

PERCORSI DECISIONALI PER LA GESTIONE
DEL BAMBINO E DELL'ADOLESCENTE



16 - 21 LUGLIO 2011

Centro Congressi Kaya Artemis
Famagosta - Cipro Nord
(Turchia)

PUBARCA PREMATURO

S. BERNASCONI

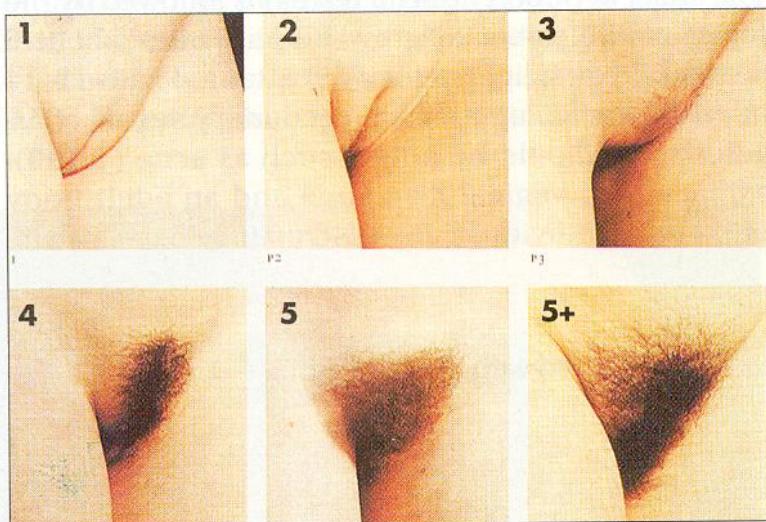
CLINICA PEDIATRICA

UNIVERSITÀ DI PARMA

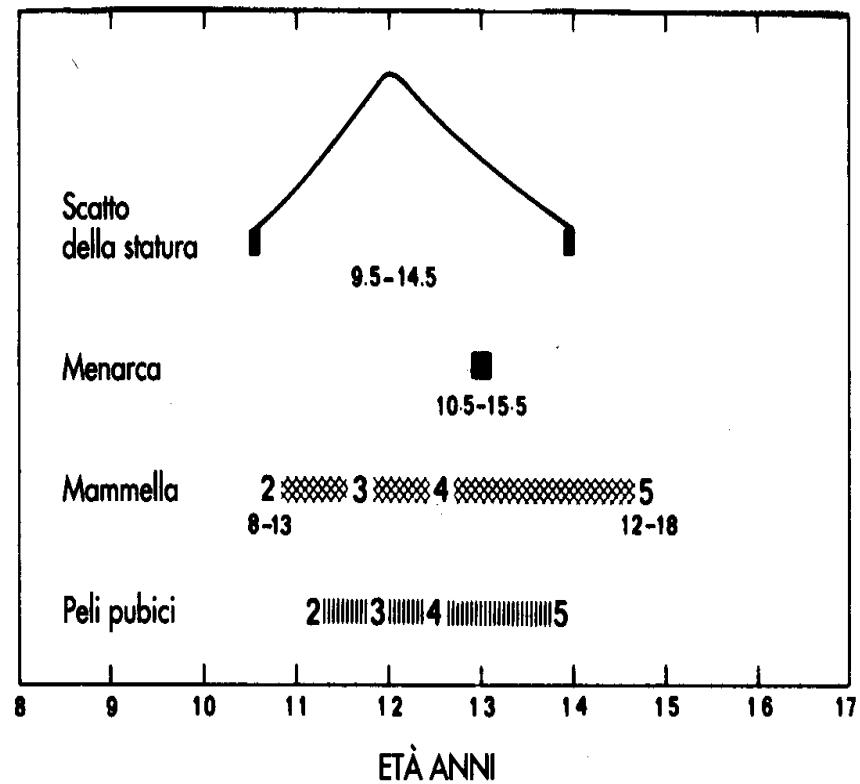
sbernasconi@ao.pr.it



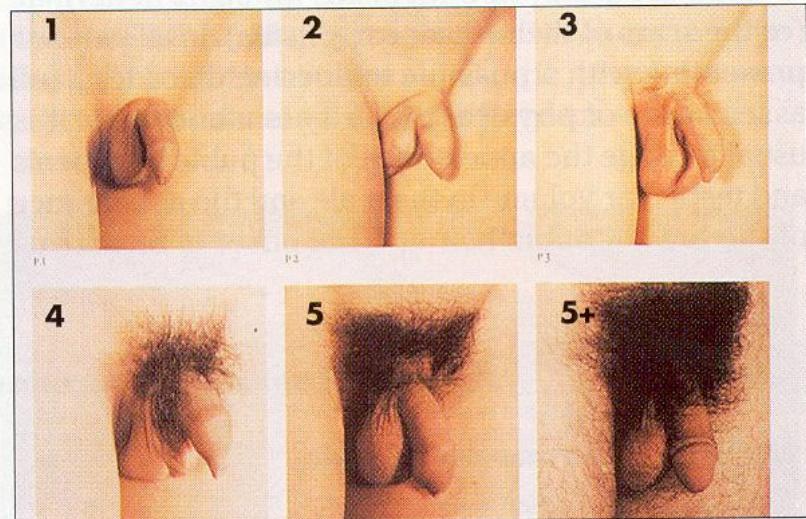
PUBARCA



1.96 Female pubic hair stages 1-5+.



PUBARCA



1.97 Male penis and pubic hair development stages 1–5+.

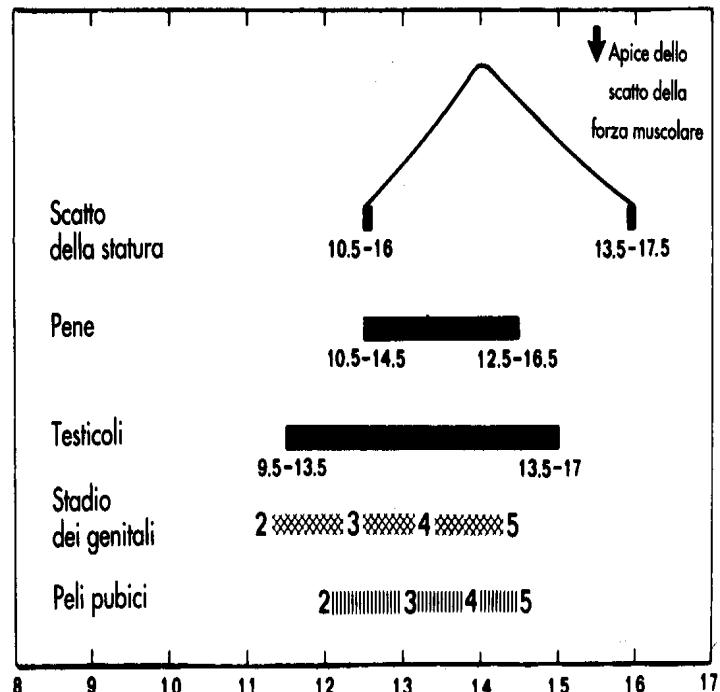


Figura 22 Schema della successione degli eventi puberali nelle donne (sopra) e nei maschi (sotto).
(Da Marshall & Tanner, 1970)

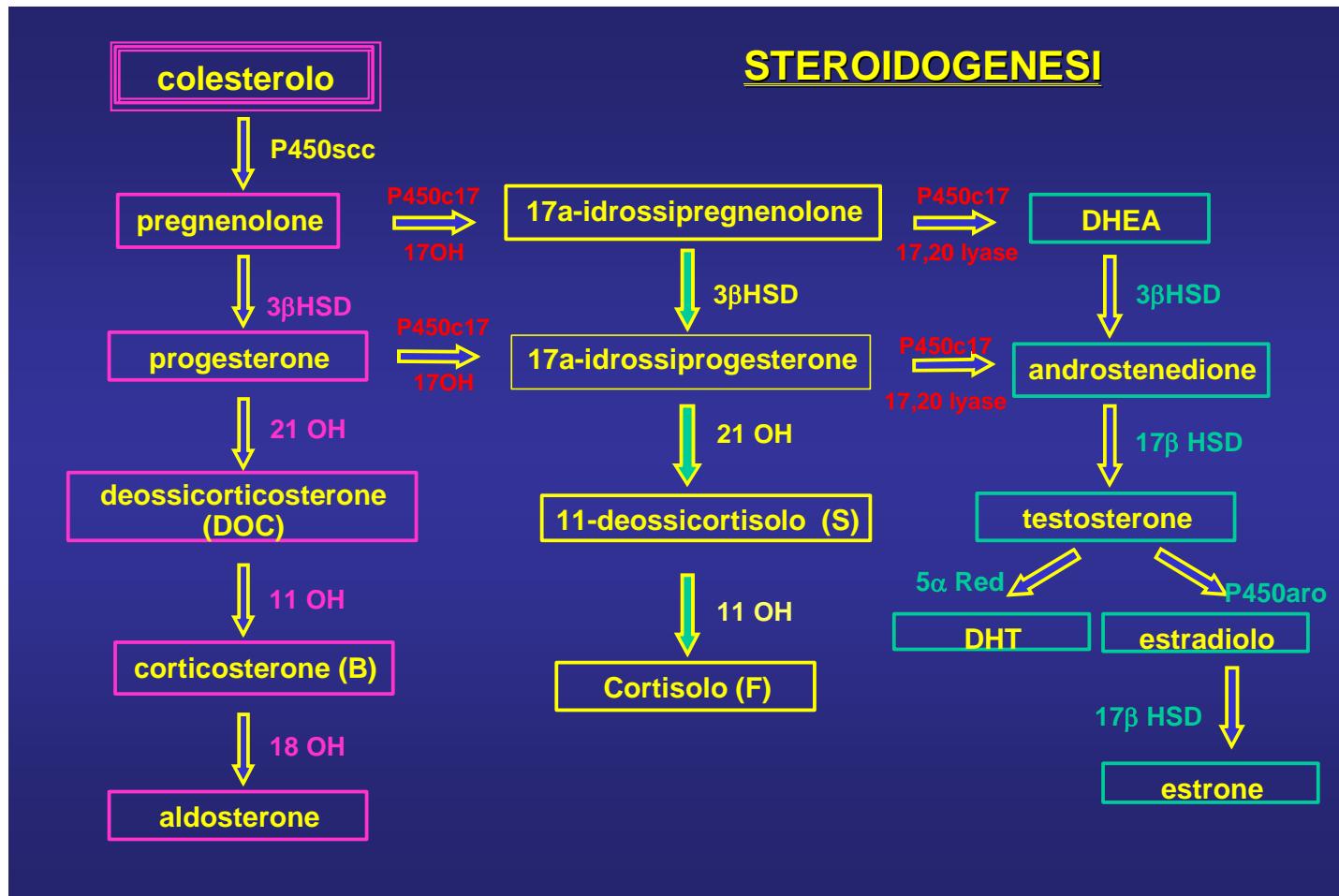


PUBARCA

These physical changes are preceded by biochemical adrenarche, which has been described to begin physiologically as early as ages 5–6 yr and consists of increased Zona Reticularis production of 5 steroids, principally dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS).



PUBARCA



PUBARCA PREMATURO

Adrenarche is a physiological mystery as it is not well understood how the development of the ZR is initiated or controlled

From the evolutionary perspective, it has been suggested that adrenarche is a key component of ‘juvenile’, a period that emerges during evolution in the late Hominids and prolongs the transition from childhood to adolescence and adult life; juvenility may serve the adaptation of body composition and metabolic status to environmental conditions

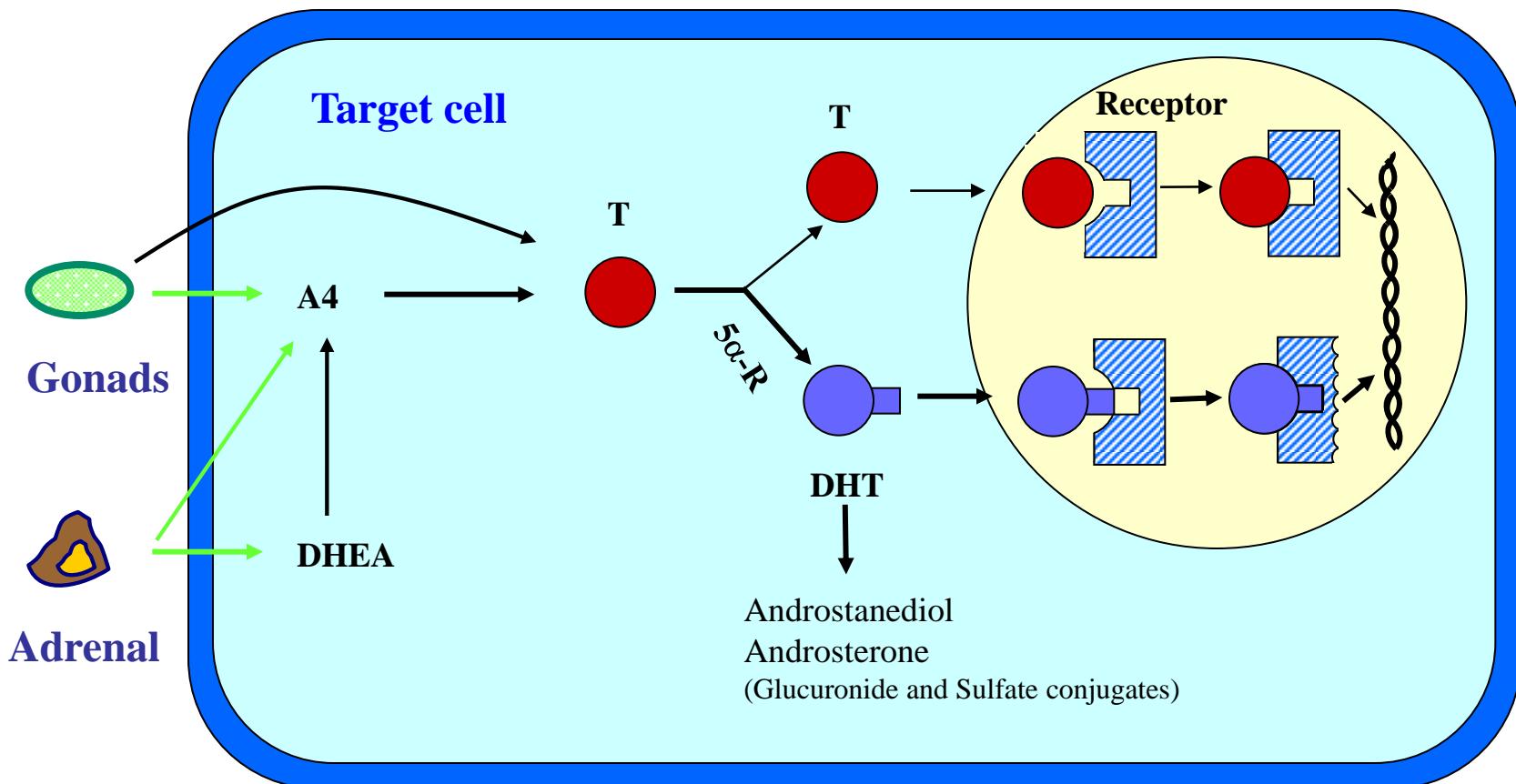
PUBARCA PREMATURO

Adrenarche is a physiological mystery as it is not well understood how the development of the ZR is initiated or controlled

From the evolutionary perspective, it has been suggested that adrenarche is a key component of ‘juvenile’, a period that emerges during evolution in the late Hominids and prolongs the transition from childhood to adolescence and adult life; juvenility may serve the adaptation of body composition and metabolic status to environmental conditions

Another interesting hypothesis refers to the neuromodulatory effects of DHEAS that may help to protect more metabolically active regions of the cerebral cortex to support brain maturation in the developing prepubertal child

ANDROGEN METABOLISM AND MECHANISM OF ACTION



PUBARCA PREMATURO

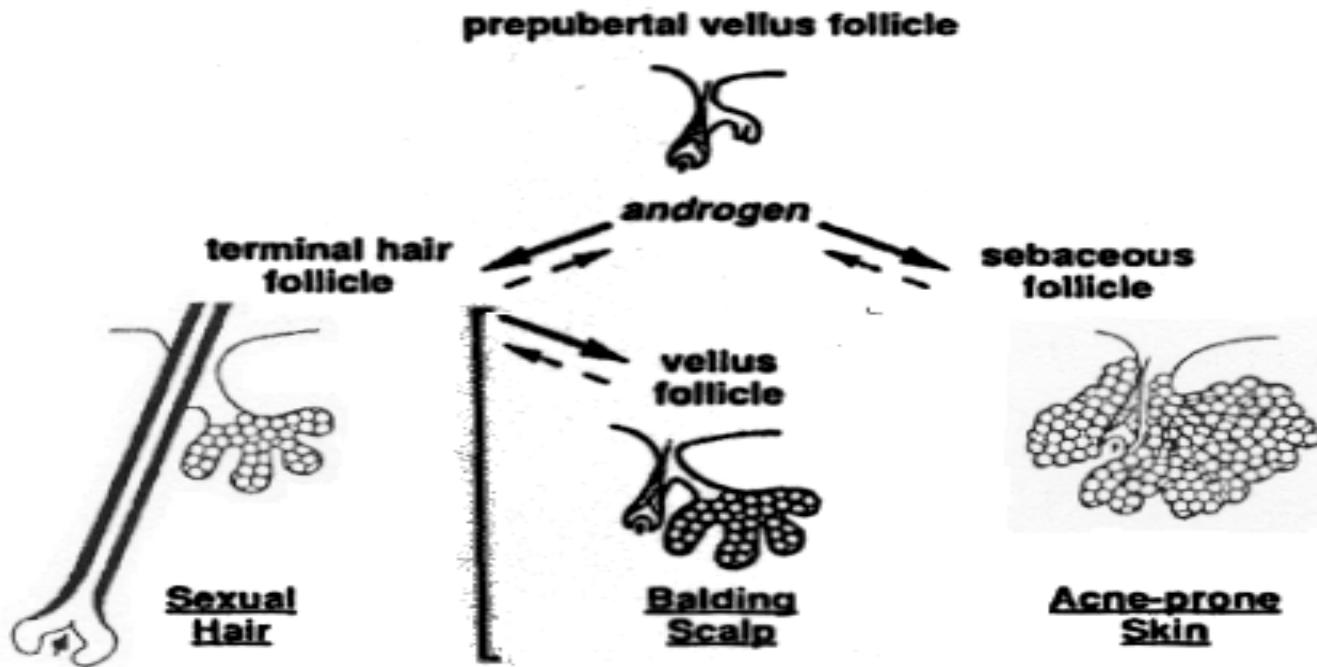


FIG. 1. Role of androgen in the development of the pilosebaceous unit. *Solid lines* indicate effects of androgens; *dotted lines* indicate effects of antiandrogens. Hairs are depicted only in the anagen (growing) phase of the growth cycle. In balding scalp (*bracketed area*), terminal hairs not previously dependent on androgen regress to vellus hairs under the influence of androgen. [Reprinted with permission from R. L. Rosenfield and D. Deplewski: *Am J Med* 98:80S–88S, 1995 (1a) © Excerpta Medica Inc.]

PUBARCA

1) Come definiamo il Pubarca Prematuro?



PUBARCA PREMATURO

Comparsa di pelo pubico prima degli 8 anni nella femmina e 9 anni nel maschio

However, the results of a large cross-sectional study carried out in 1997 suggest that the appearance of pubic hair in girls may be considered normal when it occurs after 7 years of age in white subjects, and after 6 years of age in African-Americans



PUBARCA PREMATURO

- Comparsa di pelo pubico prima degli 8 anni nella femmina e 9 anni nel maschio.
- Pelo ascellare e/o odore apocrino e/o modificazioni caratteristiche capelli possono associarsi.



PUBARCA PREMATURO

- 1) Come definiamo il pubarca prematuro?
- 2) Quale la diagnosi più frequente ?



PUBARCA PREMATURO

La diagnosi più frequente è quella di :

pubarca prematuro isolato o idiopatico



PUBARCA PREMATURO

- 1) Come definiamo il pubarca prematuro?
- 2) Quale la diagnosi più frequente ?
- 3) Quale la diagnosi differenziale ? (5 RISPOSTE)



PUBARCA PREMATURO

Tumori androgeno-secernenti

Cushing

Pubertà Precoce

Resistenza periferica ai glucocorticoidi

**Sindrome surrenogenitale variante non
classica**



PUBARCA PREMATURO

Tumori androgeno-secernenti

Cushing

Pubertà Precoce

Resistenza periferica ai glucocorticoidi

**Sindrome surrenogenitale variante non
classica**



Tumori androgeno-secernenti

- Pubarca e altri caratteri sessuali secondari rapidamente ingravescenti (virilizzazione)
- Androgeni surrenalici basali ↑↑
- GnRH test: risposta soppressa
- Soppressione con desametazone: assente



PUBARCA PREMATURO

Tumori androgeno-secernenti

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Resistenza periferica ai glucocorticoidi

**Sindrome surrenogenitale variante non
classica**

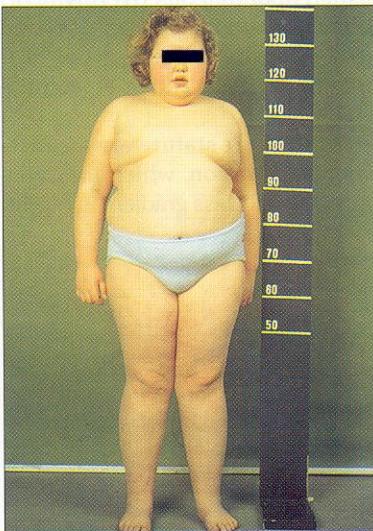


Sindrome di Cushing

Causes of the Cushing syndrome in childhood and adolescence, in order of frequency

- Iatrogenic
- Pituitary adenoma (most common in late childhood)
- Adrenal adenoma (most common in early childhood)
- Adrenal carcinoma
- Bilateral nodular hyperplasia
- Ectopic ACTH production

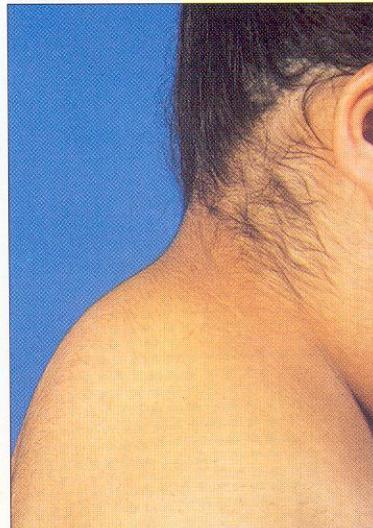
2.51 Causes of the Cushing syndrome in childhood and adolescence, in order of frequency.



2.54 Cushing disease due to pituitary adenoma. Gross obesity.



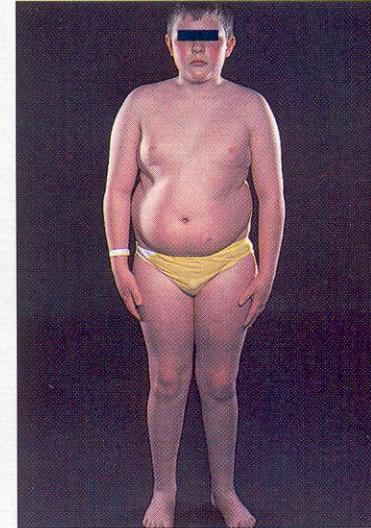
2.55, 2.56 Progression from mild to severe Cushingoid facies in child with unresectable adrenal adenoma.



2.57 Cushing syndrome with buffalo hump and hirsutism.



2.58 Iatrogenic Cushing syndrome secondary to treatment for dermatomyositis.



2.59 Pseudo-Cushing syndrome secondary to nutritional obesity. Note high cheek color. There was hypertension and skin fragility. Height was however on 95th centile. Urinary free cortisol was normal and there was later a supra-normal rate of growth.

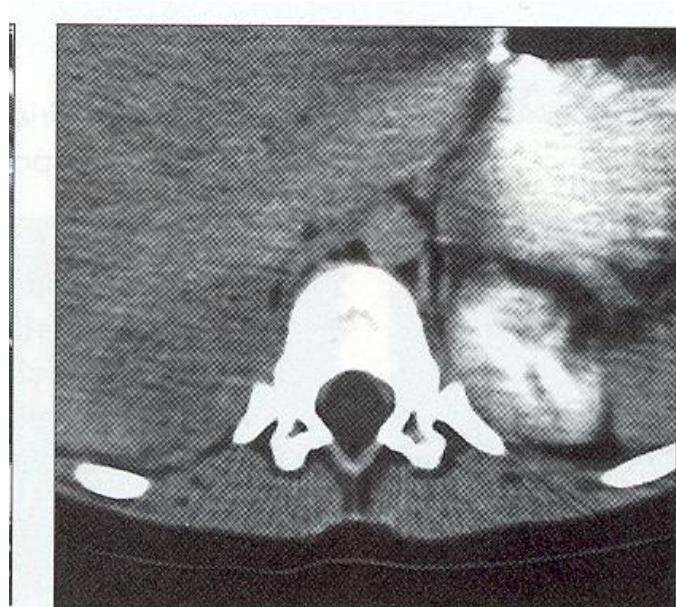
Sindrome di Cushing

Cortisolemia (h 8)	 > 25 ug/dl	 > 10 ug
Ritmo circadiano	 Abolito	
Cortisoluria (24 h)	  >100ug/1,73 mq	
ACTH basale	 < 25 pg/ml	
Delta-4 DHEAS	spesso 	

Origine surrenalica

Origine ipofisaria
(malattia)

Sindrome di Cushing



2.81 CT scan of right sided adrenal adenoma producing the Cushing syndrome. The hypo-dense tumor has displaced the right kidney downwards, the left kidney is outlined with contrast medium.(Same case as **2.34**.)

PUBARCA PREMATURO

Tumori androgeno-secernenti

Cushing

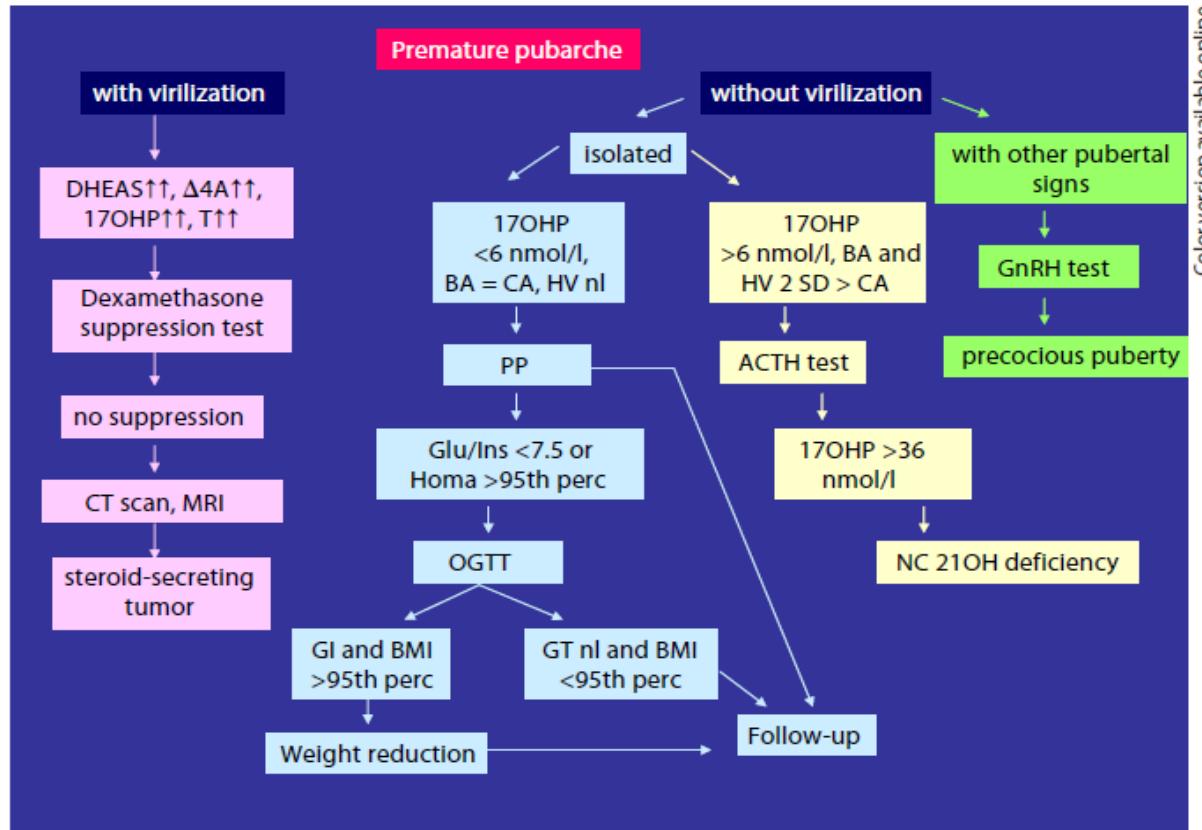
Pubertà Precoce

Resistenza periferica ai glucocorticoidi

Sindrome surrenogenitale variante non
classica



PUBERTA' PRECOCE



PUBARCA PREMATURO

Tumori androgeno-secernenti

Cushing

Pubertà Precoce

Resistenza periferica ai glucocorticoidi

Sindrome surrenogenitale variante non
classica



Resistenza ai glucocorticoidi

- Pubarca e/o altri caratteri sessuali secondari
- Androgeni surrenalici basali ↑ e cortisolo ↑↑
- GnRH test: risposta normale
- ACTH test: risposta variabile
- Soppressione con desametazone: solo con dosi molto alte

