Pubertal events, reproductive and growth hormones and predictive factors in healthy girls with Transient Thelarche

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I. BACKGROUND

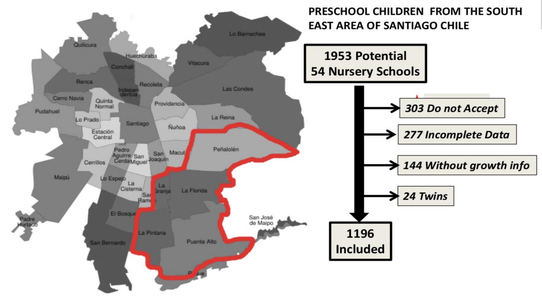
Transient Thelarche (TT) corresponds to the appearance, regression and subsequent reappearance of the breast bud in girls. Only a single study about its frequency and progression is available (Lindhardt Johansen JCEM 2017), describing 12 cases among 98, suggesting that it appears to be a peripheral occurrence independent of central puberty, not affecting subsequent pubertal progression.

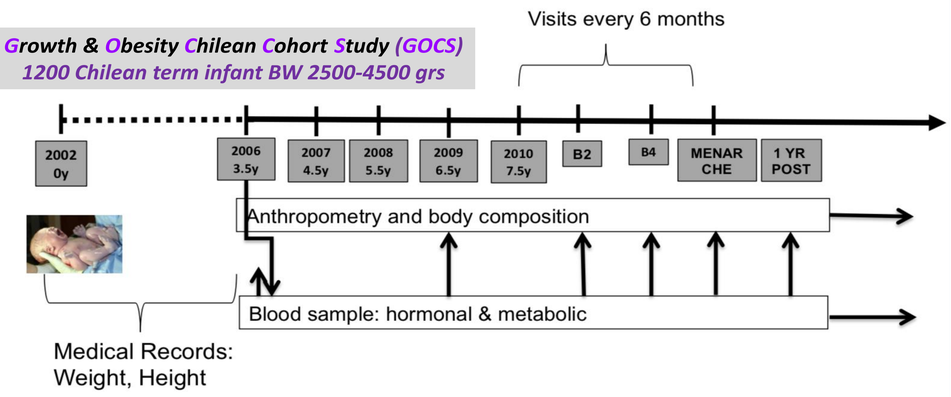
II. OBJETIVES

To determine whether TT girls (group 1), compared to those girls who do not present this event (group 2,) have:

i) A different timing/sequence of pubertal events
ii) A different pattern of reproductive and growth hormones
iii) Predictive factors associated with pubertal onset

III. SUBJECTS AND METHODS





Design: A prospective, longitudinal population-based study. **Patients:** Girls (n=508)
Assays: Hormones (table). Genotyping was performed with KASP assays (LGC Genomics, Hoddesdon, UK) in Denmark (SNPs: *FSHB* -211G>T (rs10835638), *FSHR* -29G>A (rs1394205) and *FSHR* c.2039A>G (rs6166) in 434 girls)
Statistics: Mann-Whitney, t students or Wilcoxon tests were used to compare between the groups 1 and 2 and for intragroup comparison (group 1: TT vs B2) and the results were also adjusted by BMI and age.

Hormone	Assay	Sens	Intra CV	Inter CV
Testosterone	HPLC MS/MS	0.025 ng/ml	2.6 %	4.0 %;
Androstenedione	HPLC MS/MS	0.030 ng/ml	2.4 %	5.1%
17 OH Progesterone	HPLC MS/MS	0.06 ng/ml	2.9%	5.6 %
DHEAS	HPLC MS/MS	100 ng/ml	3.5%	5.1%
LH	IRMA	0.06 mUI / ml	4.0%	5.3%
FSH	IRMA	0.06 mUI / ml	4.5%	5.6%
SHBG	IRMA	0.5 nmol/L	3.9%	6.9 %
IGF-1	RIA	5 ng/ml	8.6 %	10.2%

IV. RESULTS

A 7% (n=37) of the girls presented TT. (group 1)

Table 1: Age at presentation (years) of pubertal milestones and velocity of progression. Data are presented as average ± SD

Age	Group 1 (n=37)	Group 2 (n=471)	p
TT	7.9 ± 1.4		
Girls TT before 8 years	24 (65%)		
TT before 8 years	7.0 ± 0.7		
B2 (B2)	10.3 ± 1.1	9.2 ± 1.2	<0.001
Girls B2 before 8 years		91 (19%)	
B2 before 8 years old		7.4 ± 0.4	
PH2 before DB2	17 (46%)	108 (23%)	0.005
Pubarche	9.4 ± 1.1	9.6 ± 1.0	0.170
B4	11.2 ± 0.9	10.9 ± 0.9	0.221
Menarche	12.3 ± 0.8	12.0 ± 1.0	0.040
B2-B4	1.37 ± 0.7	1.79 ± 0.9	0.021
B2-Menarche	2.19 ± 0.8	2.74 ± 1.1	0.005
Meternal age of menarche	12.8 ± 1.8	12.7 ± 1.7	0.706

Table 2: Comparison of hormone concentration profiles at transient thelarche (TT) in girls from Group 1 according to the age of presentation, below 8 years (n=24) or at older than 8 years (n=13) and B2 adjusted by chronological age and BMI SDS at sampling time. Data are presented as means ± SD

