# Premature adrenarche is associated to precocious thelarche but not to precocious gonadarche or pubarche in Chilean adolescents

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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 above 40 µg/dl (above average for 6 to 8 yr) although within normal limits for early puberty, and minimal if any elevation of other androgens
- ✓ 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 polycystic ovarian syndrome (PCOS) and lower birth weight, which may depend on ethnic background.

## II . Aim

**To describe the risk of precocious thelarche, pubarche and gonadarche in children with premature adrenarche .**

## III. SUBJECTS AND METHODS

✓A longitudinal Chilean cohort ( ~ 20% indigenous/Mapuche origin) the Growth and Obesity Cohort Study (GOCS, n=1052, 49.9%F) followed from 2006 (born in 2002), PA defined by DHEAS (RIA) > 75th percentile for each gender ( 45.1 M, 42.0 F microg/dl at mean age 6.8±0.6 yr) (*Corvalan, AJCN 2013,97(2):318-25)*

✓In these children we performed annual clinical examination including Tanner staging together with body composition (skinfolds and bioimpedanciometry) skeletal maturation. Bone age measurements were obtained from the left hand by using an ultrasound method (BonAge; Sunlight Co)

✓At ~ age 7 y we measured serum DHEAS (RIA, DSL , Webster, TX, intra- and interassay CVs of 3.5 and 5.1 %,respectively) , IGF-I concentration ( using standardized locally developed RIA requiring sample extraction as a first step (sensitivity: 5 ng/mL; intra- and interassay CVs: 8.6% and 10.2%, respectively), Leptin (RIA, Millipore) and Insulin (RIA, Siemens Medical Solutions Diagnostics)

✓Logistic regression models adjusted by age and BMI assessed the relation between DHEAS and premature thelarche (PT <8 yr) gonadarche ( PG= testicular volume > 3 cc at age < 9 yr) and pubarche (PP,<8 yr F,<9 yr M)

## IV. RESULTS

**Results in tables are presented as mean±SD**

| | Male | Female |
|---|---|---|
| | n=535 | n=542 |
| Age yr,mean (SD) | 6.9 (0.5) | 6.9 (0.4) |
| Height SDS,mean (SD) | 0.1 (0.9) | 0.2 (0.9) |
| BMI SDS,mean (SD) | 0.9 (1.3) | 0.9 (1.0) |
| Obese n (%) | 110 (21.4%) | 75 (14.3%) |
| ≥Tanner II n (%) | 401 (75.0%) | 527 (97.2%) |
| PA n ( %) | 128 (25.6 %) | 138 (27.6%) |
| PG | 35 (7.0%) | |
| PT | | 87 (16.5%) |
| ≥TannerII(VP)n (%) | 401 (75.0%) | 521 (96.0%) |
| PP | 17 (3.2%) | 20 (3.8%) |

| Male | | | |
|---|---|---|---|
| | PA n=128 | control n=369 | p-value |
| Obesity n,% | 44, 41.1 | 86, 21.7 | <0.001 |
| PP n,% | 5, 3.9 | 11, 3.0 | ns |
| PG n,% | 10, 7.8 | 25, 6.8 | ns |
| | | | |
| Female | | | |
| | PA n=136 | control n=356 | p-value |
| Obesity n,% | 26, 37.1 | 44, 12.1 | 0.06 |
| PP n,% | 11, 8.1 | 7, 2.0 | <0.001 |
| PT n,% | 42, 30.4 | 45,12.4 | <0.001 |