PUBARCA PREMATURO

Tumori androgeno-secernenti

Cushing

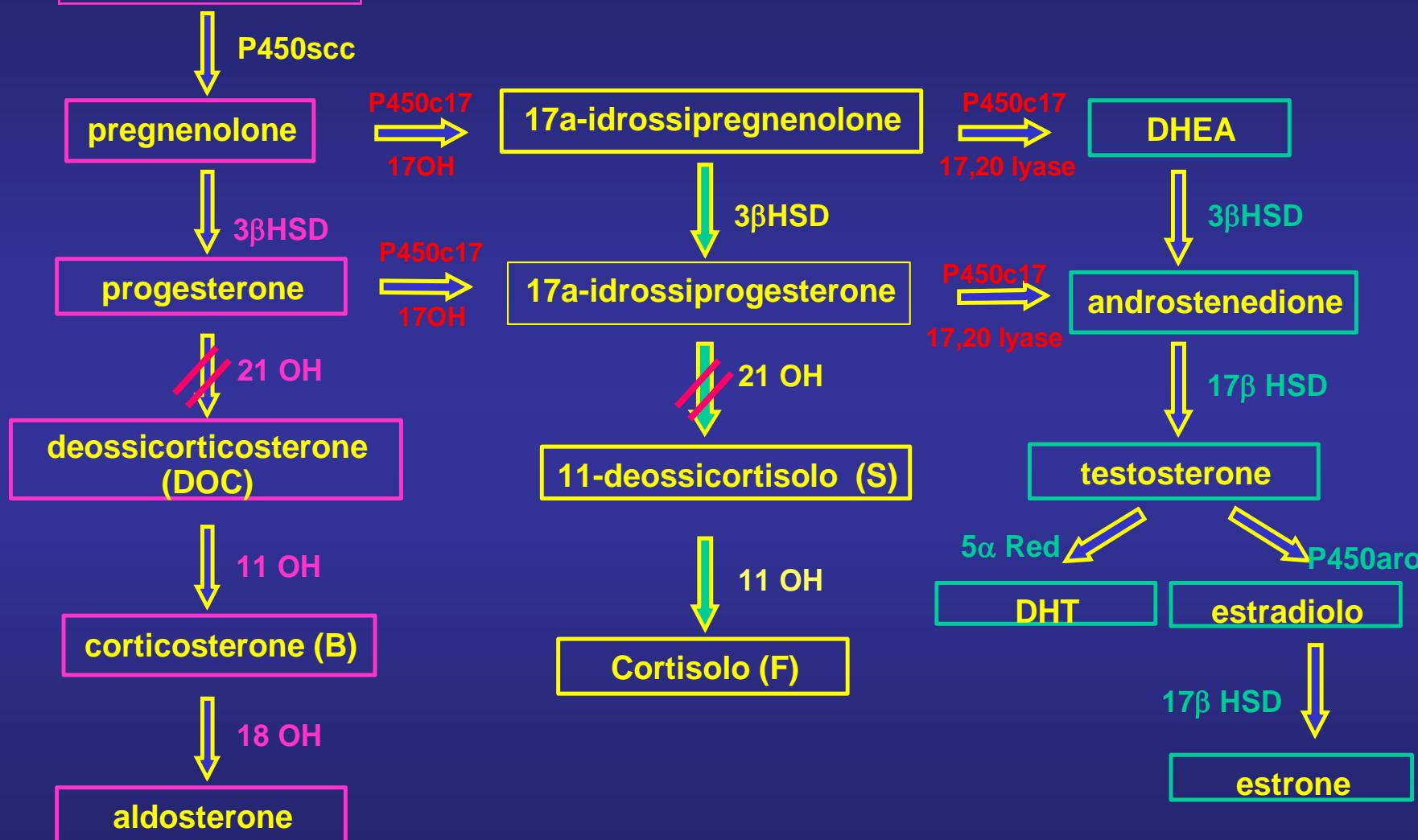
Pubertà Precoce

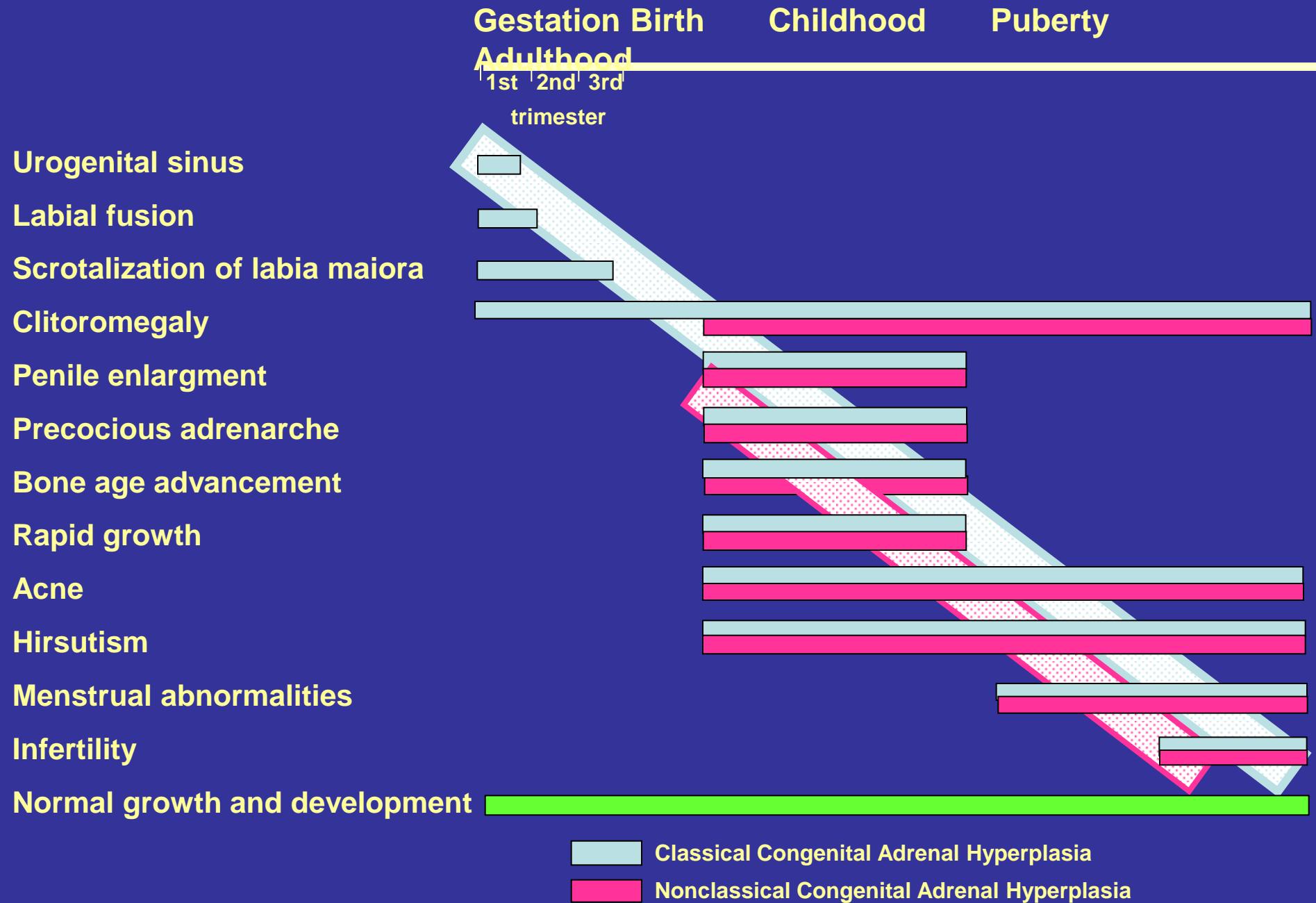
Resistenza periferica ai glucocorticoidi

