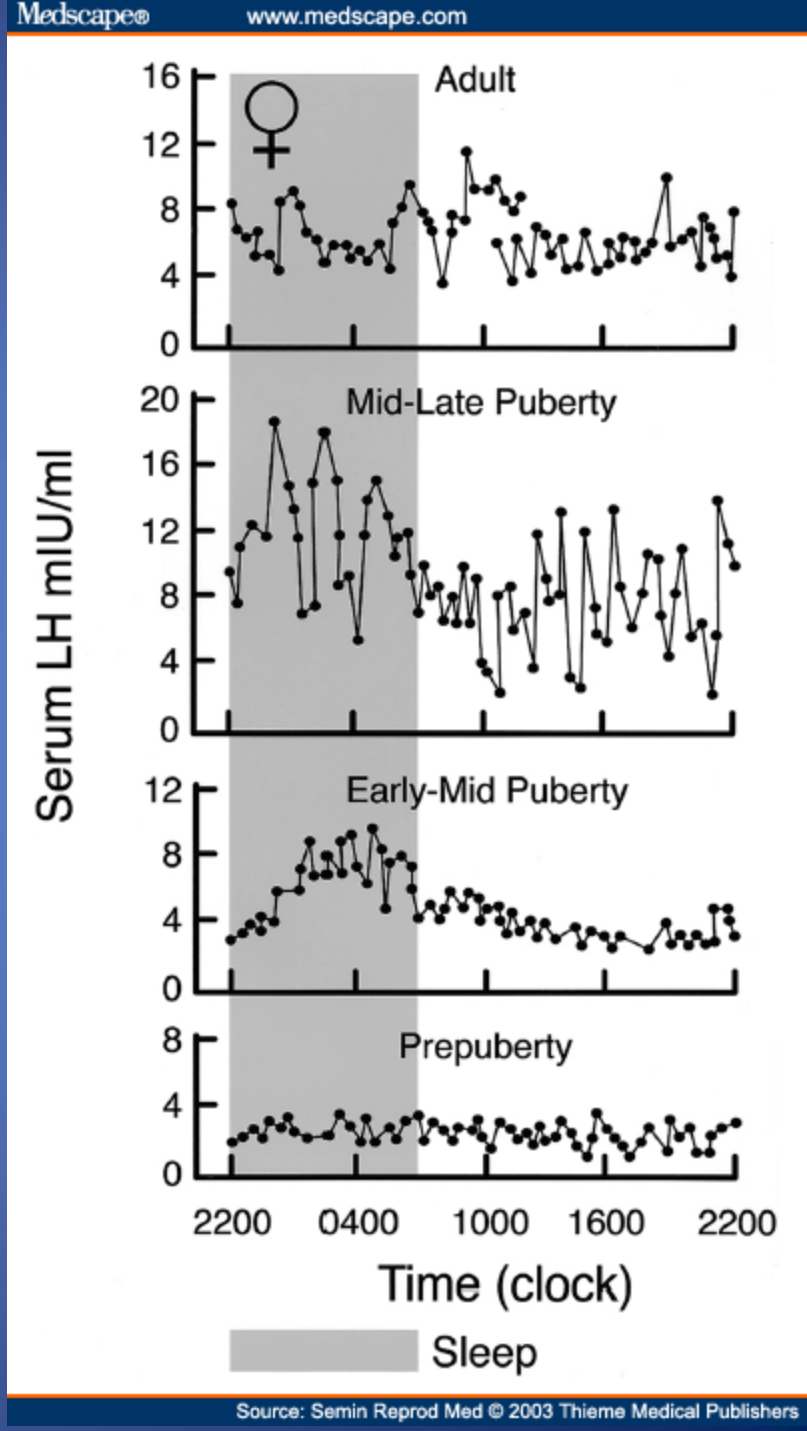


https://obgynkey.com/wp-content/uploads/2016/06/B978141605940000031X_gr2.jpg

Normal Puberty: Endocrine control

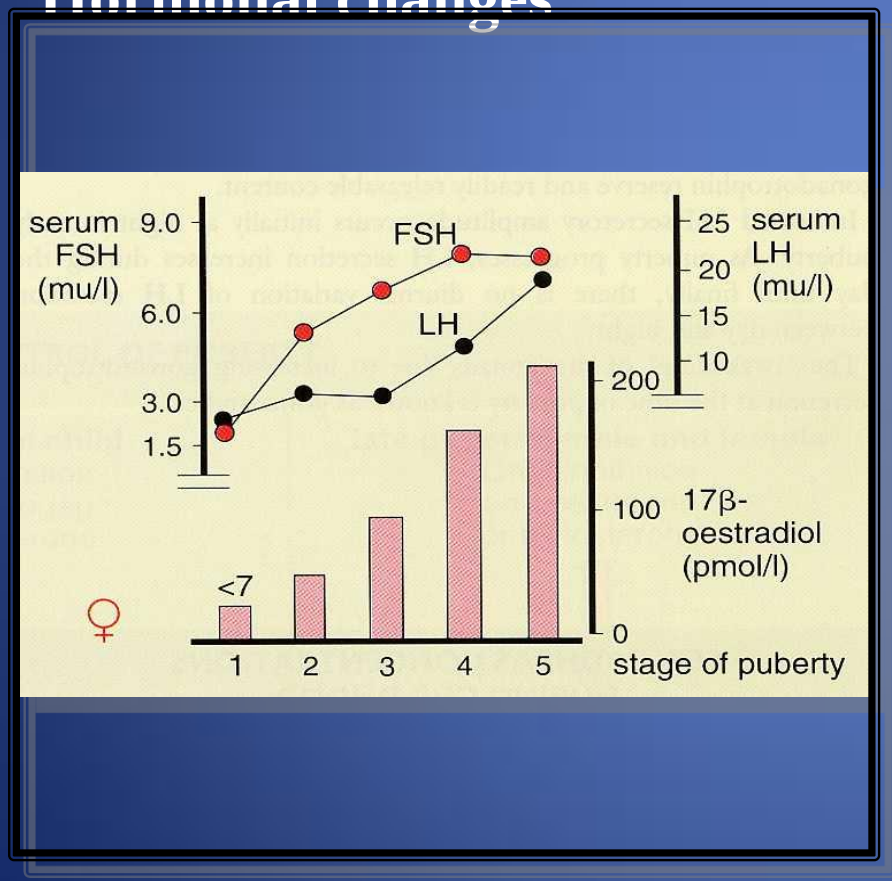
Serum LH levels throughout the pubertal stages. Note nocturnal release initially in early puberty.



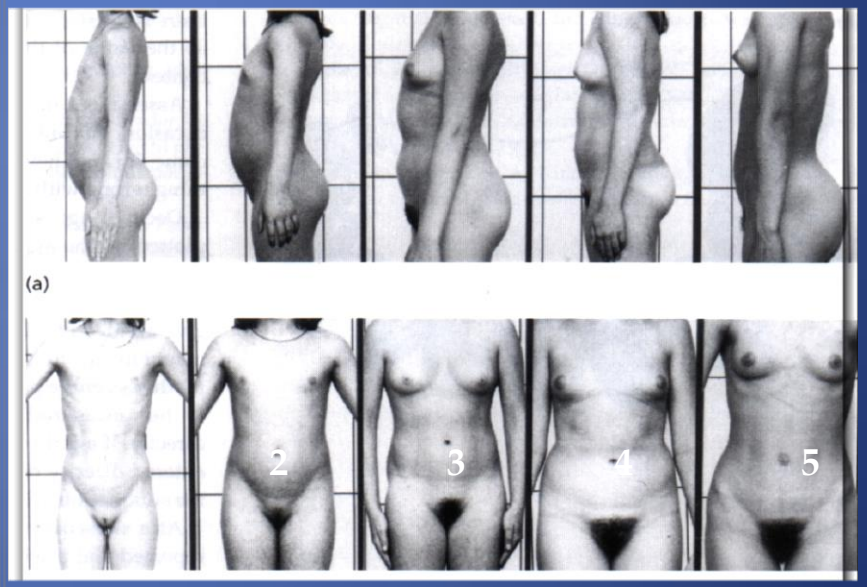


LH, FSH and E2 - PUBERTAL STAGE

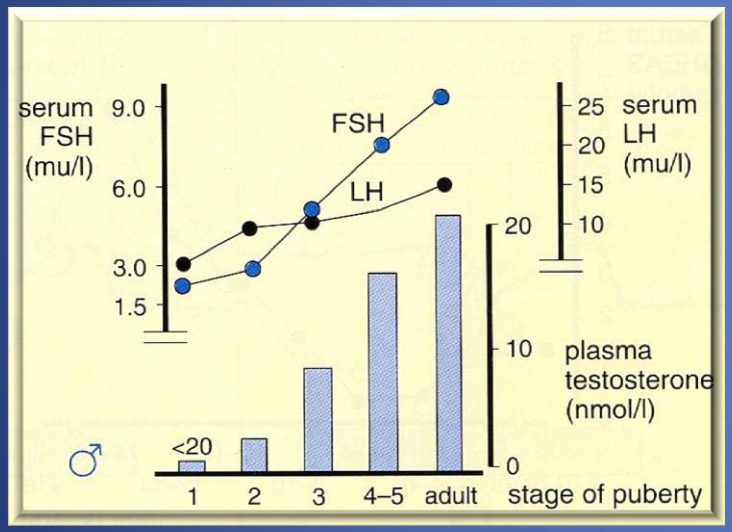
Hormonal changes

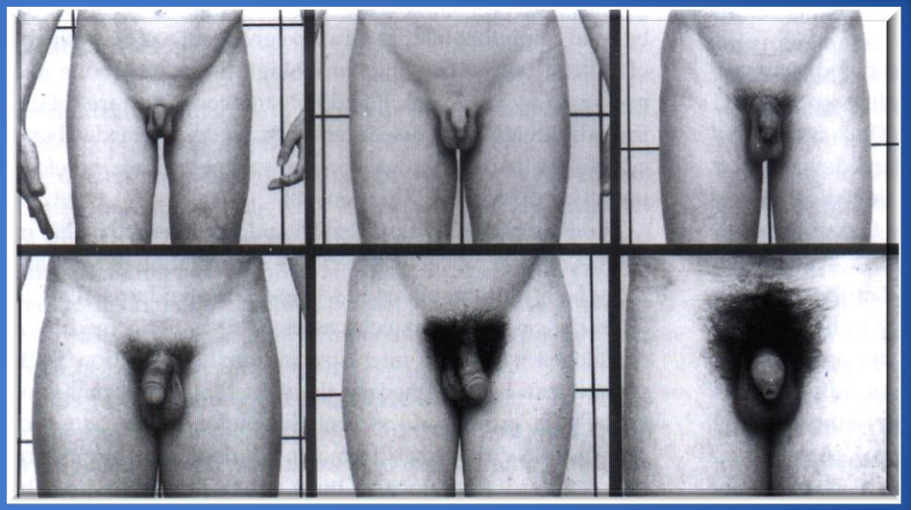


Secondary sexual characteristic changes (tanner stage)



