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### PRECOCIOUS PUBARCHE: DIFFERENTIAL DIAGNOSIS

59 patients (49 females and 10 males; aged 7 months - 9 years) were studied in the last 13 years for precocious isolated pubarche. We evaluated clinical signs, bone age (B.A.), hormonal findings (ACTH-test, LHRH-test), ultrasound examination of adrenal and gonads. We divided patients in four groups:

A) 81.3% Idiopathic precocious pubarche (HPP): with normal steroids plasma levels, high DHEAs plasma levels (47.3%), advanced B.A. (29%), advanced statural age (S.A.) (22.9%), normal pelvic ultrasonography.

B) 10.1% Late Onset CAH (LOCAH): elevated basal and after ACTH stimulus 17 OH Progesteron plasma levels in all patients, advanced B.A. (83%), advanced S.A. (50%), normal pelvic ultrasonography.

C) 6.9% Central Precocious Puberty (CPP): elevated LH plasma levels, advanced B.A. and advanced S.A. in 100%. In all patients large size of gonads were found with pelvic ultrasonography.

D) 1 female (1.7%) had adrenal adenomas demonstrated by hormonal data and adrenal ultrasound and tomography.

In conclusion: HPP is the most frequent cause of premature pubarche, a differential ethiological diagnosis can be easily performed by hormonal and ultrasound investigations.

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### \*Scientific Institute H San Raffaele, Department of Radiology, University of Milan, Italy SPONTANEOUS PUBERTAL DEVELOPMENT IN TURNER SYNDROME

We studied 114 girls with Turner syndrome aged from newborn to 30 years old. We observed spontaneous pubertal development and correlation with karyotype, statural growth and bone mineralization. 15% of the patients presented spontaneous telarche, 5% (6 girls) had spontaneous menarche at a mean age of 12 years. One of these patients had stopped menses after 7 years, another one presented oligomenorrhoea. 76% of these patients were above 50% percentile for age following Ranke chart. 23.5% of the patients with spontaneous pubertal development had 45 XO karyotype. Bone mineralization was lower than normal values in all patients with spontaneous pubertal development. There were no correlation between pelvic ultrasonography and clinical signs of pubertal development.

We conclude that clinical features are actually the best criteria to start substitute therapy.

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### PRELIMINARY RESULTS OF A MULTICENTER TRIAL OF DEPOT LEUPROLIDE ACETATE FOR CENTRAL PRECOCIOUS PUBERTY

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GnRH analogs are now preferred therapy for central precocious puberty (CPP). Although short term trials of the depot preparation of leuprolide acetate (TAP Pharmaceuticals, Inc.) have been reported, results from large series of patients are unavailable. We report the results of GnRH stimulation tests in 127 patients in screening for CPP at 9 centers over a 20 month period. Fifty-three patients (49 F, mean age 7.0 yr) with peak stimulated LH >10 IU/L (DELFTIA) and bone age (BA) advancement >1 yr were enrolled in a protocol initiating 300 ug/kg IM q4wk (7.5-15 mg) before age 9 yr in females and 10 yr in males. Follow-up GnRH stimulation tests were performed at 4, 12, 24, 36, 48, and every 24 weeks thereafter; BA was evaluated q24wk. Comparing baseline and 24wk serum levels (mean±SE), estradiol fell from 19.5±4.9 to <5 pg/ml, peak FSH from 13.3±1.1 to 1.1±0.1 IU/L, and peak LH from 33.1±4.4 to 0.8±0.2 IU/L. Peak LH did not suppress (<1.75 IU/L) in one 13 mo old female until 36 weeks of therapy. No females had detectable estradiol (>5 pg/ml) during therapy, but 3/4 males had transient detectable testosterone (>10 ng/dl). 86% of subjects showed regression or no change in Tanner breast (or genital) stage. Height velocity diminished from 11.5±0.8 to 6.5±0.7 cm/yr, but BA/CA was unchanged in the first 6 mo. There were no local injection reactions. We conclude that depot leuprolide is immediately effective in suppression of pubertal progression and gonadotropin and sex steroid production, but bone age advancement continues in the initial treatment period. Further data will assess the effect of long term therapy upon predicted and final heights.

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### FIRST YEAR RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF LOW DOSE ETHINYL ESTRADIOL FOR FEMINIZATION DURING GROWTH HORMONE THERAPY FOR TURNER SYNDROME

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The appropriate age to initiate estrogen replacement therapy in adolescents with Turner syndrome (TS) is uncertain due to the potential for a deleterious effect on skeletal maturation and final height. We report results from the initial phase of a placebo-controlled, double-blind, multicenter trial of low dose oral ethinyl estradiol (EE) in TS subjects 12 to 14.99 years old, already receiving 0.05 mg/kg/d of growth hormone, and with Tanner breast stage 1 or 2 (mean 1.2) at enrollment. Fifty-two patients were randomized to 0, 25, or 100 ng/kg/d of EE and were evaluated every 6 months. Groups were identical for age (13.3 yr), bone age (10.8 yr), karyotype, growth rate (5.7 cm/yr) and height at enrollment. The following presents results at 12 months of therapy (mean ±SD):