**Sindrome surrenogenitale variante non
classica**



STEROIDOGENESI

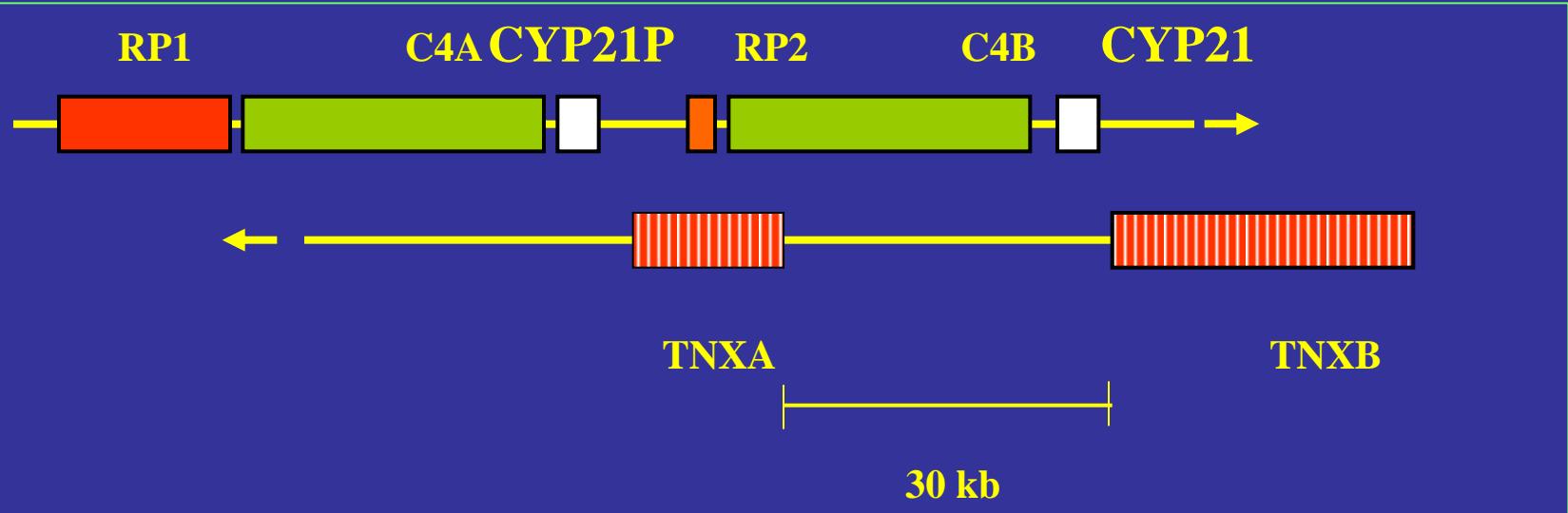




A. Location of the CYP21 genes within the HLA major histocompatibility complex on chromosome 6p21.3



B. Map of the genetic region around the CYP21 gene



White and Speiser, JCEM 2000

Genotipo

Delezione
Arg 356 Trp
Gin 318 stop
Leu 307 ins T
Cluster E6

Intron-2 splice

Ile 172 Asn

Pro 30 Leu

Val 281 Leu

Fenotipo

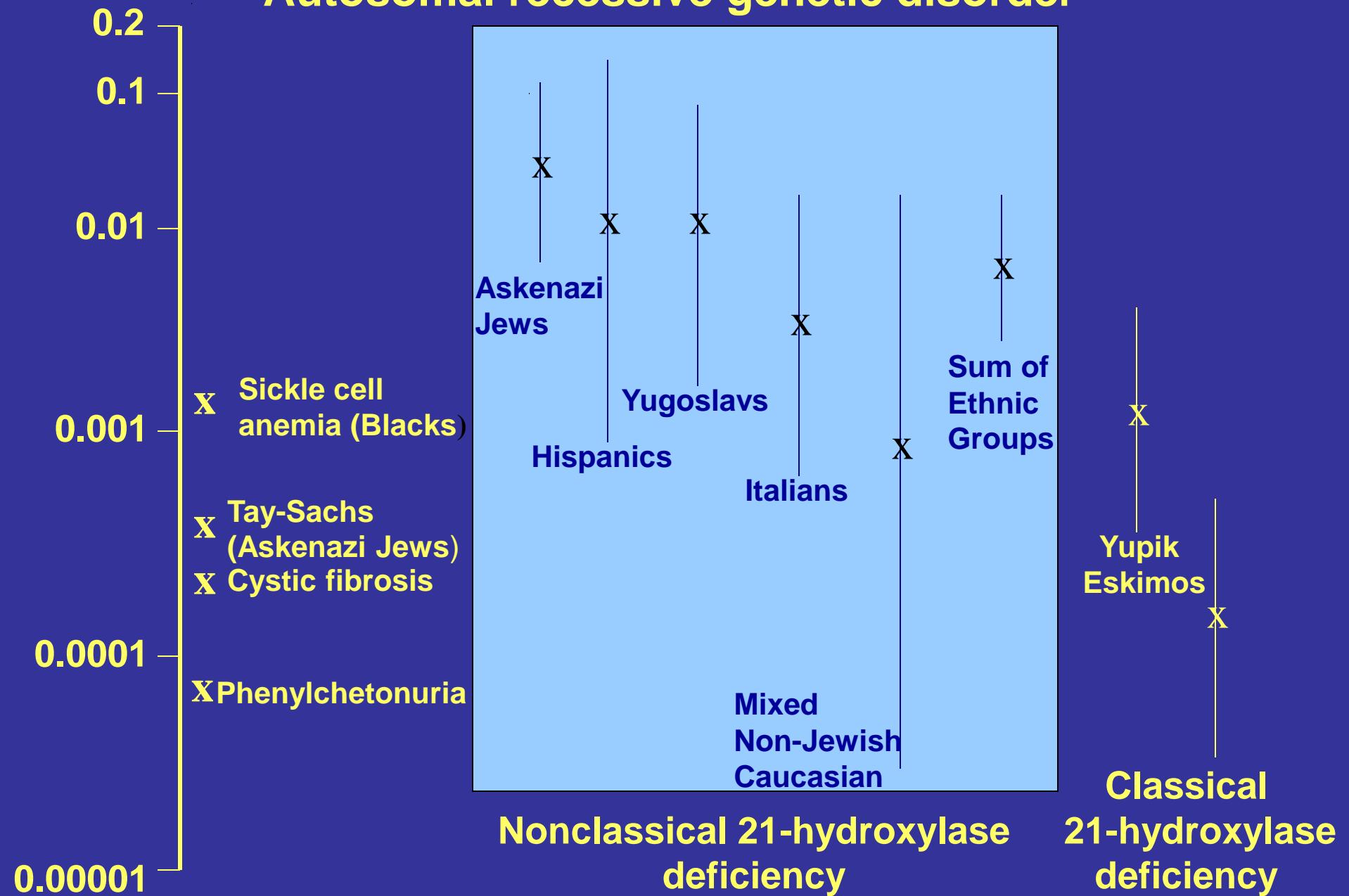
Con perdita di sali

Virilizzante semplice

Non classica

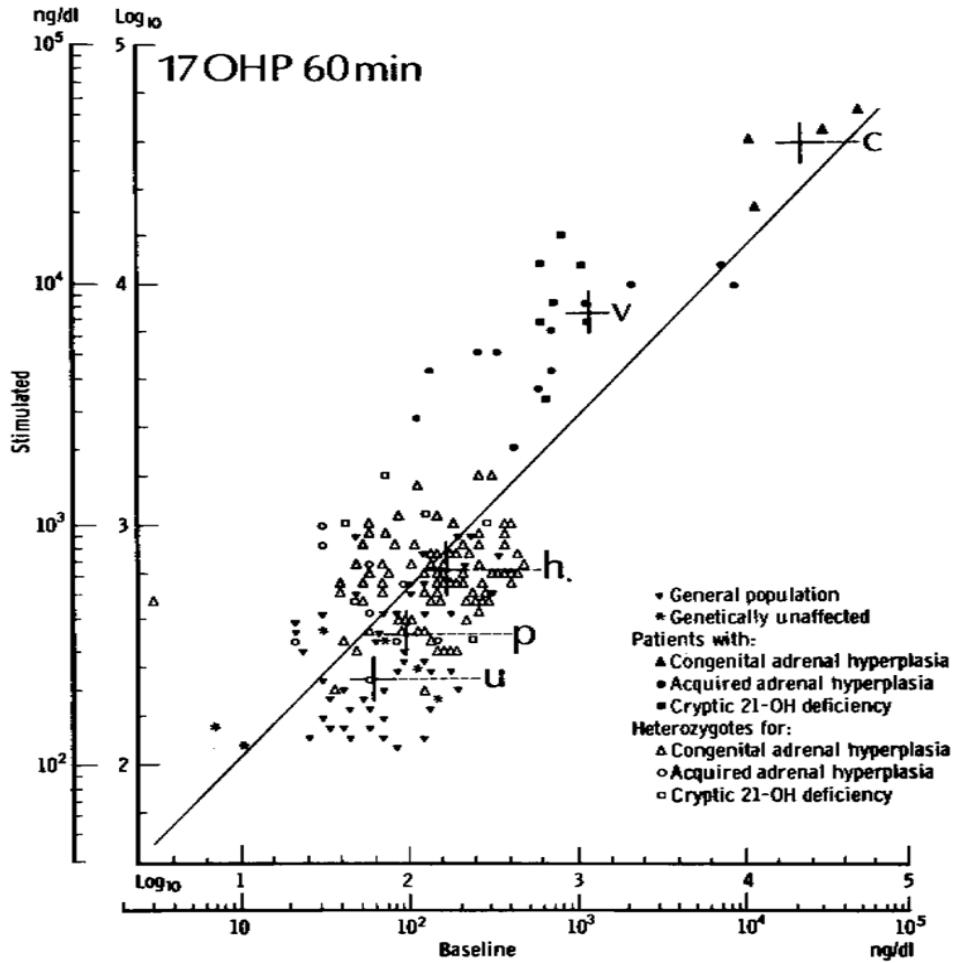
Normale

Disease frequency: Autosomal recessive genetic disorder



Deficit di 21-idrossilasi: forma non classica

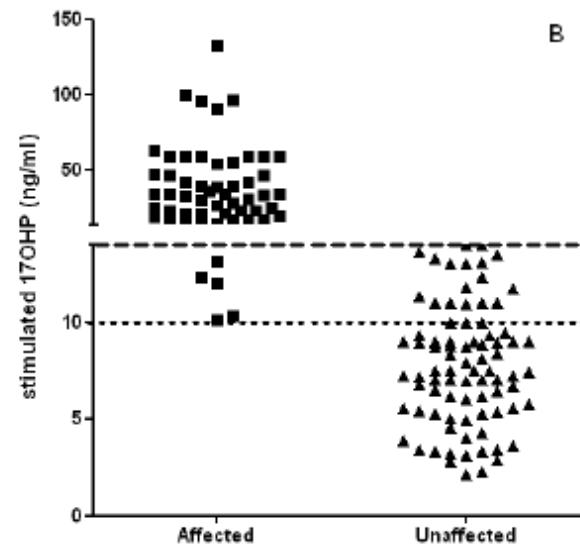
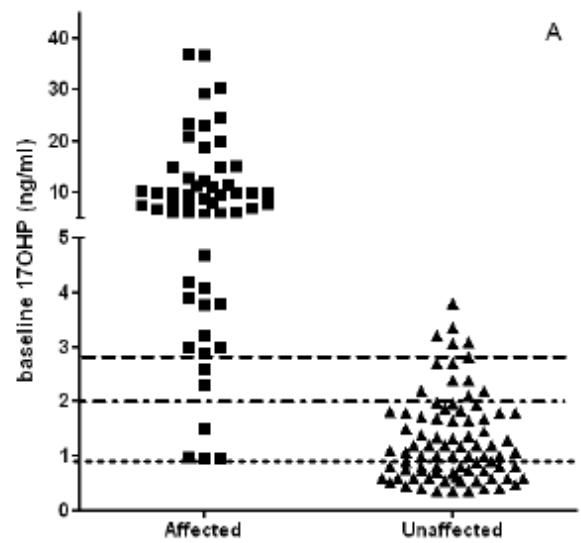
- Pubarca
- Androgeni surrenalici basali normali o ↑
- GnRH test: risposta di tipo prepuberale
- ACTH test: 17OHP ↑↑



Copyright © 1982 by Maria L New, MD

FIGURE 11. Nomogram relating baseline and 60-minute ACTH-stimulated serum 17-OHP concentrations. The mean values for each group are indicated as follows: c, CAH; v, patients with nonclassical symptomatic or asymptomatic (acquired, late-onset, or cryptic) 21-hydroxylase deficiency; h, heterozygotes for classical CAH, nonclassical symptomatic CAH (acquired or late-onset adrenal hyperplasia), and nonclassical asymptomatic CAH (cryptic 21-hydroxylase deficiency); u, family members predicted by HLA genotyping to be unaffected; and p, general population (not HLA genotyped).

Deficit di 21-idrossilasi: forma non classica



Deficit di 21-idrossilasi nei pubarchi prematuri

Autori	Casi	21-OH deficit
August et al.	16 F, 2 M	2 fratelli
Rosenfield et al	4 M	0
Granoff et al	10 F, 5 M	0
Klaplowitz et al	19 F, 2 M	0/3
Temeck et al	19 F, 4 M	7 (30%)
Morris et al	28 F, 3 M	0
Rapaport et al	30 F, 3 M	2 F (6%)
Oberfield et al	32 F, 2 M	0
Balducci et al	39 F, 2 M	2 F, 2 M (8%)
Vasconcelos et al	19 F	4 F (21%)
de Sanctis et al	63 F	3 F (5%)
del Balzo et al	21 F, 5 M	1 F (4%)
nostra casistica	125 F, 35 M	20 F, 8 M (17%)

Terapia deficit di 21-idrossilasi forma non classica (NCCAH)

- Trattamento indicato solo nelle forme sintomatiche (età ossea avanzata, prognosi staturale inferiore al target, irsutismo, irregolarità mestruali, infertilità)
- In età pediatrica, idrocortisone 10-20 mg/m². In età adulta, prednisone 5-7.5 mg/die o desametazone 0.25-0.5 mg/die
- Utilizzare il dosaggio più basso che permetta una buona soppressione degli androgeni surrenalici e una crescita adeguata
- Monitoraggio terapia: livelli ematici di 17OHP tra 1 e 10 ng/ml. Androstenedione e testosterone adeguati all'età.

PUBARCA PREMATURO

La diagnosi più frequente è quella di :

pubarca prematuro isolato o idiopatico



PUBARCA PREMATURO

Pubarca prematuro **idiopatico**: caratteristiche cliniche

- Assenza di altri segni puberali
- Velocità di crescita n- \uparrow
- Età ossea n- \uparrow



PUBARCA PREMATURO

- 1) Come definiamo il pubarca prematuro?**
- 2) Quale la diagnosi più frequente ?**
- 3) L'altezza finale è normale ?**



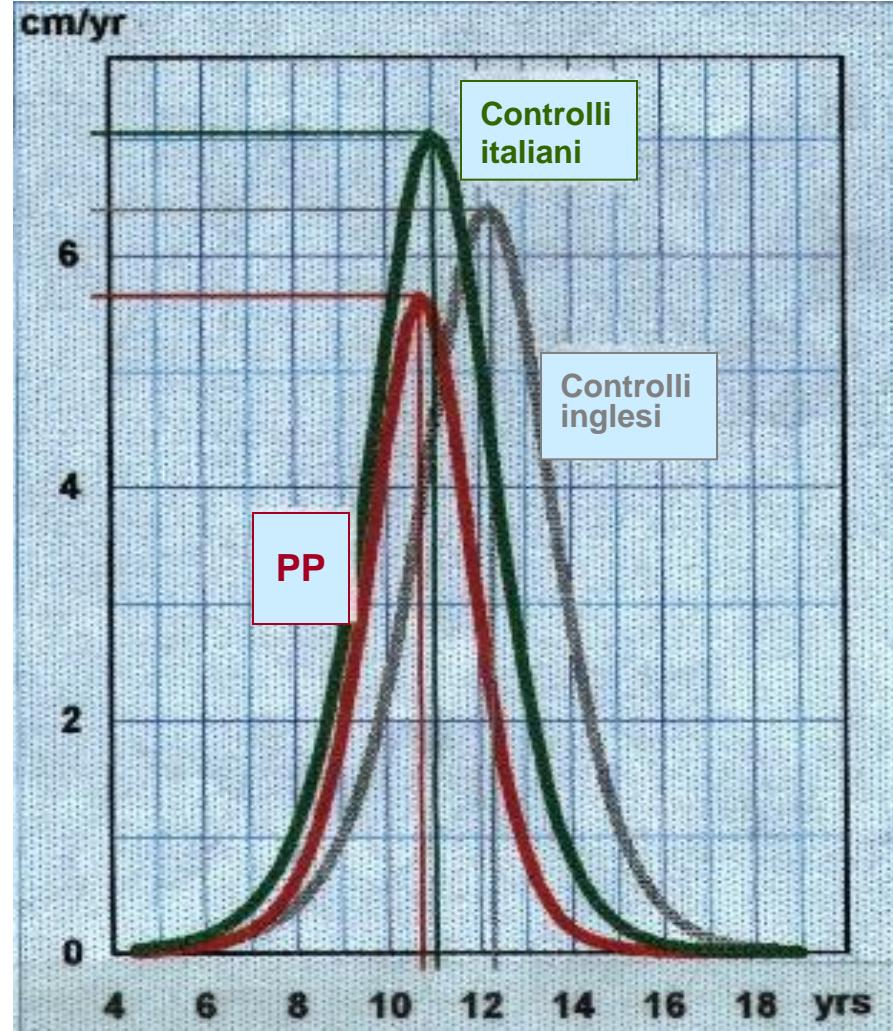
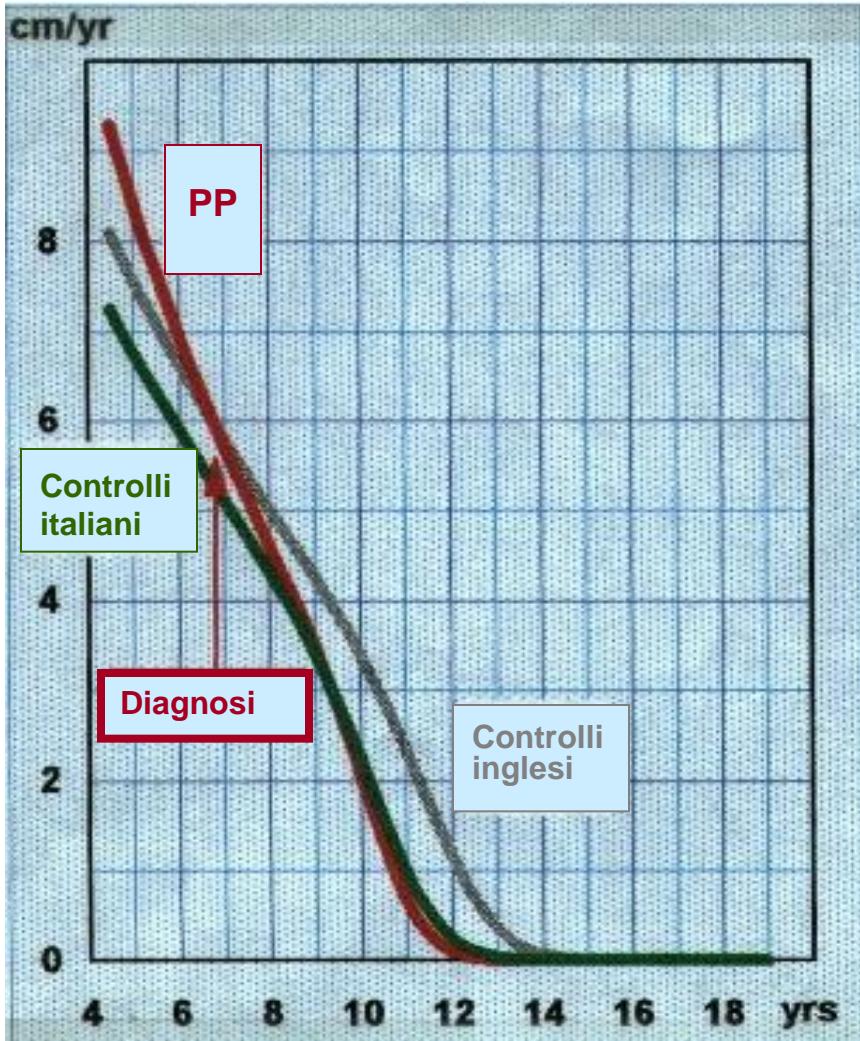
PUBARCA PREMATURO

