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IMPORTANCE OF BONE AGE (BA) FOR SUBSEQUENT RESPONSE TO BUSERELIN THERAPY IN CENTRAL PRECOCIOUS PUBERTY (CPP).

In patients with CPP, we lack criteria to determine optimal age when GnRH agonist therapy should be stopped. In 18 patients with CPP (16 girls, 2 boys) treated with buserelin intranasally (1.2 to 1.8 mg/day) for 1 to 3 yrs (mean: 2.3 yrs), we examined whether BA affected the subsequent rates of growth and of bone maturation. During therapy, pubertal development showed regression in 10 patients and arrest in 8, while mean (± 1SD) height velocity (pre-treatment, 10.7 ± 3.6 cm/yr) decreased to 6.5 ± 1.5, 4.6 ± 1.4 and 3.6 ± 1.2 cm/yr after 1, 2 and 3 yrs of treatment, respectively. In order to evaluate the growth rates vs the rates of bone maturation, SD Scores (SDS) of height for BA (TW_2, RUS) were calculated before and during the 1st, 2nd and 3rd yrs of therapy. The difference in SDS of height for BA observed during therapy (range: -1.2 to +1.2 SD) were directly related (r = +0.51) to BA (range: 10.1 to 13.7 yrs). This was because increase in BA resulted in a reduced ΔBA/ΔCA (range: 1.9 to 0.1, r = -0.58). Thus, although height velocity is decreasing with age and duration of buserelin therapy, the concomitant reduction in BA velocity results in an apparent growth saving effect occurring with advancement in BA. Therefore, study of BA does not provide arguments for stopping GnRH agonist therapy. Possible criteria related to the capacity of achieving a residual growth spurt after stopping treatment warrant further evaluation.

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ADVERSE CHANGES IN SERUM BONE GLA-PROTEIN (BGP) AND ALKALINE PHOSPHATASE (AP) IN PRECOCIOUS PUBERTY (PP) DURING THERAPY.

Serum concentrations of BGP, AP, IGF-1 and peak growth hormone (GH) after clonidine were studied in 10 girls and 2 boys, aged 6.2-8.7 years, with central PP during treatment with a combination of LHRH analogue and cyproterone-acetate (CA) for 1.5-2.5 years. Linear growth declined from 11.3 ± 0.6 cm/year (mean±SEM) to 6.0 ± 0.6 in the first 6 months of therapy and further to 3.7 ± 0.6 after 2.5 years. Serum BGP levels were elevated prior to therapy compared with age-matched children ($p<0.001$). During the first 6 months of treatment serum BGP decreased ($p<0.05$) but then showed a significant increase ($p<0.01$) during the following 2 years to levels not different from pretreatment values. Serum AP decreased throughout the study especially in the first 6 months ($p<0.001$). Peak serum GH values decreased ($p<0.05$) after initiation of therapy, whereas serum IGF-1 remained significantly elevated ($p<0.001$) for age. In normal puberty serum levels of BGP and AP reflect bone formation and these parameters together with IGF-1 increase during the skeletal growth spurt. In this study serum AP seems to reflect the declining linear growth rate concomitant with an increase in serum BGP. Thus our data indicate a different bone turnover in PP during treatment with LHRH analogue and CA.

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PREMATURE THELARCHE VARIANT : A NEW SYNDROME OF PRECOCIOUS SEXUAL MATURATION.

Studies of gonadotrophin pulsatility and pelvic ultrasound morphology distinguish between isolated premature thelarche (IPT) and central precocious puberty (CPP) (Eur J Pediatr 1986; 145:190). We have observed 6 girls (age range, 2.2 - 6.9 yrs) with premature sexual development which fitted neither diagnostic category.

Features characteristic of IPT were absent pubic hair (n=6), fluctuating breast size (n=4), a small uterus on ultrasound without an endometrial echo (n=6). Features more consistant with CPP were accelerated growth (n=5) and progressive breast enlargement (n=2). Ovarian ultrasound morphology showed that all 6 girls had ovaries containing large numbers of small cysts between 3 - 4 mm in diameter.

5 girls had predominant FSH response to i/v GnRH. The results of overnight serum gonadotrophin secretion were not typical of CPP or IPT. Discrete LH and FSH pulses were seen with neither predominating.

5 girls were treated unsuccessfully with intranasal ($D\text{-}Ser^6$) GnRH but 2 girls responded to subcutaneous administration. 2 girls had spontaneous regression of breast development after intranasal therapy ceased.

We believe that our patients represent a spectrum between IPT and CPP which is relevant for prognosis and treatment as well as for understanding disorders of ovarian maturation.