LH, FSH and Testosterone and PUBERTAL STAGE

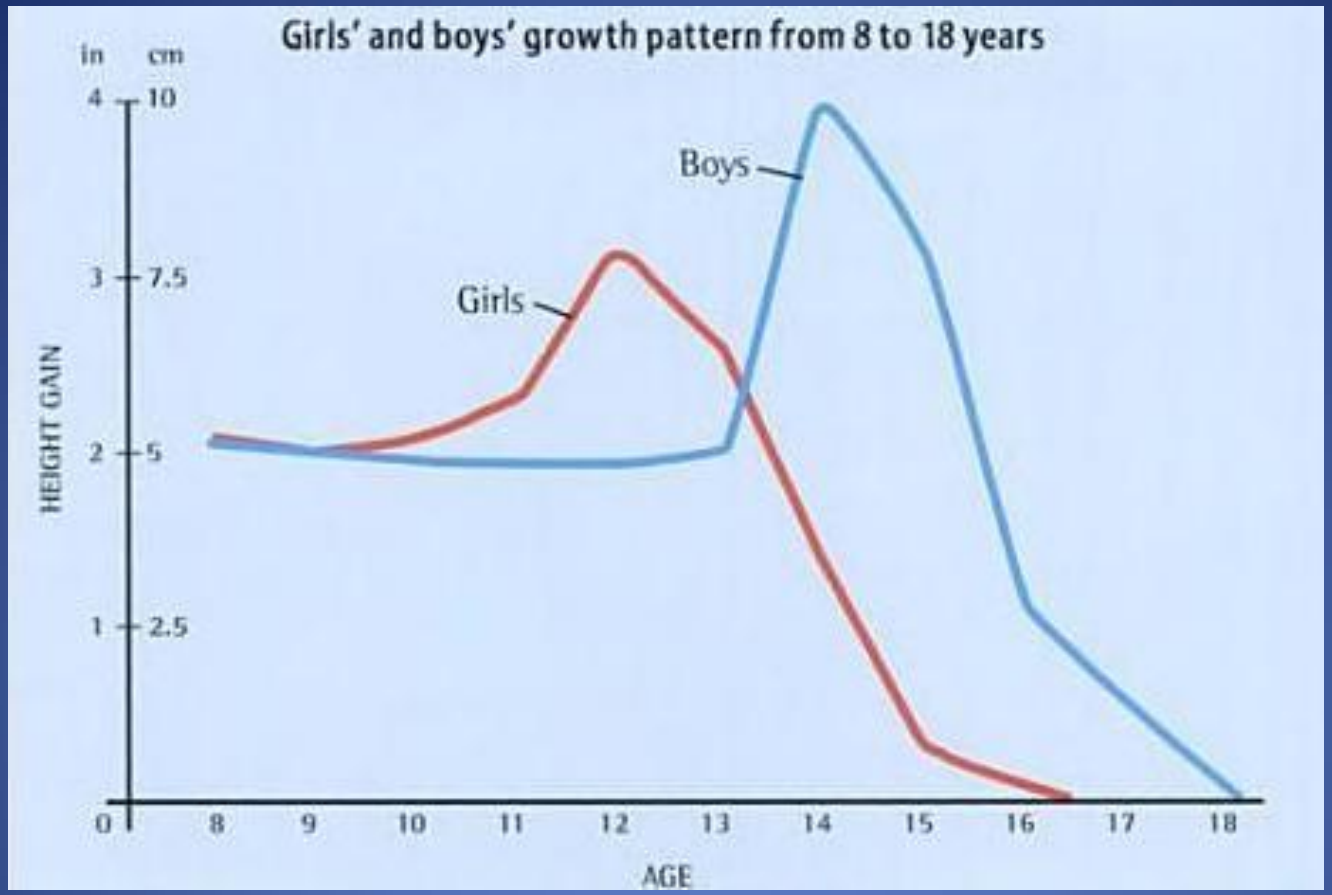




The diagnosis and differential diagnosis of normal variants and pathological types of puberty

Early normal or pathological puberty		Late normal or pathological puberty	
Pathological entity	**Normal variant**	**Normal variant**	**Pathological entity**
True precocious puberty	Mammary gland hyperplasia of the newborn	(Pubertas tarda)	Hypergonadotropic hypogonadism
Precocious pseudopuberty	Premature thelarche	(Pubertas tarda)	Hypogonadotropic hypogonadism
Premature adrenarche	Premature pubarche	(Pubertas tarda)	
	Constitutional or idiopathic acceleration of growth and puberty	Constitutional or idiopathic delay of growth and puberty	

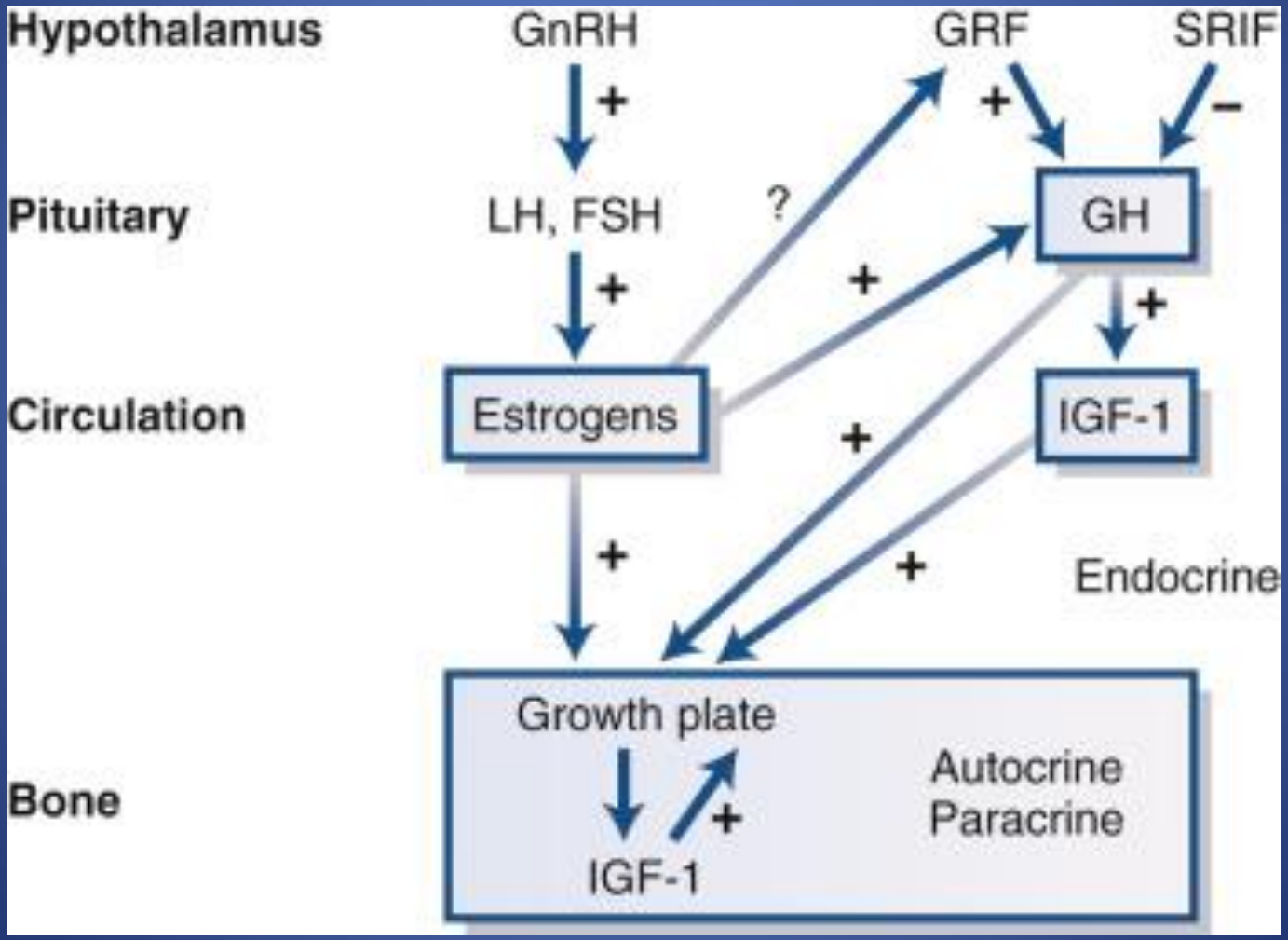
Brämswig & Dübbers. Dtsch Arztebl Int. 2009;106:295–304.



GROWTH IN ADOLESCENT

Normal variants of growth were found in 82% of children whose height decreased at the third percentile (-2 SD) but in only 50% of those whose height decreased at the first percentile (-3 SD) of the mean for age. (Lacy et al. Arch Dis Child 1974;49:417–24)

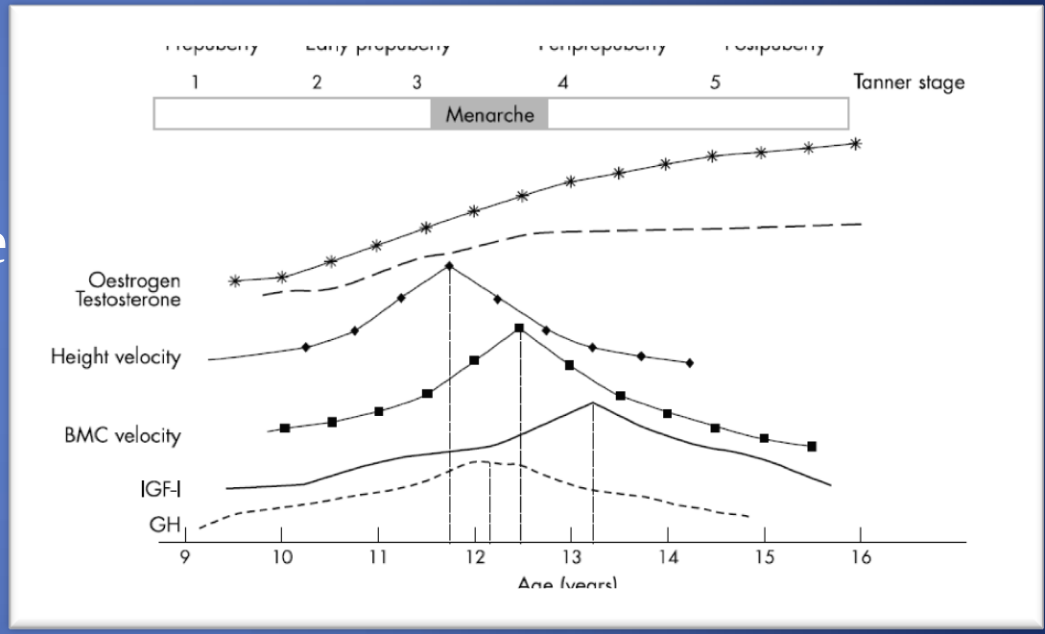
Interactions of the major growth-promoting hormones during puberty.



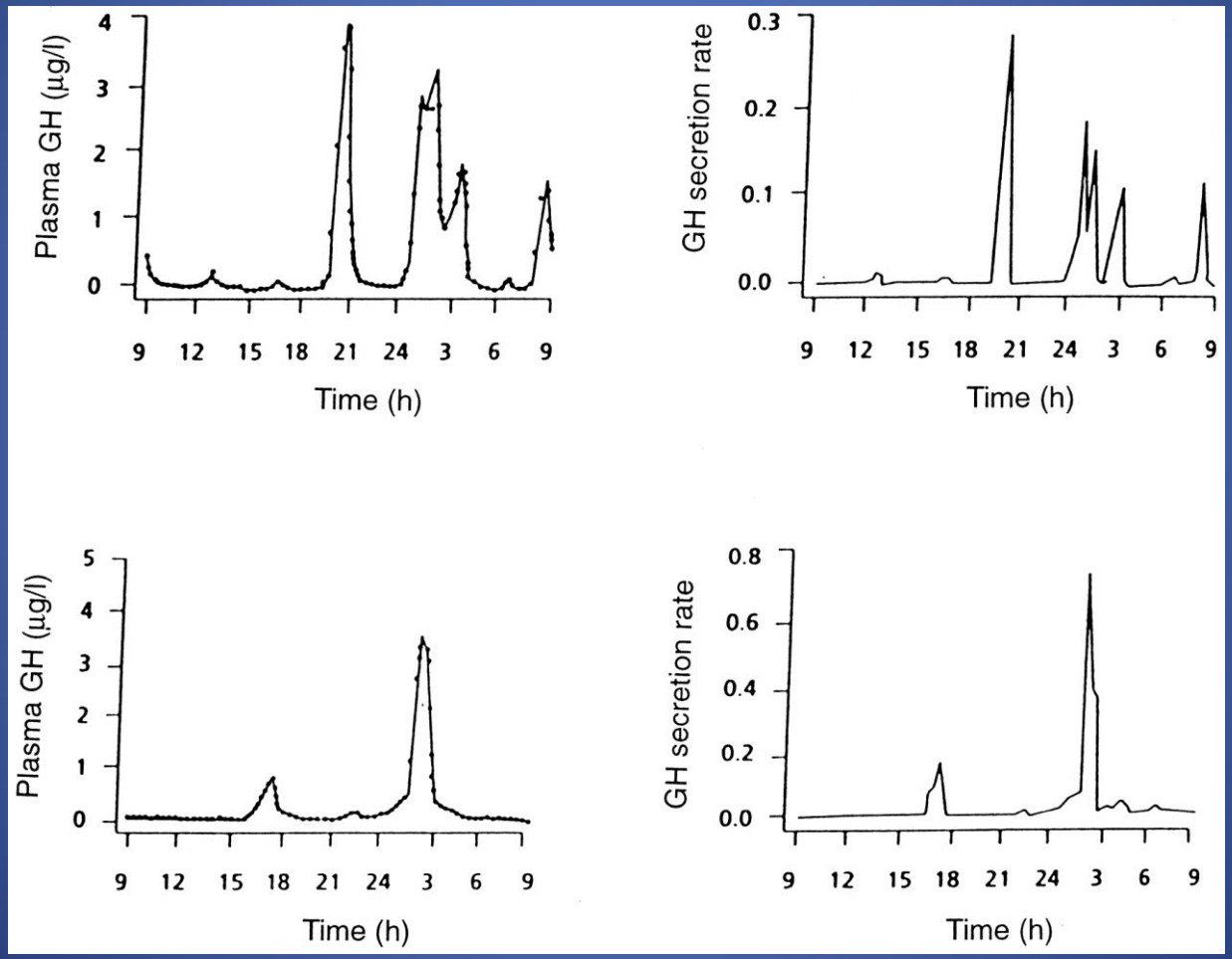
Styne, Grumbach. Williams Textbook of Endocrinology. 2016. p1074-1218