Pubarca prematuro **idiopatico**: caratteristiche cliniche

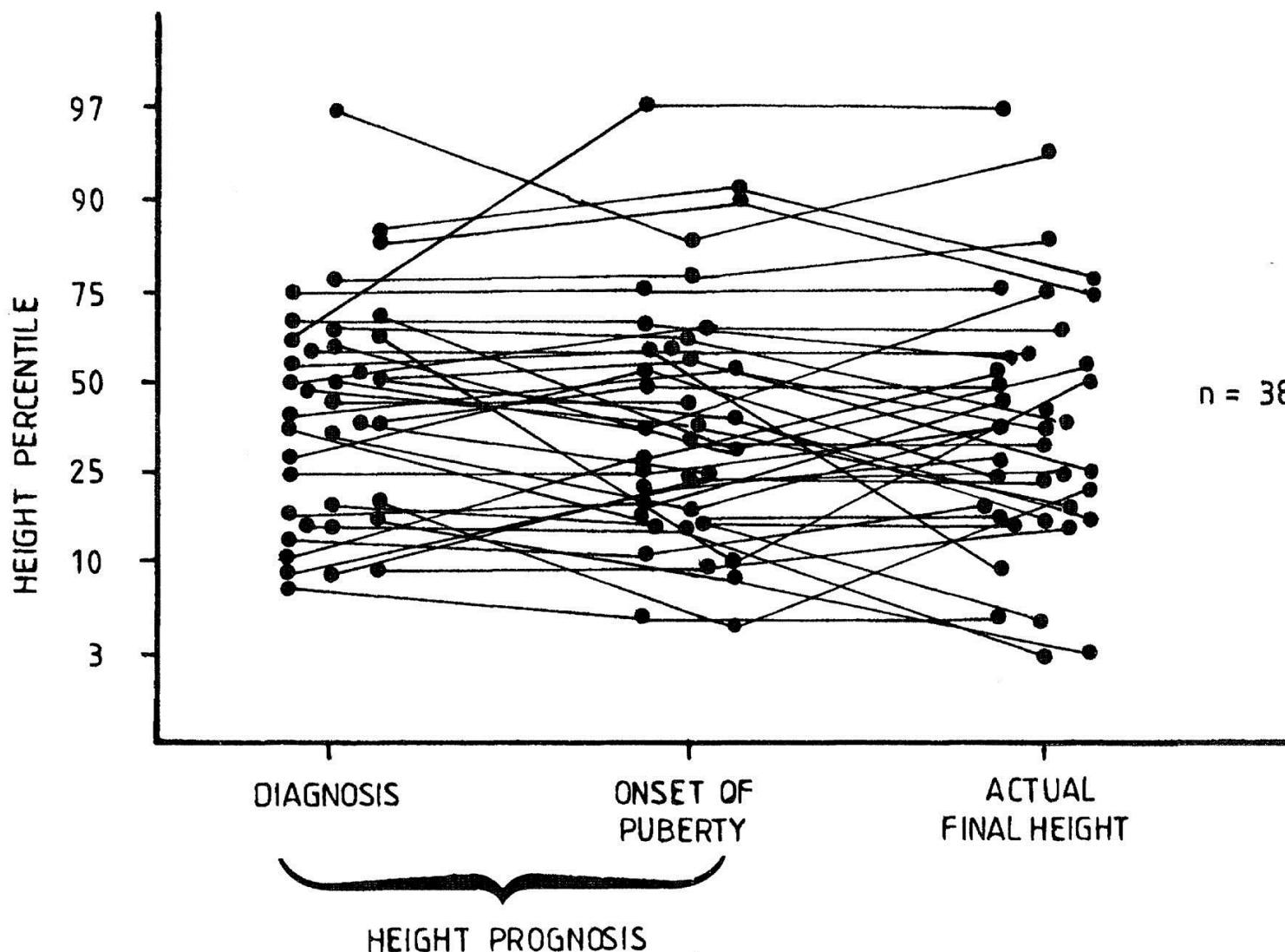
- *Altezza finale in accordo con il target genetico*

Componente prepuberale puberale della velocità di crescita (modello PB1)

J Ped Endocrinol Metab 2000



PUBARCA PREMATURO



J.Clin.Endocrinol.Metab. 1992

PUBARCA PREMATURO

n	PC (cm) alla diagnosi	PC (cm) a Tanner II	Altezza finale (cm)	Altezza parentale (cm)
38	158.4 ± 6.3	158.4 ± 5.6*	160.0 ± 5.3	155.6 ± 5.3*

Media ± DS; * correlazione con altezza finale, p<0.0001

PC: prognosi di crescita

PUBARCA PREMATURO

- 1) Come definiamo il pubarca prematuro?
- 2) Quale la diagnosi più frequente ?
- 3) L'altezza finale è normale ?
- 4) Qual è la prognosi ?



PUBARCA PREMATURO



NON SO RISONDERE



CERCHERO' DI FARLO



PUBARCA PREMATURO

Clinical spectrum of premature pubarche: Links to metabolic syndrome and ovarian hyperandrogenism

Rev Endocr Metab Disord (2009) 10:63–76

Lourdes Ibáñez · Rubén Díaz · Abel López-Bermejo ·
María Victoria Marcos

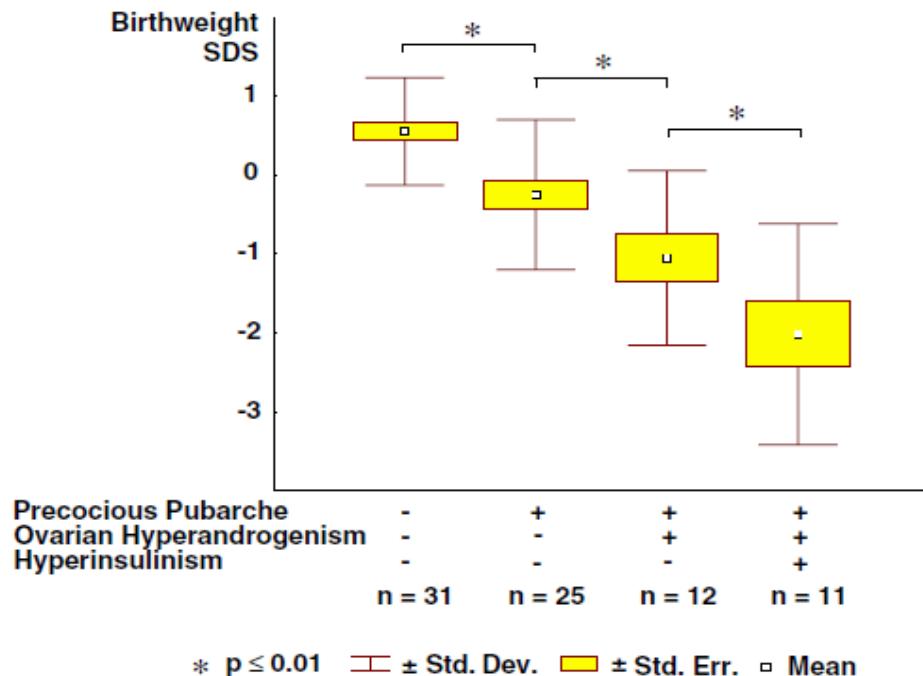


Fig. 6 Birth weight scores of postmenarcheal control girls (−, − and −) and postmenarcheal girls with a history of precocious pubarche without ovarian hyperandrogenism and without hyperinsulinemia (+, − and −); with ovarian hyperandrogenism and without hyperinsulinemia (++, −), and with both ovarian hyperandrogenism and hyperinsulinemia (++ and +). Redrawn with permission from Ibáñez et al. [43]



PUBARCA PREMATURO

REVIEW

Premature adrenarche: novel lessons from early onset androgen excess

Jan Idkowiak, Gareth G Lavery, Vivek Dhir, Timothy G Barrett, Paul M Stewart, Nils Krone and Wiebke Arlt

European Journal of Endocrinology (2011) 165 189–207

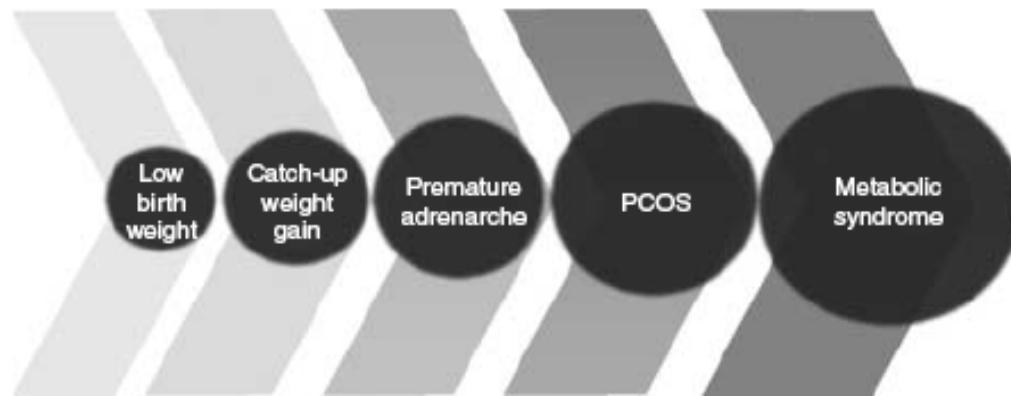
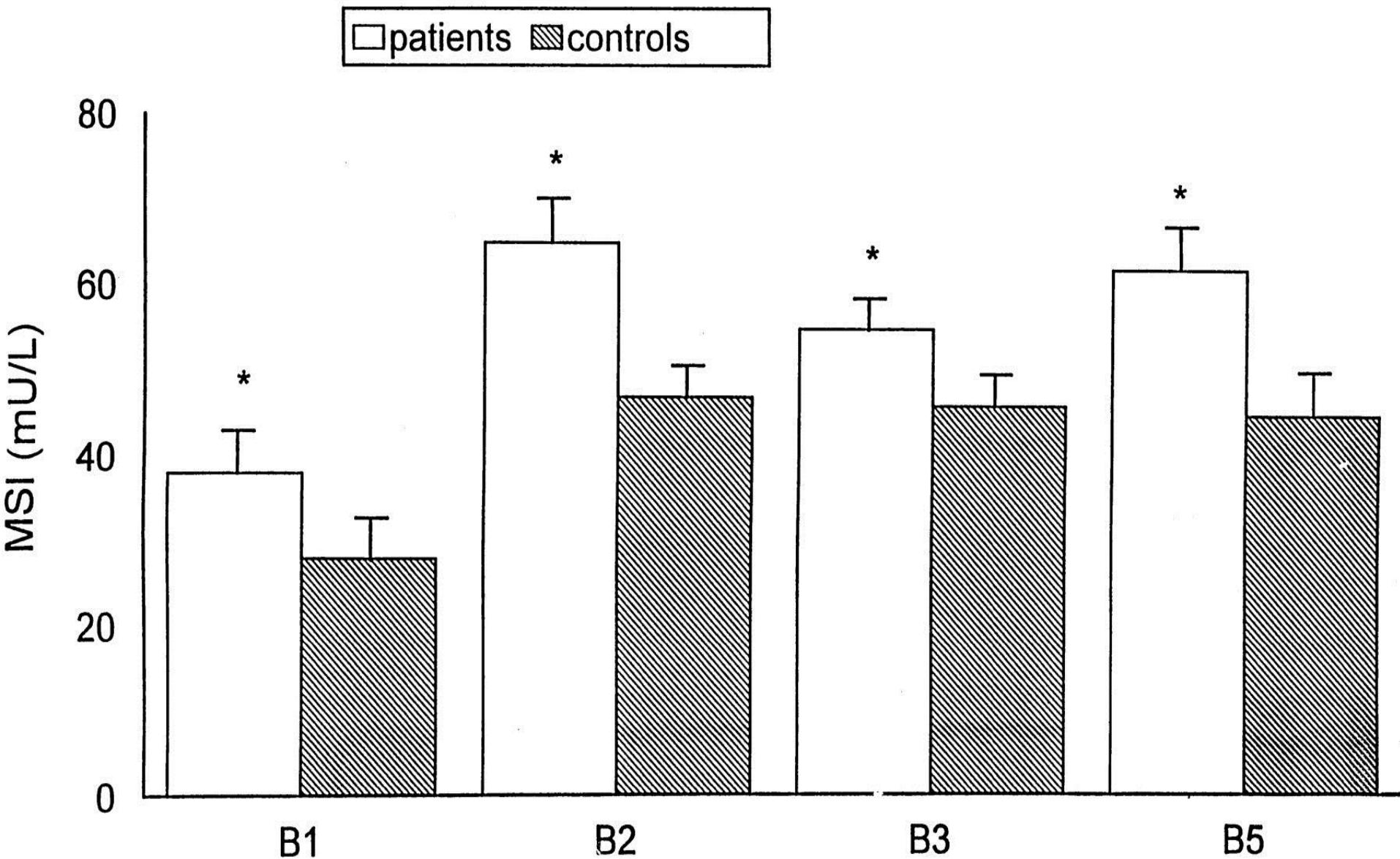


Figure 1 Graphic representation of a potentially causally related pattern of subsequent events linking low birth weight to premature adrenarche, polycystic ovary syndrome and the development of the metabolic syndrome later in life. This order of events is not consistently supported by all studies in the field as discussed in the text.





MSI= Mean Serum Insulin

J Clin Endocrinol Metab 1997

Clinical and US features, plasma T and D4-A levels, and LH/FSH ratios in oligomenorrheic patients, regularly menstruating patients and controls

Patients	Age (yr)	BMI (kg/m ²)	Hirsutism score	PCO on US	LH/FSH ratio	T (nmol/L)	D4
Oligomenorrheic (n=16)	15.8+1.8	21.9+1.7	13.9+3	8	2+1.2	2.9+1	11+2
Regularly menstruating (n=19)	15.2+1.2	22.7+1.8	7.4+1.8	3	1.4+0.9	1.4+0.5	6.8+2
Controls (n=12)	15.3+1.3	21.6+3.1	5.1+0.7	0	1.1+0.8	1.1+0.4	5.1+2

Criteri diagnostici di PCOS

PCOS Consensus
Workshop Group (Rotterdam 2003)

Presenza di almeno 2 dei seguenti criteri:

- Oligo- o anovulazione
- Segni clinici (irsutismo, acne) e/o biochimici (T libero) di iperandrogenismo
- Ovaio policistico ed esclusione di altre patologie (NCCAH, tumori androgeno-secernenti, sindrome di Cushing)



Criteri diagnostici di PCOS

PCOS Consensus Workshop Group (Rotterdam 2003)

Ovaio policistico

**“Presenza di 12 o piu’ follicoli
con diametro di 2-9 mm in ogni
ovaio, e/o volume ovarico
aumentato (>10 ml)**



Insulin sensitization early after menarche prevents progression from precocious pubarche to polycystic ovary syndrome

L.Ibanez et al J. Pediatr. 2004

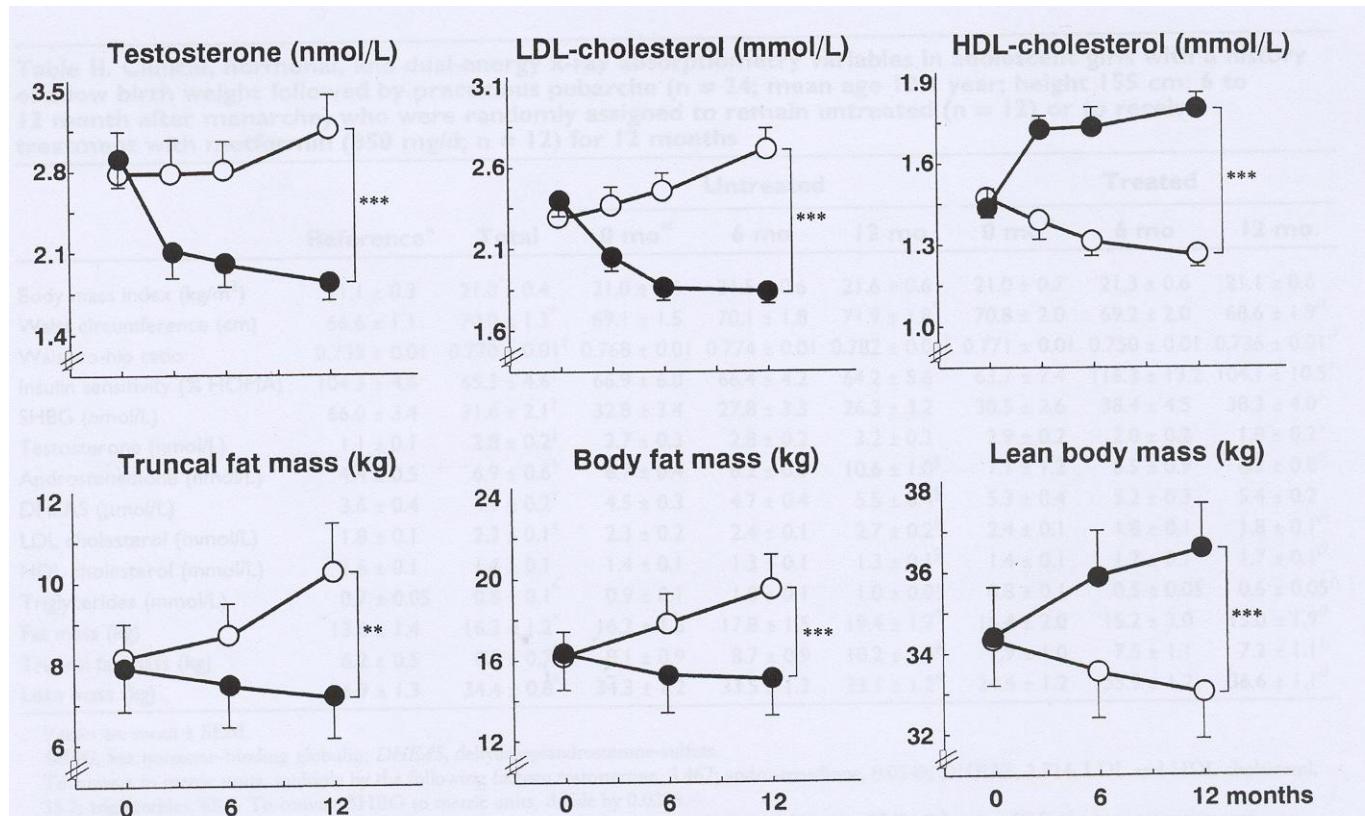


Figure. Serum testosterone and LDL and HDL cholesterol, together with body composition indexes (by dual-energy x-ray absorptiometry) in 24 postmenarcheal girls (mean age, 12.4 years) who had a small size at birth followed by precocious pubarche in childhood. Girls were randomly assigned to remain untreated ($n = 12$; open dots) or to receive metformin (850 mg/d; $n = 12$; closed dots) for 12 months. Values are shown as mean \pm SEM. ** $P < .005$; *** $P < .0001$; broken lines indicate mean reference values (Table II).



PUBARCA PREMATURO



NON SO RISPONDERE



PUBARCA PREMATURO

Department of Pediatrics-University of Parma

Patients with Premature Pubarche

- total n. 160*

- $F = 125$

- $M = 35$



PUBARCA PREMATURO

PA GIRLS AT BIRTH (n.=76)

	<u>Mean (SD)</u>	
Gestational age (wk)	39.26 (2.1)	
Weight (kg)	3.15 (0.6)	
Length (cm)	49.33 (3.5)	
Weight-SDS ¹	+0.17 (1.3)	n.s.
Length-SDS ¹	-0.04 (1.3)	n.s.

n.s.: vs northern italian population (*Bertino et al., 1999*)



PUBARCA PREMATURO

Girls with Premature Adrenarche Have Accelerated Early Childhood Growth

(J Pediatr 2009;154:882-7)

PAULINA UTRAINEN, MD, RAIMO VOUTILAINEN, MD, PHD, AND JARMO JAÄSKELÄINEN, MD, PHD

Table I. Demographic, anthropometric, and metabolic features of girls with PA and control girls

	PA (n = 54)	Control (n = 52)	P
At birth			
BW, g	3495 (3110, 3740)	3535 (3270, 3910)	.30
BL, cm	50.0 (48.0, 51.0)	50.3 (49.1, 52.0)	.04*
BW SDS	-0.19 (-0.74, 0.65)	-0.09 (-0.48, 0.66)	.63
BL SDS	-0.12 (-0.69, 0.72)	0.23 (-0.30, 1.03)	.13
Ponderal index, g/cm ³	2.80 (2.69, 2.90)	2.78 (2.61, 3.02)	.57
Gestational age, weeks	40.3 (38.9, 41.0)	40.4 (39.4, 41.1)	.63*
PSEH SDS	0.27 (-0.20, 0.83)	0.12 (-0.26, 0.57)	.16
At examination			
Age, years	7.6 (7.1, 8.1)	7.5 (6.8, 8.0)	.32
Height, cm	131 (126, 136)	125 (120, 128)	<.001†
Weight, kg	31.8 (26.3, 37.0)	24.6 (22.4, 27.8)	<.001*
Height SDS	1.2 (0.6, 1.8)	0.0 (-0.6, 0.6)	<.001†
Sitting/total height, %	53.7 (53.1, 54.3)	53.7 (53.1, 54.4)	.95
BMI, kg/m ²	17.7 (15.7, 22.2)	15.7 (14.8, 17.4)	<.001*
BMI SDS	0.76 (-0.02, 2.31)	-0.11 (-0.61, 0.82)	<.001
Weight-for-height, %	111 (99, 135)	101 (95, 111)	.002*
Mean serum insulin, mU/L	35.6 (28.6, 43.0)	23.1 (19.6, 25.6)	.006‡
Serum IGF-1, nmol/L	24 (19, 30)	19 (16, 24)	.031†
Serum DHEAS, μmol/L	2.1 (1.4, 2.6)	0.6 (0.5, 0.7)	<.001†



Data are reported as median (interquartile range) unless noted otherwise. Mean serum insulin, mean serum insulin concentration during the 2-hour OGTT. Conversion multipliers to metric units: DHEAS, $\mu\text{g}/\text{dL} = 36.9 \times \mu\text{mol}/\text{L}$; IGF-1, $\text{ng}/\text{dL} = 765 \times \text{nmol}/\text{L}$.

Independent-samples *t*-test unless noted otherwise.

*Mann-Whitney test.

†Covariance analysis adjusted for current BMI SDS and age.

‡Covariance analysis adjusted for current BMI SDS.