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INFLUENCE OF LOW OR HIGH ESTROGEN ACTIVITY ON GROWTH AND PLASMA Sm-C IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY (CPP)

The effect of low or high E2 levels on Sm-C and growth have not been evaluated in children over prolonged periods. In this study we investigated the relationship between plasma E2 and Sm-C levels and pubertal growth in 21 girls with CPP, aged 4.5-8.8 yrs, after a mean duration of puberty of 1.1±0.2 yrs. They were divided into 2 groups according to their estrogen activity as assessed by plasma E2 ("low E"< 30 pg/ml) and by vaginal maturation index (VMI). Sm-C was measured in unextracted plasma. For both groups the mean CA and duration of puberty were similar. GH peak AITT was normal in all. $p<0.01$*, 0.001**.

m±SEM	E2 pg/ml	VMI	BA-CA (yr)	cm/yr	Sm-C u/ml
I low E	23±6	23±7	1.7±0.5	8.2±0.6	1.2±0.15
	**	*	*	NS	**
II high E	52±5	49±3	2.7±0.2	8.3±0.6	2.6±0.13

In groups I and II combined, E2 correlated positively with Sm-C ($r=0.57$, $p<0.01$) but not with growth rates. Low E activity increased growth with normal Sm-C levels. High E activity was not more growth stimulating but accelerated BA. Group I patients followed over 2 yrs accelerated their growth without changing of predicted final height.

In conclusion these data showed the biphasic effect of E2 and suggest that low E activity may stimulate growth by a GH mediated or even direct skeletal effect.

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STUDY OF TESTICULAR ANTI-MULLERIAN HORMONE IN PERSISTENT MULLERIAN DUCT SYNDROME.

Persistent Müllerian duct syndrome was diagnosed at surgery for inguinal hernia and/or bilateral cryptorchidism in 6 otherwise normal XY boys aged 2 mos to 7 yrs, including 3 brothers. In two cases, the inguinal hernia contained the uterus and tubes, tightly attached to both testes. In the other patients, the hernial sac contained initially only the homolateral testis and tube, but gentle traction exteriorized the uterus and contralateral testis, suggesting that, in this syndrome, testicular position depends on the location of the fallopian tube. Testicular biopsies were studied by immunohistochemistry using a polyclonal antibody specific for anti-Müllerian hormone (AMH), and by AMH bioassay, using the rat fetal Müllerian duct as target organ. In normal boys, immunohistochemistry detects AMH up to 6 yrs (Tran & all., 1987). In 4 patients from 2 sibships, both techniques gave negative results, indicating that persistence of Müllerian derivates resulted from AMH deficiency. In two unrelated cases, however, immunoreactive AMH was present, and biologically active, suggesting either target organ insensitivity to AMH or fetal testicular AMH production starting after the end of the AMH-sensitive window of Müllerian development. We conclude that the persistent Müllerian duct syndrome is etiologically heterogeneous and may therefor follow different patterns of inheritance.

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RECIPROCAL CHANGES IN 5α-REDUCTASE (5αR) AND 17β-OXIDOREDUCTASE (17OR, E.C.1.1.1.64) ACTIVITY IN HUMAN FORESKIN BEFORE PUBERTY.

The activity of 5αR in human genital skin has been shown to be high during the first months of life and to decrease thereafter. However, no comparable data are available on 17OR which is involved in the reversible interconversion of testosterone (T) and 4-androstenedione (A), two potential substrates for 5αR. We measured these enzymes in foreskin homogenates obtained from normal newborns and boys up to 8 yrs of age using A as a substrate in a radioenzymatic assay. Foreskin from 32 boys were first pooled in 5 age groups (1, newborns; 2, 1-6 mo; 3, 6-12 mo; 4, 1-3 yrs; 5, 3-8 yrs) for the simultaneous determination of 5αR and 17OR. Additional samples (n = 27) representative of the same age groups were then processed individually. The activity of 5αR is significantly higher (Kruskal-Wallis test: p = .002) in newborns than in older children. In contrast, 17OR is very low at birth (41 ± 3 $pmol.h^{-1}.mg^{-1}$ protein, mean ± SEM, n = 7) and increases steadily (group 5: 279 ± 135, n = 6). Despite large interindividual variation, these values are significantly different (p = .001). The low activity of foreskin 17OR in the normal infant is surprising since testicular production of T which also involves 17OR activity is high during this period. This suggests a tissue-specific regulation of 17OR. Moreover, maturation of this enzyme in human foreskin appears to be independent of gonadal function. Whether the reciprocal changes in 5αR and 17OR in foreskin are causally related remains to be established.