GH in puberty

- GH secretion ↑ in accordance with LH/FSH ↑ at onset
- Girl higher basal levels during puberty – maximal approximately at menarche and subsequently decline
- GH secretion highly pulsatile – most occur during sleep
- Sex steroid increases amplitude more than frequency



Growth hormone secretion and pulse



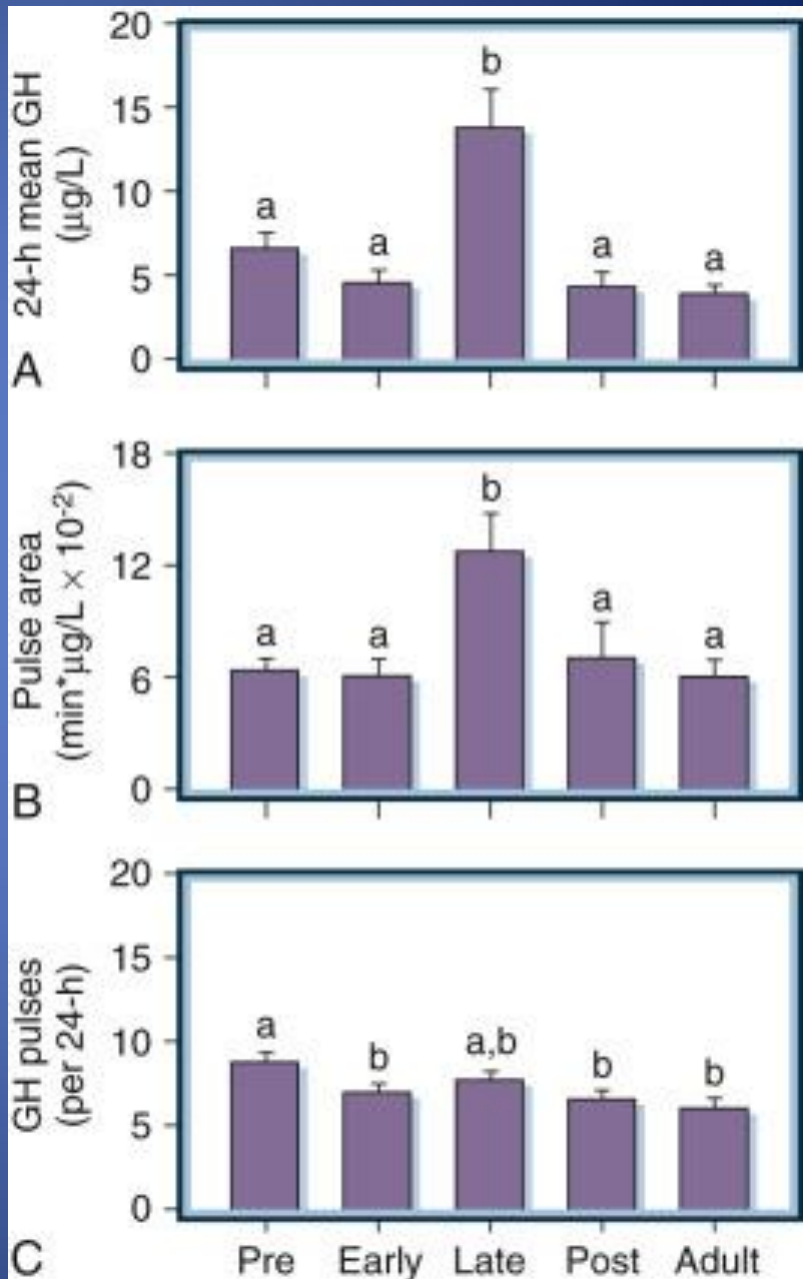
Muller et al. Physiological Reviews.1999;79:511-607

ALTERATIONS IN THE PULSATILE PROPERTIES OF CIRCULATING GROWTH HORMONE CONCENTRATIONS DURING PUBERTY IN BOYS

A, The 24-hour and standard error (+SE) levels of growth hormone (GH) for groups of normal boys at varied stages of pubertal maturation

B, The mean (+SE) area under the GH concentration-versus-time curve for individual GH pulses, as identified by the cluster pulse detection algorithm.

C, The number of GH pulses (+SE), as detected by the cluster algorithm, in the 24-hour GH concentration profiles for boys in each of the pubertal study groups.