EE dose (ng/k-d)	n	Growth vel (cm/yr)	ΔTanner Br	ΔBA (mo)	ΔPAH (cm)
0	11	5.4 ±1.4	0.5 ±0.9	11.4 ±5.7	1.0 ±3.8
25	14	5.6 ±1.5	0.9 ±0.7	13.3 ±6.7	1.4 ±3.2
100	16	5.1 ±1.1	1.4 ±0.6	16.7 ±10.6	-0.5 ±4.8

The addition of EE during GH therapy in 12-15 yo girls with TS resulted in dose-dependent breast development and commensurate increases in skeletal maturation, which occurred in the absence of change in height velocity. Significant reduction in PAH could not be ascertained. We conclude that either 25 or 100 ng/kg-d EE, with coordinate therapeutic risk and benefit, may be useful in inducing feminization in Turner syndrome.

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### HEIGHT VELOCITY (HV) DURING PUBERTY IN RELATION TO BONE AGE (BA).

It is generally assumed that HV and BA correlates well with chronological age (CA). 83 girls aged 9.9 ± 0.3 yrs and 58 aged 6.9 ± 0.3 yrs as well as 79 boys aged 10.9 ± 0.2 yrs and 71 aged 7.9 ± 0.3 yrs were followed longitudinally during 5.1 ± 1.4 and 4.6 ± 1.4 yrs, respectively. Heights, bone ages (determined by two independent observers, by the method of Greulich & Pyle, using the score system) were recorded every 6 months.

In girls, 105 of them presented a peak HV of 8.6 ± 1.2 cm/yr (mean ± 1 SD) at a mean CA of 11.8 ± 0.8 yrs. Mean BA was 12.2 ± 0.8 yrs. Mean peak HV for bone age was 8.2 ± 1.6 cm/yr. In advanced puberty, peak HV occurring before CA=10.6 yrs (-1.5 SD for age), mean peak HV was 8.8 ± 1.1 cm/yr for CA, mean BA was 11.9 ± 0.8 yrs, 1.3 ± 0.8 yrs in advance for CA. In retarded puberty, peak HV occurring after CA=13.0 yrs (+1.5 SD), mean peak HV was 7.9 ± 1.1 cm/yr for CA, mean BA was 12.2 ± 0.8 yrs, 0.8 ± 0.8 yrs delayed.

In boys, 70 of them presented a peak HV of 10.0 ± 1.2 cm/yr at a mean CA of 13.9 ± 1.1 yrs and a mean BA of 13.4 ± 0.8 yrs. Mean peak HV for bone age 10.8 ± 2.4 cm/yr. In advanced puberty, peak HV occurring before CA=12.8 yrs (-1.5 SD for age), mean peak HV was 11.0 ± 1.2 cm/yr and 10.8 ± 2.4 cm/yr for a mean BA of 13.5 ± 0.8 yrs, 1.2 ± 0.5 yrs in advance for CA. In retarded puberty, mean peak HV occurring at 15.7 ± 0.6 yrs (+1.5 SD for age), mean peak HV was 9.5 ± 1.9 cm/yr, mean BA was 13.6 ± 0.9 yrs, 1.5 ± 0.7 yrs delayed for CA. In both sexes, mean peak HV for BA was similar for all the groups.

In total, there is a good agreement between CA and BA in normal puberty. Peak HV decreases with CA. Because of discrepancies for HV between CA and BA in advanced and in delayed puberty, it is suggested that evaluation of HV in pubertal children during growth treatment be made in relation to BA rather than CA.

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### DIURNAL RHYTHMS OF TESTOSTERONE AND LUTEINIZING HORMONE IN BOYS BEFORE AND DURING THE ONSET OF PUBERTY.

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Secretory rhythms in LH and testosterone (T) before and during the onset of puberty were studied. Forty boys (28 prepubertal and 12 pubertal) with short stature aged 4.4 to 19.3 yr participated to this study. Blood samples for LH and T measurements were drawn every 20 min for 24 h after obtaining consent. All the subjects were followed up by measuring height and weight and evaluating pubertal development every 3 months for 1 to 7 yr (mean 3.4 yr). There were definite diurnal rhythms in both LH and T in all of the subjects. Serum T showed maximum level at 0400-0800 h which delayed to the LH peak, decreased gradually and attained minimum level at 2000-2400 h. The ratio of T levels during 0400-0800 h period to the whole 24-h were 1.38 ± 0.16 (mean ± SD) at prepuberty and it rose to 1.87 ± 0.08 at midpuberty. Mean 24 h LH levels rose with age; they were 0.15, 0.76 and 0.98 IU/l at 1-2 yr before, at 0-1 yr before and at the time of onset of puberty, respectively. There were no significant changes in LH pulse frequency with the pubertal development. All of the 40 boys showed positive cross-correlation between the LH and T concentrations. Mean lag time of the diurnal rhythms in T to LH was 7.1 ± 2.8 h at prepuberty. It decreased with developing puberty and came to 1.4 ± 0.9 h at midpuberty. In conclusion, the diurnal rhythms of T and LH are already exist before the onset of puberty. There is a delay in the diurnal rhythm of T to LH and the lag time decreases with developing puberty.