Premature adrenarche in girls at pubertal onset is associated with high androgens, but lower AMH concentrations

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DISCLOSURE:
Nothing to disclose

I. BACKGROUND

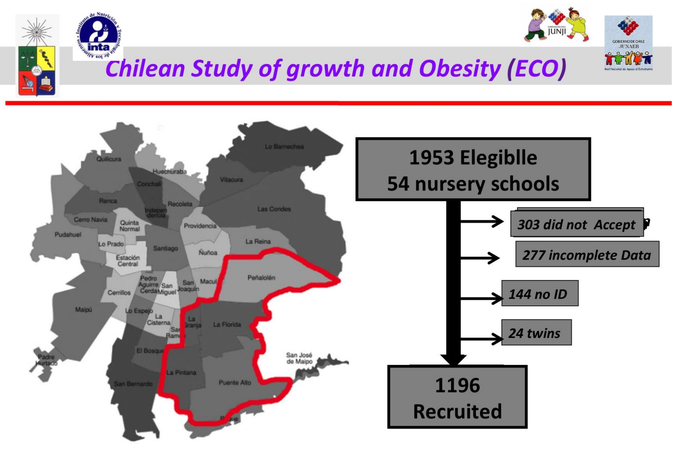
- ✓ Adrenarche is a progressive maturational process of the adrenal zona reticularis resulting in increased secretion of the adrenal androgen precursor DHEA and its sulphate ester DHEA, being clinically evident approximately 2 yr before the onset of puberty.
- ✓ Premature adrenarche (PA) is defined biochemically by increased levels of DHEA and 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 ~ 40 µg/dl (above average for 6 to 8 yr)
- ✓ Early infancy weight gain has been also associated with increased metabolic risk, earlier puberty, and premature adrenarche (PA).
- ✓ PA has been considered a benign condition until recently, where association to increased metabolic risk has arisen.
- ✓ 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 .
- ✓ AMH has been postulated as a useful marker reflecting increased antral follicle pool.

II. AIM: To determine whether PA in children at pubertal onset (TII) determines:

1. An increase in ovarian and adrenal androgens
2. Differences in AMH levels

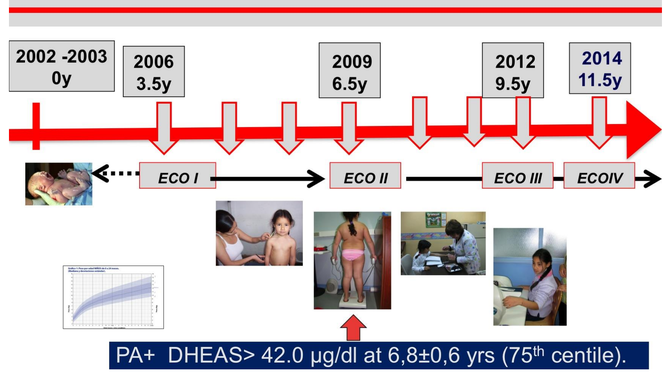
III. SUBJECTS AND METHODS

Chilean Study of growth and Obesity (ECO)



GOCS: 1200 PRE-School children

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



PA+ DHEAS> 42.0 µg/dl at 6,8±0,6 yrs (75th centile).

✓Annual clinical examination: Tanner staging, body composition (skinfolds and bioimpedanciometry) and skeletal maturation (BonAge; Sunlight Co).
✓TII was defined age at telarche in girls (B2)
✓At ~ age 7 y we measured serum DHEAS (RIA, DSL , Webster, TX (sens= 2.5 µg/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 : An early morning fasting sample for Testosterone (sens= 0.02 ng/ml, intra CV= 2.1% and inter CV=4.0%), Androstendione (sens= 0.04 ng/ml, intra CV= 3.2% and inter CV=5.1%) and 17OH Progesterone (sens= 0.05 ng/ml, intra CV= 2.5% and inter CV=5.6%) were measured by HPLC-MS/MS. Estradiol was measured by RIA (Pantex, sens= 5.0 pg/ml intra CV =5.7% and inter CV= 7.9%). FSH (sens= 0.15 mUI/ml, intra CV= 3.3% and inter CV=4.1%), LH (sens= 0.08 mUI/ml, intra CV= 3.7% and inter CV=4.9%) and SHBG (sens= 1.0 nmol/L, intra CV= 3,9% and inter CV= 6,9) were measured by IRMA (Izotop). Serum AMH was assayed using an AMH/MIS ELISA kit (Beckman Coulter Inc., sensitivity 0.1 ng/ml, intra CV = 5.3% and inter CV = 8.7%).
✓Statistics: multiple regression lineal models were used to assess the relation between PA and anthropometric and metabolic profile at TII, adjusting by chronologic age at DHEAS sampling . Further Adjustments performed by were body mass index (BMI) & HOMA. A survival analysis was used to estimate median age of Tanner attainment.

IV. RESULTS

Results in tables are presented as mean±SD

Clinical characteristics

	AP + (n=101)		AP - (n=297)		
	Mean	DS	Mean	DS	p-value
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

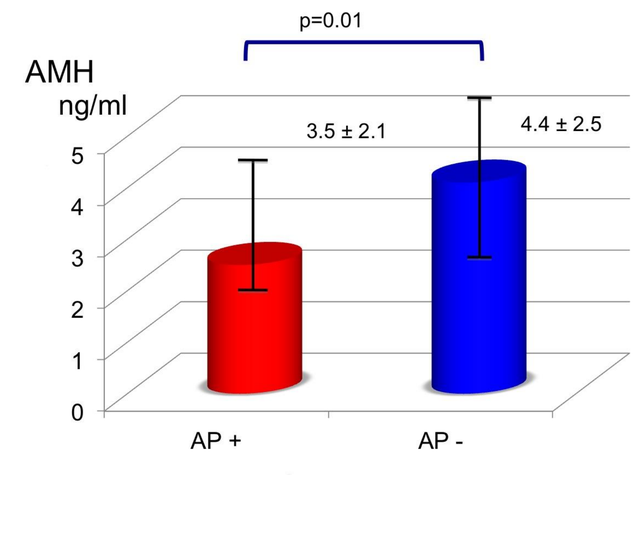
At TII, girls who developed were heavier

Goal 1: To determine whether PA in children at pubertal onset (TII) determines an increase in ovarian and adrenal androgens

	AP + (n=70)		AP - (n=200)		
	Mean	DS	Mean	DS	p-value
17OHP (ng/ml)	0.26	0.17	0.29	0.23	0.35
Androstendione (ng/ml)	0.32	0.19	0.26	0.14	0.01
Testosterone (ng/ml)	0.08	0.05	0.06	0.04	0.03
LH (mUI/ml)	0.50	0.57	0.47	0.53	0.67
FSH (mUI/ml)	2.53	1.79	2.70	1.77	0.45
Estradiol (pg/ml)	17.81	15.45	16.11	11.80	0.34

These differences persisted after adjustments by body mass index (BMI SDS) and HOMA . Androstendione p<0.0001, Testosterone p<0.005, AMH p<0.05, FAI p <0.05

Goal 2 To determine whether PA in children at pubertal onset (TII) determines differences in AMH concentrations



V. CONCLUSIONS

•Girls with history of PA initiated their puberty at an earlier age.

•At this stage of puberty (TII) they were heavier and also showed a mild hyperandrogenism in concert with lower concentrations of AMH.

•Continuous follow-up of this cohort is a unique opportunity to address prospectively the interrelationships of PA and PCOS development which development which is not possible at this stage.

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

DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS