

High DHEAS (HD) in girls determines earlier pubertal maturation and mild hyperandrogenism throughout pubertal development

P1 -020



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DISCLOSURE:

Nothing to disclose

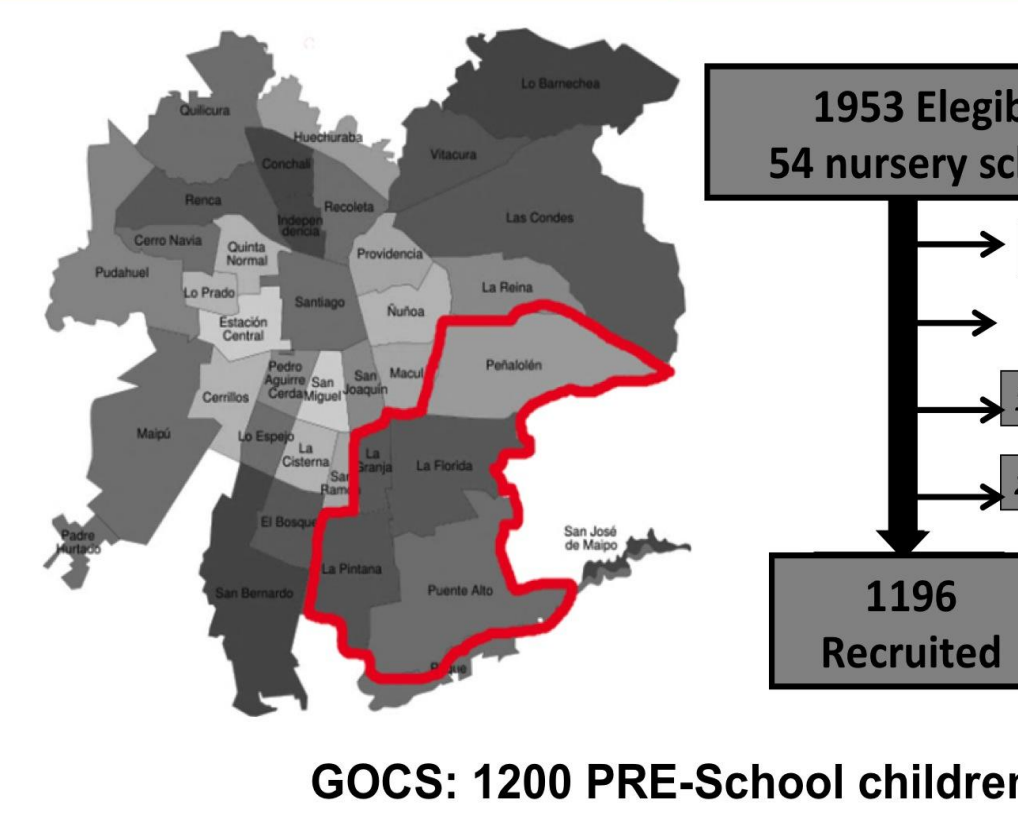
I. BACKGROUND

- Adrenarche is a progressive maturational process of the adrenal zona reticularis resulting in increased secretion of the adrenal androgen precursor DHEA and its sulphate ester DHEAS, being clinically evident approximately 2 yr before the onset of puberty.
- Premature adrenarche (PA) is defined biochemically by increased levels of DHEAS before the age of 8 yr in girls and 9 ys in boys and clinically recognized by the presence of signs of androgen action including adult-type body odour, oily skin and axillary and pubic hair growth.
- This is traditionally indicated by a DHEA-S level within normal limits for early puberty $\approx 40 \mu\text{g/dl}$ ($1.08 \mu\text{mol/L}$) (above average for 6 to 8 yr)
- Premature adrenarche is associated with increased adiposity and metabolic risk.
- Early infancy weight gain has been also associated with increased metabolic risk, earlier puberty, and premature adrenarche (PA).
- Areas of controversy regarding associated co-morbidities are earlier puberty, polycystic ovarian syndrome (PCOS) and lower birth weight, which may depend on ethnic background.
- PCOS is characterized by hyperandrogenism and ovulation dysfunction which is difficult to ascertain during adolescent years.