PUBARCA PREMATURO

Intrauterine Growth Retardation Predisposes to
Insulin Resistance But Not to Hyperandrogenism in
Young Women

(*J Clin Endocrinol Metab* 84: 3945–3949, 1999)

D. JAQUET, J. LEGER, D. CHEVENNE, P. CZERNICHOW, AND C. LEVY-MARCHAL

TABLE 2. Serum androgens concentrations in the IUGR-born and control women taking hormonal contraception

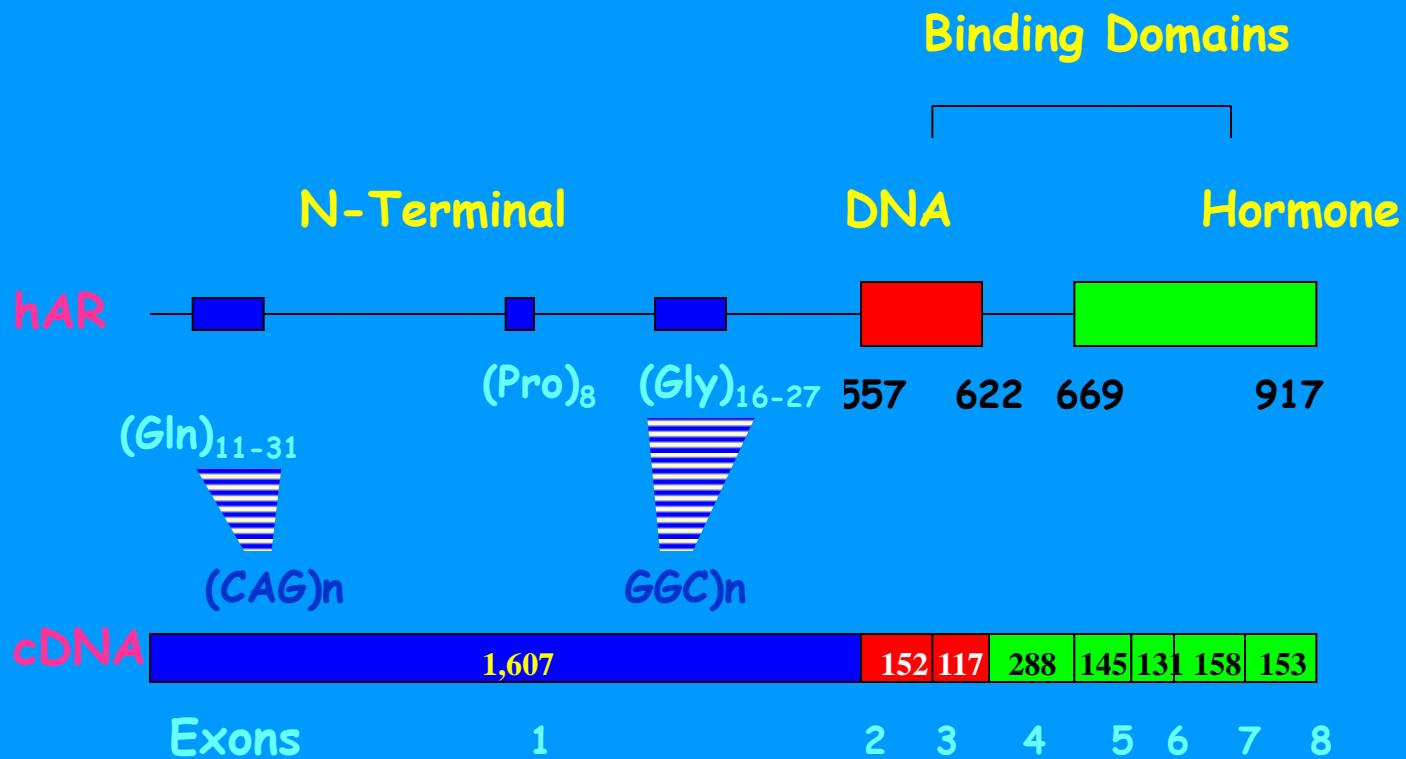
	IUGR (n = 53)	Control (n = 72)	P value
$\Delta^4\text{A}$ (ng/mL)	1.71 ± 0.62	1.84 ± 0.63	0.20
DHEAS (ng/mL)	1884 ± 920	1877 ± 876	0.96
Testosterone (ng/mL)	0.45 ± 0.19	0.47 ± 0.24	0.86
SHBP (nmol/L)	102.1 ± 45.3	98.2 ± 39.7	0.78
FAI	0.60 ± 0.56	0.60 ± 0.57	0.85

Results are given as the mean ± SD. Differences between IUGR and controls were tested using Student's *t* test. $\Delta^4\text{A}$, Δ^4 -Androstenedione; DHEAS, dehydroepiandrosterone sulfate; SHBP, sex hormone-binding protein; FAI, free androgen index (testosterone × 100/SHBP).

In summary, hyperinsulinemia observed in young women born with IUGR is not associated with hyperandrogenism. Consequently, our results do not support the hypothesis of a common *in utero* programming of hyperandrogenism and hyperinsulinemia. (*J Clin Endocrinol Metab* 84: 3945–3949, 1999)



SCHEMATIC DIAGRAM OF THE hAR PROTEIN and cDNA



PUBARCA PREMATURO

Decreased Androgen Receptor Gene Methylation in Premature Pubarche: A Novel Pathogenetic Mechanism?

A. Vottero,* M. Capelletti,* S. Giuliodori, I. Viani, M. Ziveri, T. M. Neri, S. Bernasconi, and L. Ghizzoni

(*J Clin Endocrinol Metab* 91: 968–972, 2006)

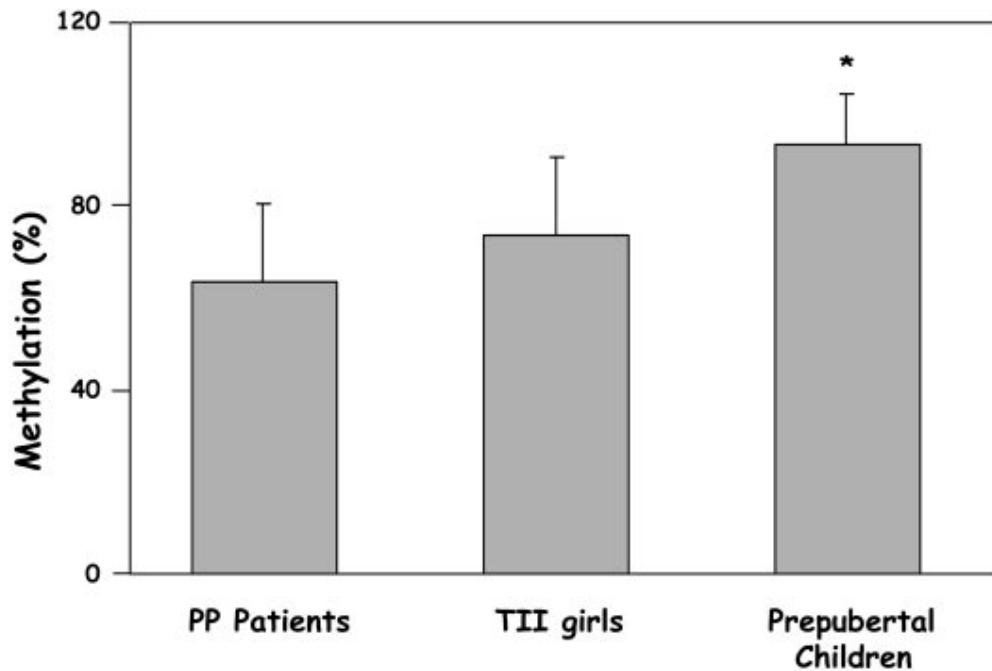


FIG. 2. Androgen receptor gene methylation in PBLs from prepubertal children, girls with Tanner stage II of pubertal development (TII), and PP patients. Mean \pm SD; *, $P < 0.01$ vs. TII girls and PP patients. Methylation (%), Percentage of the methylated over the total amount of DNA.



Eziologia pubarca prematuro idiopatico

- Precoce maturazione zona reticolare (Anderson D.C., 1980).
- Alterata metilazione del gene del recettore degli androgeni (cromosoma X)
(Vottero A. et al. 2006).

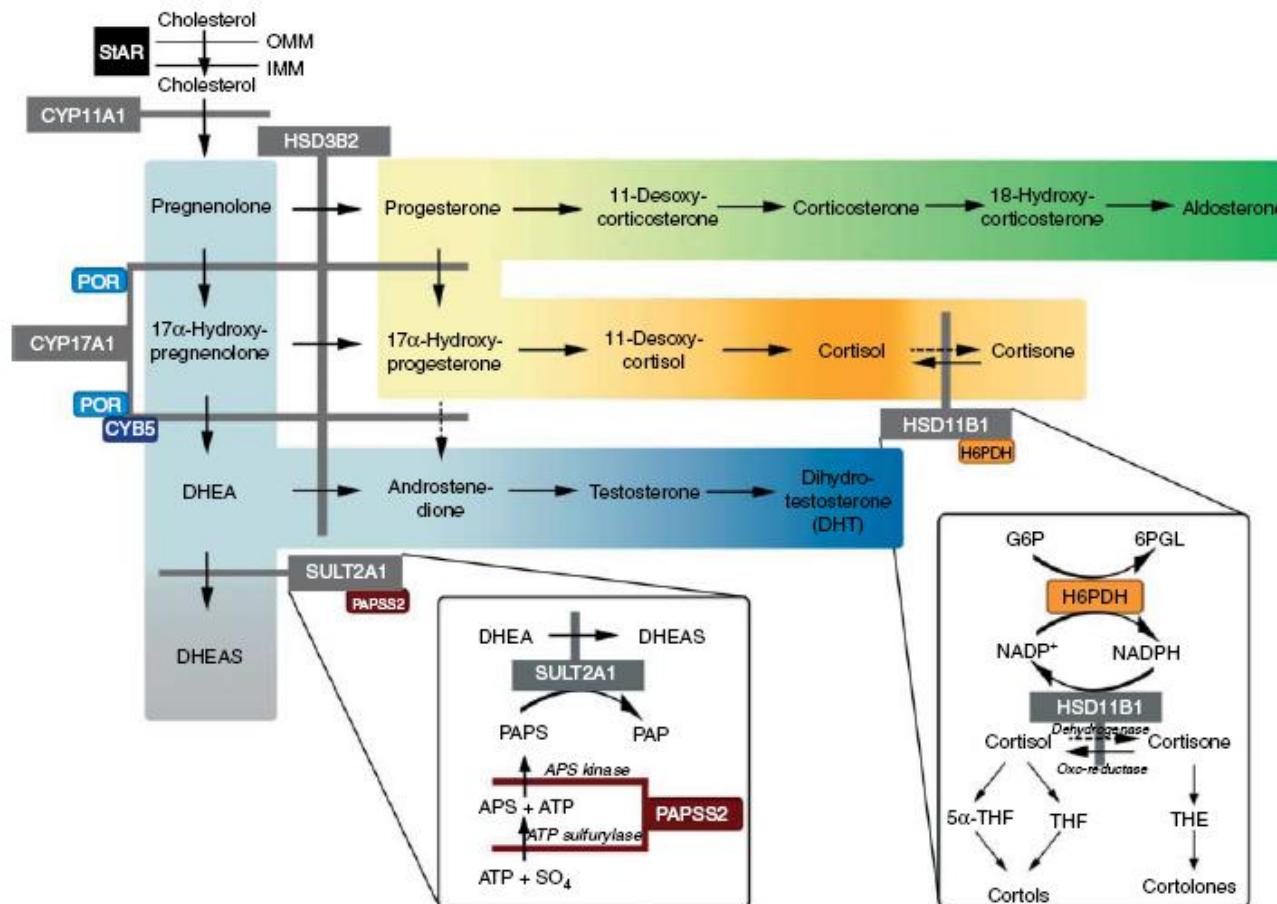
PUBARCA PREMATURO

REVIEW

Premature adrenarche: novel lessons from early onset androgen excess

Jan Idkowiak, Gareth G Lavery, Vivek Dhir, Timothy G Barrett, Paul M Stewart, Nils Krone and Wiebke Arlt

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