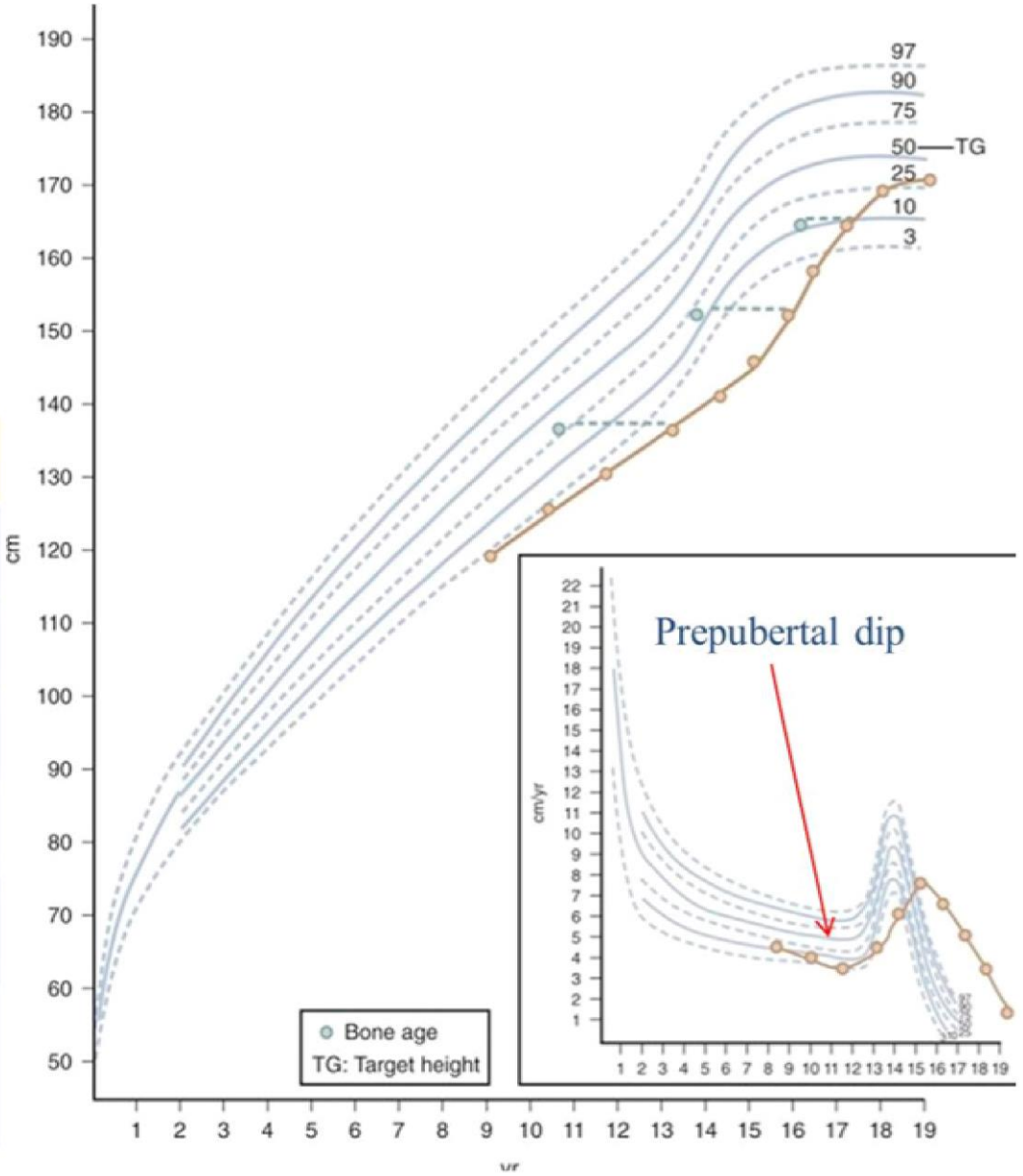


Cooke DW, Divall SA, Radovick S. In: Williams Textbook of Endocrinology. 2016. p 964-1073

Constitutional Delay of Growth and Puberty

Feature	Constitutional Short Stature
1) Sex	More common in boys
2) Family History	Of delayed puberty
3) Height Velocity	Normal
4) Puberty	Delayed
5) Bone Age	Less than chronological age
6) Final Height	Normal

atiality series Endocrinology 2nd edition



Constitutional Delay of Growth and Puberty vs Hypogonadotrophic Hypogonadism

Test	CDGP	HH
Testicular volume	> 4 mL	< 4 mL
Basal T	>1.7 nmol/L	< 1.7 nmol/L
T response to hCG (1500 U EODIMX3)[13]	> 8 nmol/L	< 3 nmol/L
LH after GnRH test (Nafarelin 0.1 mg/m^2)[14]	Increment > 4.6 U/L	Incre ment < 2 U/L
LH (3 h) after tripyorelin (0.1 mg/m^2)[12]	LH > 14	LH < 14
T after hCG × 3 days[12]	T > 9 nmol/L	T < 9 nmol/L
LH (4 h) after decapeptyl (0.1 mg/m^2)[13]	LH > 8 U/L	LH < 8 U/L
T (7th day) after hCG ×3 (EOD)[13]	T > 8 nmol/L	T < 8 nmol/L
T after 24 h of IM low-dose hCG (15 U/kg-once)[15]	T > 6 nmol/L	T < 6 nmol/L
LH after low-dose GnRH (10 mcg IV)[16]	++ Response	No response

Soliman & de Sanctis.Indian J Endocrinol Metab. 2012;16:698-705

LAB REFERENCE VALUE

IGF-1 (Insulin-like Growth Factor 1)

BLOOD ASSAYS

MALE CHILDREN - RANGES BY TANNER STAGE:

	Tanner 1		Tanner 2 & 3		Tanner 4 & 5	
Age	Range (ng/mL)	Mean (ng/mL)	Range (ng/mL)	Mean (ng/mL)	Range (ng/mL)	Mean (ng/mL)
3 Years	20 – 141	63				
4 Years	25 – 157	73				
5 Years	30 – 174	84				
6 Years	37 – 192	96				
7 Years	44 – 211	109				
8 Years	52 – 231	123	39 – 264	121		
9 Years	61 – 252	137	52 – 304	146		
10 Years	71 – 275	153	67 – 347	174		
11 Years	82 – 299	170	86 – 393	206	277 – 673	449
12 Years	93 – 324	188	106 – 443	240	265 – 652	433
13 Years	106 – 350	207	130 – 497	277	241 – 612	401
14 Years	120 – 377	227	156 – 554	318	220 – 574	372
15 Years	127 – 391	237	185 – 616	362	199 – 537	343
16 Years			201 – 648	386	180 – 501	316
17 Years					161 – 467	290
18 Years					144 – 434	266
Total N Subjects	Tanner 1:	254	Tanner 2 & 3:	199	Tanner 4 & 5:	111

(The IGF-1 reference intervals by pubertal tanner stage reflect ranges and means based on asymmetric curves. Please contact the laboratory for Z-Score calculations based on the asymmetric curves with transformed data.)