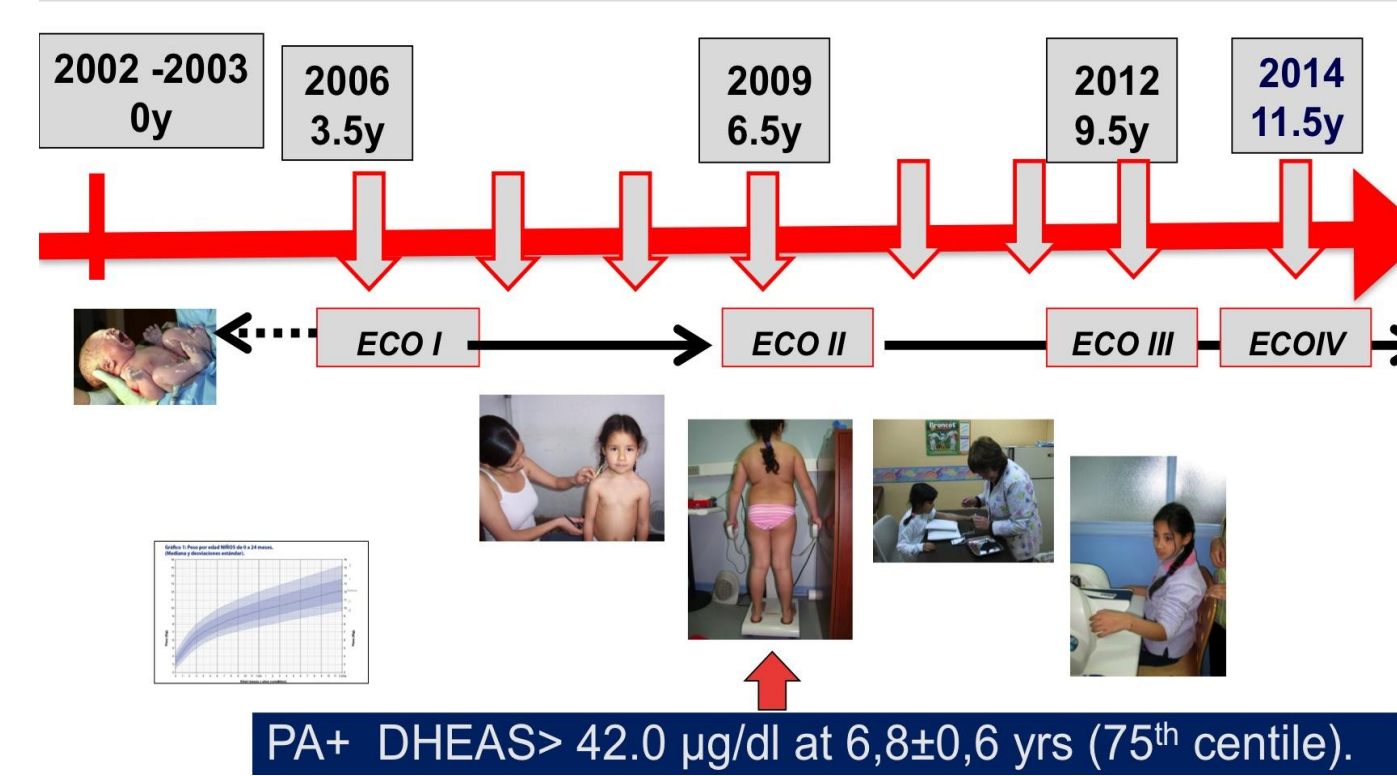
II. Hypothesis Premature adrenarche increases risk of earlier puberty and ovarian hyperandrogenism independent of birth weight and adiposity

III. Objectives : in girls with biochemical adrenarche i) determine timing of pubertal events ii) determine pattern of Ovarian morphology/hormones and adrenal hormones