| Male | PG | control | p-value | PP | control | p-value |
|---|---|---|---|---|---|---|
| BMI SDS | 1.8±1.5 | 0.9±1.2 | <0.001 | 1.1±1.1 | 0.9±1.3 | ns |
| Height SDS | 0.7±0.8 | 0.1±0.9 | <0.001 | 0.5±0.7 | 0.1±0.9 | 0.08 |
| BW (k) | 3.7±0.4 | 3.4±0.4 | ns | 3.3±0.4 | 3.4±0.4 | ns |
| Insulin µg/dl | 5.8±2.2 | 5.5±1.9 | ns | 5.1±0.4 | 5.5±2.0 | ns |
| IGF-I ng/dl | 207±60 | 187±62 | 0.06 | 189±63 | 188±62 | ns |
| Leptin ng/dl | 6.5±4.9 | 5.6±3.7 | ns | 4.8±2.6 | 5.7±3.8 | ns |
| | | | | | | |
| Female | PT | control | p-value | PP | control | p-value |
| BMI SDS | 1.1±1.0 | 0.8±1.1 | 0.03 | 1.1±1.1 | 0.9±1.1 | ns |
| Height SDS | 0.6±1.0 | 0.1±0.9 | <0.001 | 0.7±1.0 | 0.2±0.9 | <0.001 |
| BW (k) | 3.4±0.4 | 3.4±0.4 | ns | 3.4±0.4 | 3.4±0.4 | ns |
| Insulin µg/dl | 5.7±1.9 | 5.6±1.6 | ns | 5.2±0.6 | 5.6±1.7 | ns |
| IGF-I ng/dl | 191±46 | 174±42 | <0.001 | 190±42 | 176±43 | ns |
| Leptin ng/dl | 6.0±3.8 | 6.0±4.2 | ns | 5.6±3.3 | 6.0±4.2 | ns |

**Crude and adjusted Odds ratio and 95%CI between PA and PG, PT and PP**

| | OR1 | 95%CI | OR2 | 95%CI | OR3 | 95%CI | OR4 | 95%CI |
|---|---|---|---|---|---|---|---|---|
| Male PG | 1,2 | 0.5; 2.5 | 1,4 | 0.6; 3.0 | 0,9 | 0.4; 2.3 | 0,9 | 0.4; 2.1 |
| Male PP | 1,3 | 0.4; 3.9 | 1,3 | 0.4; 3.9 | 1,2 | 0.4; 3.7 | 1,2 | 0.4; 3.7 |
| Female PT | 3,1 | 1.9; 5.0 | 3,4 | 2.1; 5.7 | 3,2 | 1.9; 5.3 | 2,9 | 1.7; 5.0 |
| Female PP | 4,4 | 1.7; 11.6 | 3,7 | 1.3; 10.3 | 3,6 | 1.3; 10.5 | 3,6 | 1.2; 10.4 |

**1: crude model, 2: adjusted by age & birthweight, 3: adjusted by model 2+BMI, 4: adjusteb by model 3+ insulin, leptin & IGF1**

- ▪PG was observed in 7% of boys, PT 17% in girls and PP was 3% & 4% respectively
- ▪<u>In females</u> we observed a 16.5% of PT, 3.8 % of PP
- ▪In girls with PA we observed 30.4% of PT, 8.1% of PP % , 37% of obesity, all significantly higher than girl with no PA.
- ▪Girls with PA, had a 3.1 OR of PT (p<0.001) which increased to 3.4 when adjusted by DHEAS sampling age and BW (p<0.001)
- ▪Girls with PA, had a 4.4 OR of PP (p<0.005) which decreased to 3.6 (p<0.05) when adjusted by DHEAS sampling age , BW and BMI
- ▪The OR for PT or PP with additional adjustments by the remaining metabolic or anthropometry markers did not change

- ▪<u>In males</u> we observed a 8.7% of PG , and 4.3 % PP
- ▪In boys with PA we observed 7.7% of PG and 3.9% of PP, similar to those with no PA, but boys with PA had significantly % of obesity (41% vs 22%)
- ▪Boys with PA had no additional risk of PG or PP compared to non PA boys.

## V. CONCLUSIONS

In Chilean adolescents, precocious events of pubertal development were, in line with worldwide secular trend of earlier sexual maturations. PA was only associated with PT and PP in females. In boys only obesity was the main determinant of PG. Continuous follow-up of this cohort is a unique opportunity to address prospectively the interrelationships of PA, early growth, adiposity as determinants of gonadarche, pubertal rate and sequence progression and ovarian function.

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