Ranges continued on next page

IGF-1 (Insulin-like Growth Factor 1)

BLOOD ASSAYS

FEMALE CHILDREN - RANGES BY TANNER STAGE:

	Tanner 1		Tanner 2		Tanner 3		Tanner 4 & 5	
Age	Range (ng/mL)	Mean (ng/mL)	Range (ng/mL)	Mean (ng/mL)	Range (ng/mL)	Mean (ng/mL)	Range (ng/mL)	Mean (ng/mL)
3 Years	26 – 162	77						
4 Years	32 – 179	88						
5 Years	39 – 198	100						
6 Years	47 – 217	113						
7 Years	55 – 238	127						
8 Years	64 – 259	142	89 – 369	181				
9 Years	74 – 282	158	96 – 399	196	192 – 568	350		
10 Years	85 – 306	175	104 – 431	212	192 – 568	350	279 – 664	446
11 Years	97 – 332	194	112 – 466	229	192 – 568	350	268 – 646	433
12 Years	110 – 358	213	121 – 504	247	192 – 568	350	248 – 612	406
13 Years			131 – 545	267	192 – 568	350	229 – 579	380
14 Years			136 – 566	278	192 – 568	350	211 – 547	356
15 Years					192 – 568	350	194 – 516	332
16 Years							177 – 487	309
17 Years							162 – 458	287
18 Years							147 – 430	266
Total N Subjects	Tanner 1:	138	Tanner 2:	158	Tanner 3:	114	Tanner 4 & 5:	155

(The IGF-1 reference intervals by pubertal tanner stage reflect ranges and means based on asymmetric curves. Please contact the laboratory for Z-Score calculations based on the asymmetric curves with transformed data.)

Ranges continued on next page

Sex Steroid – Tanner Staging HPLC/MS-MS

PUBERTY — **Testosterone**

Male				Female			
Tanner Stage	Age (years)	Range (ng/dL)	Mean (ng/dL)	Tanner Stage	Age (years)	Range (ng/dL)	Mean (ng/dL)
1	<9.8	<3		1	<9.2	<3	
2	9.8 – 14.5	3 – 17	8	2	9.2 – 13.7	5 – 12	8
3	10.7 – 15.4	8 – 33	19	3	10.0 – 14.4	7 – 19	12
4	11.8 – 16.2	22 – 52	36	4	10.7 – 15.6	4 – 13	7
5	12.8 – 17.3	24 – 65	43	5	11.8 – 18.6	3 – 18	9

PUBERTY — **Estradiol**

Male				Female			
Tanner Stage	Age (years)	Range (pg/mL)	Mean (pg/mL)	Tanner Stage	Age (years)	Range (pg/mL)	Mean (pg/mL)
1	<9.8	5.0 – 11	8.0	1	<9.2	5.0 – 20	8.0
2	9.8 – 14.5	5.0 – 16	11	2	9.2 – 13.7	10 – 24	16
3	10.7 – 15.4	5.0 – 25	16	3	10.0 – 14.4	7.0 – 60	25
4	11.8 – 16.2	10 – 36	22	4	10.7 – 15.6	21 – 85	47
5	12.8 – 17.3	10 – 36	21	5	11.8 – 18.6	34 – 170	110

Gonadotrophin – Tanner Staging ECL

PREPUBERTAL CHILDREN
12 Months – 8 Years: 0.02 – 0.3

PUBERTY **Luteinizing Hormone**

Male				Female			
Tanner Stage	Age (years)	Range (mIU/mL)	Mean (mIU/mL)	Tanner Stage	Age (years)	Range (mIU/mL)	Mean (mIU/mL)
1	<9.8	0.02 – 0.3	0.09	1	<9.2	0.02 – 0.18	0.06
2	9.8 – 14.5	0.2 – 4.9	1.8	2	9.2 – 13.7	0.02 – 4.7	0.72
3	10.7 – 15.4	0.2 – 5.0	1.9	3	10.0 – 14.4	0.10 – 12.0	2.3
4 – 5	11.8 – 17.3	0.4 – 7.0	2.6	4 – 5	10.7 – 18.6	0.4 – 11.7	3.3

PREPUBERTAL CHILDREN	MALE	FEMALE
12 Months – 8 Years:	0.26 – 3.0	1.0 – 4.2

PUBERTY **Follicle Stimulating Hormone**

Male				Female			
Tanner Stage	Age (years)	Range (mIU/mL)	Mean (mIU/mL)	Tanner Stage	Age (years)	Range (mIU/mL)	Mean (mIU/mL)
1	<9.8	0.26 – 3.0	0.98	1	<9.2	1.0 – 4.2	2.1
2	9.8 – 14.5	1.8 – 3.2	2.5	2	9.2 – 13.7	1.0 – 10.8	4.0
3	10.7 – 15.4	1.2 – 5.8	2.9	3	10.0 – 14.4	1.5 – 12.8	5.1
4	11.8 – 16.2	2.0 – 9.2	4.4	4	10.7 – 15.6	1.5 – 11.7	6.4
5	12.8 – 17.3	2.6 – 11.0	6.1	5	11.8 – 18.6	1.0 – 9.2	4.9

Reference Lab

Age Group	Testosterone*		LH (IU/L)**		FSH (IU/L)**		Estradiol*	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Newborn	75-400	20-64						
Prepubertal							<1.5	<1.5
Tanner stage 1	<16	<16	0.3-2	≤ 2	≤ 3.7	0.4-6.7	0.5-1.1	0.5-2
Tanner stage 2	<167	<40	0.3-5.1	≤ 6.5	≤ 12.2	0.5-8.7	0.5-1.6	1-2.4
Tanner stage 3	7-762	<60	0.3-6.9	0.3-17.2	≤ 17.4	1.2-11.4	0.5-2.5	0.7-6
Tanner stage 4	25-912	<62	0.5-5.3	0.5-26.3	0.3-8.2	0.7-12.8	1-3.6	2.1-8.5
Tanner stage 5	110-975	<68	0.8-11.8	0.6-13.7	1.1-12.9	1/0-11/6	1-3.6	3.4-17

Note: *esoterix from Williams textbook of endocrinology
** Mayo Clinic

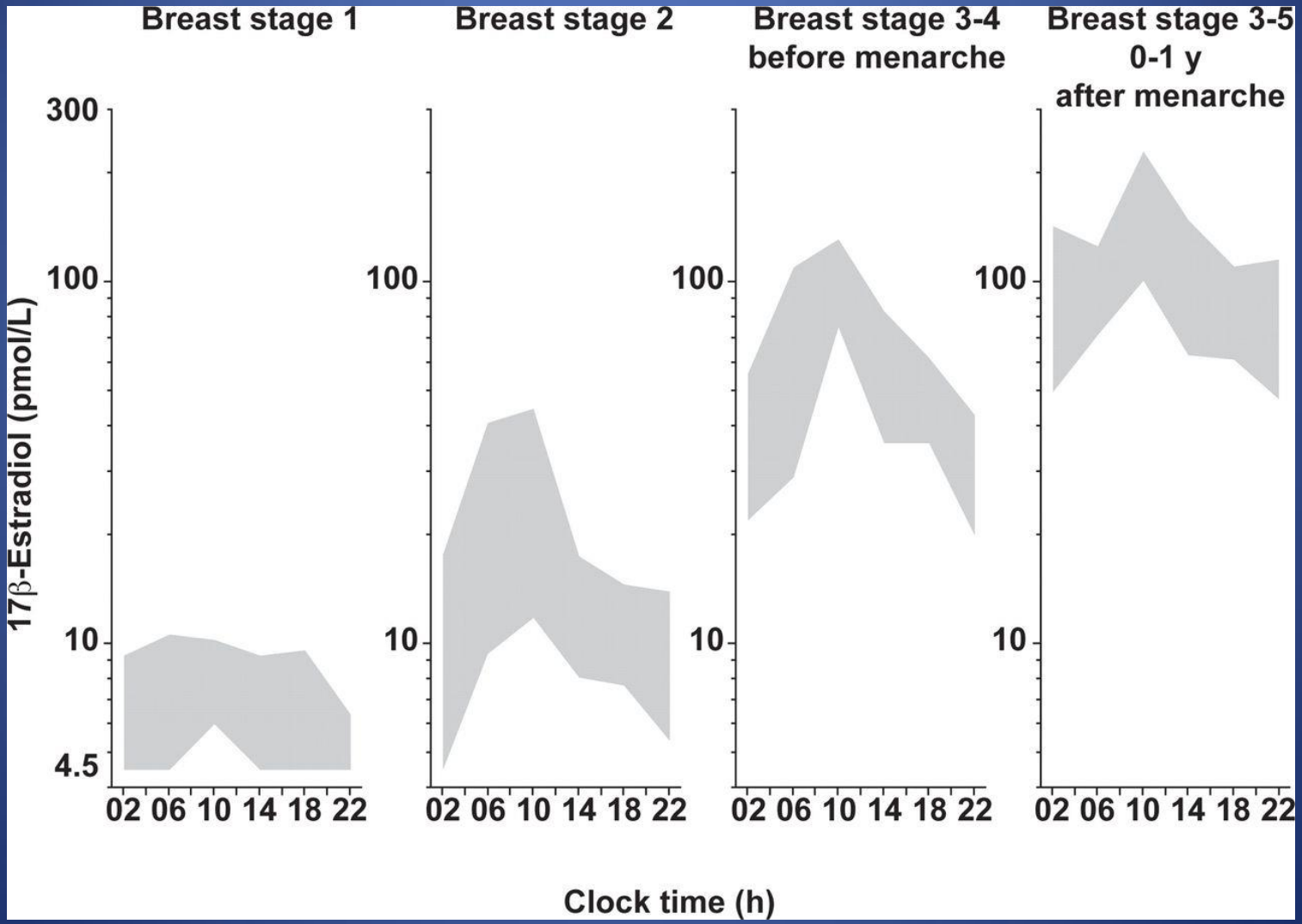
TABLE 25-5

Mean Values of Various Body Measurements and Serum Hormone Levels by Pubertal Stage in Boys (Ohio)*

Variable	PS1	PS2a	PS2b	PS3	PS4	PS5
Age (yr)	11.44 (NS)	12.18	12.79	13.74	14.63	15.19
Height (cm)	144.2	149.8	154.6	162.3	169.9	173.3
Weight (kg)	38.18	41.65	47.27	54.67	61.11	66.88
Body mass index (kg/m^2)	18.1	18.4	19.5	20.6	21.0	22.2
Testosterone (nmol/L [ng/dL])						
Blacks	0.8 (23)	3.0 (86)	4.9 (141)	11.5 (331)	13.4 (338)	15.5 (449)
Whites	0.6 (16)	2.9 (83)	4.6 (132)	9.7 (281)	13.3 (383)	14.6 (422)
Free testosterone (pmol/L [ng/dL])	11 (0.33)	60 (1.74)	114 (3.28)	294 (8.49)	413 (11.9)	504 (14.5)
DHEAS (µmol/L [µg/dL])	2.71 (99.7)	3.31 (121.8)	4.04 (148.7)	4.75 (175.0)	5.08 (187.0)	5.89 (217.0)
TeBG (nmol/L)	34.6 (NS)	33.3 (NS)	28.4	21.5	14.4	10.7

Styne, Grumbach. Williams Textbook of Endocrinology. 2016. p1074-1218

24-hour secretion pattern of serum estradiol in healthy prepubertal and pubertal girls



Conclusion

- Significant hormonal changes during puberty
- Hormonal levels interpretation accordant with pubertal stage
- Hormone characteristic important to correct interpretation
- Normal hormonal levels during puberty identical to optimal health status of adolescent