III. SUBJECTS AND METHODS



Chilean Study of growth and Obesity (ECO)
1200 Chilean term infant BW 2500-4500 grs



- TII was defined age at thelarche in girls (B2)
- At \sim age 7 y n=492 g we measured serum DHEAS (RIA, DSL, Webster, TX (sens= $2.5 \mu\text{g/dl}$, intra CV= 3.5% and inter CV= 5.1 %), Insulin (RIA, Siemens Medical Solutions Diagnostics, Sens=0.5 mUI/ml, CV intra=8.6%, CVinter=10.2%) and glycemia (GOD-PAP).
- At Tanner II, IV and 1 yr post menarche : an early morning fasting sample for: Testosterone, Androstendione and 17OH Progesterone measured by HPLC-MS/MS. Estradiol measured by RIA. FSH, LH and SHBG measured by IRMA (Izotop). Serum AMH was assayed using an AMH/MIS ELISA kit (Beckman Coulter Inc.) + DHEAS+ Glycemia and insulin.
- Statistics: Mann-Whitney test was used to compare difference in the medians of high DHEAS group (HD) and normal DHEAS (ND). Logistic regression models to assess the relation between DHEAS and anthropometric, metabolic and gonadal hormones were adjusted by chronologic age at DHEAS sampling and BMI SDS. A survival analysis was used to estimate median age of Tanner attainment.

IV. RESULTS

Results in tables are presented as mean \pm SD

Table 1: Number of assessed girls

	B2	B4	1 yr post
ND	398	316(72%)	270
HD	101	121(28%)	101
	410 (83%)	437 (89%)	371 (75%)

Table 2: Clinical characteristics

	HD	ND	p
Age (yr)			
Thelarche (T)	9.5 \pm 1.1	9.7 \pm 1.1	<0.05
Pubarche (P)	9.3 \pm 0.2	9.8 \pm 0.2	<0.001
B4	11.1 \pm 0.8	11.4 \pm 0.9	<0.001
Menarche	11.6 \pm 0.9	12.0 \pm 0.9	<0.01
B2-Menarche	2.6 \pm 1.1	2.5 \pm 1.1	=0.86
B2 before P2	67%	61%	<0.05

Table 3: Anthropometric characteristics

	AP + (n=101)		AP - (n=297)		p-value
	Mean	DS	Mean	DS	
Age yr	8.8 (95%CI: 7.9-9.3)		9.3 (95%CI: 9.1-9.6)		
Weight (kg)	34.64	8.28	34.93	8.46	0.77
Height (cm)	133.80	8.00	136.02	7.86	0.02
Waist/hip ratio	66.09	8.71	65.69	8.81	0.69
Weight SDS	1.09	1.11	0.81	0.96	0.06
Height SDS	0.25	1.02	0.05	0.95	0.07
BMI SDS	1.10	1.13	0.78	1.08	0.01

At TII, girls who developed were heavier

These differences persisted after adjustments by body mass index (BMI SDS) and HOMA.

Table 4: Pubertal development

	n=96 HD=35	n=216 HD=66	p
Birth weight (K)	2.5-3.0	3.0-4.0	
	Age (Yr)	Age (Yr)	
Thelarche	8.9 \pm 1.2	9.4 \pm 1.3	<0.01
Pubarche	10.0 \pm 0.9	10.2 \pm 0.9	<0.05
Menarche	11.6 \pm 0.9	11.9 \pm 0.9	<0.01

B2, B4, 1 yr postmenarche HD

No differences in glycemia, insulin, Total Cholesterol, LDL, visfatin, HOMA

B2
~ lower HDL 46.3 \pm 10.6 vs 49.2 \pm 11.2 (p = 0.05)

1 yr post-menarche
higher insulin 12.8 \pm 7.8 vs 11.0 \pm 5.4 (p = 0.01)
higher TG 103.5 \pm 60.6 vs 90.6 \pm 39.2 (p = 0.02)