	Group 1		p	Group 1		p
	TT < 8 years	TT ≥ 8 years		TT (n=37)	B2	
DHEAS µgr/dl	25.6 ± 8.2	32.8 ± 6.3	0.009	28.0 ± 6.2	65.0 ± 4.5	<0.001
Testosterone ng/ml	0.03 ± 0.004	0.05 ± 0.007	<0.001	0.03 ± 0.01	0.09 ± 0.04	<0.001
Androstenedione ng/ml	0.17 ± 0.05	0.20 ± 0.02	0.046	0.16 ± 0.02	0.31 ± 0.08	<0.001
IGF-1 ng/ml	166 ± 0.8	158 ± 22	0.082	164 ± 10	233 ± 14	<0.001
AMH ng/ml	3.3 ± 1.4	3.5 ± 1.2	0.666	2.9 ± 0.6	4.4 ± 0.4	<0.001
LH mUI/ml	0.11 ± 0.004	0.21 ± 0.085	<0.001	0.13 ± 0.08	0.84 ± 0.61	<0.001
FSH mUI/ml	2.3 ± 0.5	2.5 ± 0.6	0.286	2.3 ± 0.2	3.0 ± 1.5	0.013
SHBG ng/ml	69.4 ± 20.0	63.9 ± 24.5	0.466	67.6 ± 20.9	53.9 ± 20.2	<0.001
Insulin µUI/ml	8.9 ± 1.1	9.5 ± 1.4	0.159	9.1 ± 0.8	14.7 ± 4.7	<0.001
Estradiol pg/ml	6 ± 0.5	7 ± 1.0	<0.001	6 ± 0.9	20 ± 8	<0.001
FAI	0.16 ± 0.06	0.41 ± 0.29	<0.001	0.2 ± 0.2	1.0 ± 0.9	<0.001

Table 3: Comparison of hormone concentration profiles during Breast Tanner 2,4 and 1 year post menarche in girls from Group 1 versus Group 2 adjusted by chronological age and BMI SDS at sampling. Data are presented as means ± SD

	B2			B4			1 year post menarche		
	Group 1	Group 2	p	Group 1	Group 2	p	Group 1	Group 2	P
DHEAS µgr/dl	65.0 ± 4.5	65.8 ± 10.8	0.599	93.1 ± 19.4	93.5 ±9.4	0.843	79.2 ± 7.5	93.4 ± 8.4	<0.001
Testosterone ng/ml	0.09 ± 0.04	0.08 ± 0.02	0.011	0.2 ± 0.05	0.2 ± 0.01	1.000	0.2 ± 0.03	0.2 ± 0.005	1.000
Androstenedione ng/ml	0.31 ± 0.08	0.31 ± 0.08	1.000	0.71 ± 0.11	0.82 ± 0.04	<0.001	0.88 ± 0.1	0.92 ± 0.1	0.058
IGF-1 ng/ml	233 ± 14	238 ± 22	0.193	367 ± 89	270 ± 11	<0.001	256 ± 18	247 ± 9	<0.001
AMH ng/ml	4.4 ± 0.4	4.1 ± 0.4	<0.001	2.9 ± 0.4	2.4 ± 0.2	<0.001	4.2 ± 0.8	3.3 ± 0.3	<0.001
LH mUI/ml	0.84 ± 0.61	0.52 ± 0.17	<0.001	4.7 ± 0.7	3.9 ± 0.2	<0.001	3.5 ± 0.2	4.0 ± 0.5	<0.001
FSH mUI/ml	3.0 ± 1.5	2.8 ± 0.6	0.108	6.0 ± 0.4	5.7 ± 0.3	<0.001	5.6 ± 0.8	6.1 ± 0.3	<0.001
SHBG nmol/L	53.9 ± 20.2	63.6 ± 13.9	<0.001	39.6 ± 10.1	45.8 ± 7.8	<0.001	43.6 ± 7.9	39.4 ± 8.4	0.018
Insulin µUI/ml	14.7 ± 4.7	8.9 ± 1.0	<0.001	13.1 ± 2.7	12.6 ± 2.7	0.350	9.2 ± 2.2	11.6 ± 2.4	<0.001
Estradiol pg/ml	20 ± 8	17 ± 3	<0.001	31.9 ± 3.5	43.4 ± 2.1	<0.001	27.7 ± 2.0	33.9 ± 0.9	<0.001
FAI	1.0 ± 0.9	0.6 ± 0.3	<0.001	1.8 ± 0.9	1.7 ± 0.4	0.253	1.9 ± 0.6	2.1 ± 0.5	0.061

Girls did not present differences in anthropometry throughout follow-ups, neither in age at maternal menarche nor in genetic variants that were studied.

V. CONCLUSIONS. Our findings in this large cohort confirm that TT

appears to be a frequent event which does not appear to be mediated by HPG axis activation, adiposity, peripheral conversion of androgens to estrogens, or genetic variations in FSHβ/FSHR. These findings suggest that environmental exposure may play a role, especially for earlier ages at TT. We confirmed that TT girls entered puberty more frequently by the pubarche pathway and the subtle differences in hormonal levels at the initiation of puberty and later, suggest that a follow-up of this cohort is necessary to confirm the benign nature of this phenomenon.