	HD	ND	p	HD	ND	p	HD	ND	p
17 OH prog ng/ml	0.26 \pm 0.17	0.29 \pm 0.23	0.413	0.42 \pm 0.25	0.43 \pm 0.25	0.77	0.47 \pm 0.27	0.54 \pm 0.35	0.080
Androstendione ng/ml	0.34 \pm 0.20	0.26 \pm 0.14	0.002	0.89 \pm 0.40	0.78 \pm 0.33	<0.005	0.95 \pm 0.36	0.89 \pm 0.37	0.146
Testosterone ng/ml	0.08 \pm 0.05	0.07 \pm 0.04	0.020	0.20 \pm 0.10	0.18 \pm 0.09	0.06	0.20 \pm 0.07	0.19 \pm 0.08	0.513
DHEAS $\mu\text{g/dl}$	102.7 \pm 39.7	53.2 \pm 20.9	<0.001	128.2 \pm 56.4	77.9 \pm 34.9	<0.001	132.5 \pm 55.2	77.9 \pm 37.5	<0.001
AMH ng/ml	3.69 \pm 2.1	4.30 \pm 2.5	0.047	2.3 \pm 1.52	2.54 \pm 1.66	0.117	3.40 \pm 2.2	3.40 \pm 1.90	0.939
LH UI/L	0.59 \pm 0.65	0.49 \pm 0.55	0.217	4.06 \pm 3.03	3.86 \pm 3.36	0.613	3.40 \pm 2.30	4.10 \pm 3.20	0.086
FSH UI/L	2.78 \pm 1.90	2.80 \pm 1.80	0.950	5.65 \pm 1.84	5.81 \pm 1.98	0.494	5.80 \pm 1.90	6.20 \pm 2.90	0.186
SHBG nmol/L	62.0 \pm 21.8	65.3 \pm 26.8	0.379	42.7 \pm 20.4	47.5 \pm 19.7	<0.05	34.2 \pm 14.1	42.0 \pm 18.4	<0.001
Estradiol pg/ml	18.8 \pm 14.0	16.5 \pm 12.7	0.191	47.0 \pm 48.9	41.0 \pm 29.1	0.151	29.4 \pm 26.0	34.1 \pm 40.3	0.282
FAI	0.54 \pm 0.47	0.46 \pm 0.54	0.308	1.93 \pm 1.28	1.52 \pm 1.30	<0.05	2.44 \pm 1.56	1.91 \pm 1.31	<0.001

	Tanner 2			Tanner 4			Year after menarche		
	HD	ND	p	HD	ND	p	HD	ND	p
Weight change > 0.67 SDS	22 (22.5)	76 (25.1)	0.88	21 (21)	73 (28.4)	0.2	23 (23)	74 (27.4)	0.2
BMI > 2 SDS	20 (20.4)	37 (12.2)	0.07	18 (18)	32 (12.5)	0.2	24 (24)	36 (13)	0.01
Glycemia mg/dl	89.9 \pm 7.8	88.3 \pm 7.1	0.05	87.7 \pm 8.7	86.6 \pm 6.6	0.1	86.4 \pm 7.0	85.0 \pm 7.1	0.09

V. CONCLUSIONS

*Girls with high DHEAS presented earlier breast and pubic hair (9.3 vs 9.8 yr) development, menarche (11.7 vs. 12 yr) and higher BMI SDS throughout puberty. Time between B2 and menarche was similar as well as ovarian size 1 yr after menarche. HOMA-IR was only higher at B2 however HD group showed persistent mild hyperandrogenism.

*Conclusion: in Chilean adolescents, PA is associated with earlier breast, pubic hair and menarche and higher BMI SDS throughout puberty. We believe our findings support that adrenarche is not a benign process and continuous follow-up of this cohort is a unique opportunity to address prospectively the interrelationships of PA, early growth and adiposity as determinants of ovarian function and metabolic risks.

Supported by Fondecyt 1140447 1120326, WCRF:2010/245. Contact info vmericq@med.uchile.cl

