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J.H.Brämswig*, E. Jerzenbeck*, G.Schellong* (Intr. by W. v.Petrykowski)
Department of Pediatrics, University Children's Hospital, 44 Münster, West-Germany

A RETROSPECTIVE ANALYSIS OF THE PSYCHOSOCIAL SITUATION BEFORE, DURING AND AFTER THERAPY IN 202 WOMEN TREATED FOR EXTREMELY TALL STATURE

A questionnaire was sent to 240 adult women previously treated for extremely tall stature. 202 (84.2%) responded. Their mean age was 21.0 ± 1.9 (SD) years. 157 women recalled, that they were extremely tall already in childhood with growth related problems described by 89 of them. For the majority expected and/or actual height problems were the reasons for treatment. The considerable weight gain during therapy was the most frequently mentioned side-effect. Today, 186 women have a positive or mostly positive and only 9 a negative attitude towards their present height (180.6 ± 4.2 cm). Some height related problems with clothes, furniture, public appearance etc. still existed in about 10 - 30 % of them. Questioned about their "ideal height" most women wished to be 175.4 ± 3.8 cm. 176 women responded with "yes" to the question, if they would positively reconsider treatment. Thus, therapy for tall stature meets with general approval in most treated women.

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G.K.Hinkel*, J.Arand* (Introd.by R. Illig)
Children's Hospital, Medical Academy "Carl Gustav Carus" Dresden, GDR

INFLUENCE OF LOW DOSES OF ANABOLICS ON GROWTH, DEVELOPMENT AND PERFORMANCE OF CHILDREN AND YOUTH WITH CONSTITUTIONAL GROWTH RETARDATION (CGR)

In a long-term study 66 boys with CGR and psychosocial problems were treated with low doses of 4-chlor-dehydro-methyl-testosterone (0,1 mg per kg body weight for 8 weeks, intervals of 4 weeks) for 2,7 ± 1,3 years and followed up to the 20th year of life. A control group without such treatment included 26 boys.

Results:

1. Skeletal maturity at the beginning of therapy and difference of final and predicted body height show a negative correlation. If therapy starts at bone age of less than 10 years the predicted height will not be reached (- 6,1 ± 7,3 cm). On the contrary predicted height is not diminished when treatment with anabolics starts when the bone age is 10 years or more (- 0,5 ± 3,3 cm).
2. Matched pairs of 19 treated boys with an identical control group (bone age of 10 years or more at beginning of the therapy) revealed no difference of the predicted and final body height at the age of 20 years.

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Z. Dickerman, R.J. Barkey*1, R. Prager-Lewin*, F. Gahnem*, Z. Laron. Inst. Pediat. Adolesc. Endocr. Beilinson Med. Ctr., Petah Tikva, Sackler Sch. Med., Tel Aviv Univ. & Dept. Pharmacol. Fac. Med.[1], Technion Haifa, Israel.

LOW IMMUNOREACTIVE (IR), NORMALLY BIOACTIVE LH IN MALES WITH DELAYED PUBERTY.

Low IR-LH basal and LRH-stimulated (50 mcg/m^2, iv) plasma levels were repeatedly found in 8 boys, aged 14-16 yrs with delayed puberty (basal IR-LH .8+.3, peak 2.2+.8 vs 1.2+.4 and 9.2+ 3.7 mIU/ml respectively in matched controls). At spontaneous termination of puberty, 3½ yrs following referral, with still low IR-LH, their LH bioactivity was compared with that of 8 matched controls, using a rat leydig cell bioassay system with LER-907 (NPA) as standard. The plasma LH bioactivity was estimated to be .33+.1 and .2+.05 for the basal LH and .8+.2 and .83+.2 mIU/ml for the LRH-stimulated plasma in both groups, respectively. The ratio of the LH-bioactivity to IR-LH was found to be higher in the patients (1.89+.4) than in the control group (.8+.1, $p < .05$).

In 3 of the patients low IR-LH levels were found also during sleep, with no significant change from the wake time IR-LH plasma levels.

The plasma testosterone levels of the patients were normal (400+80 ng/dl) and increased following a prolonged LRH stimulation (500 mcg iv over 3 hrs) in 4 of the patients (530+60 ng/dl).

It is concluded, that in some boys with delayed puberty consistently low IR-LH plasma levels with normal LH-bioactivity may be found.

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G. Butler*, F.C.W. Wu*, C.J.H. Kelnar
MRC Reproductive Biology and Cytogenetic Units and Royal Hospital for Sick Children, Edinburgh, Scotland, U.K.

EFFECTS OF SHORT TERM PULSATILE GnRH STIMULATION ON SPONTANEOUS EPISODIC LH/GnRH SECRETION IN PREPUBERTAL AND HYPOGONADOTROPHIC MALES

LH pulses are detectable in some prepubertal children but accurate determination of pulse frequency has been limited by the sensitivity of the LH RIA, the low pituitary responsiveness to GnRH and the relatively short periods of sampling. 8 males aged 12.0 to 19.8 years with delayed puberty and/or growth delay were studied to determine whether pituitary responsiveness can be amplified, and endogenous LH/GnRH pulse frequency accurately assessed, by short term low dose (0.1 ug/Kg) pulsatile GnRH priming. GnRH was administered subcutaneously every 2 hours between 23.00 and 09.00h for 7 days by portable minipumps. Before and after the 7-day treatment, blood samples were obtained at 10 minute intervals for 8-12 hours between 20.00-08.00h for RIA measurement of gonadotrophins and T followed by I/V GnRH (0.25 ug/kg) test.

In 4 patients with a significant pre-treatment nocturnal LH rise, pulsatile GnRH stimulation did not significantly increase endogenous LH pulse frequency or amplitude. In 4 subjects with probable Kallmann's syndrome or idiopathic hypogonadotrophic hypogonadism, responses to I/V GnRH increased dramatically (LH 5.6 ± 0.5 fold, FSH 6.5 ± 2.3 fold). In 2 of them no LH pulses were observed before or after GnRH priming and only FSH pulses (4/12h and 1/12h) post-stimulation. In the other 2, LH pulses increased from zero to 7/12h and 3 to 6/8h respectively.

These data show that nocturnal pulsatile GnRH priming can augment pituitary responsiveness and increase the number of detectable gonadotrophin secretory episodes only in prepubertal patients without pre-existing nocturnal LH elevation. Increasing GnRH pulse amplitude may be a major mechanism in pubertal initiation. Short term pulsatile GnRH priming may be useful in distinguishing permanent hypogonadotrophic hypogonadism from constitutionally delayed puberty.

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J.HONOUR, R.STANHOPE*, P.HOLOWNIA*, C.G.D.BROOK.
Cobbold Laboratories and Department of Chemical Pathology, Middlesex Hospital, London, ENGLAND

A SENSITIVE OESTRADIOL ASSAY FOR USE IN GIRLS WITH DISORDERS OF SEXUAL MATURATION.

Low plasma oestradiol concentrations are difficult to determine for a number of reasons of which the bridge recognition phenomenon (iodination at the same locus as the site for hapten formation) is one factor which limits assay sensitivity. Hence using an antibody to oestradiol-6-CMO-BSA and homologous label (oestradiol -6-iodohistamine) the "minimal detectable concentration" is 18pmol /L even with measurements in triplicate. We have evaluated a heterologous configuration at the site of attachment of oestradiol to the antibody (oestradiol-11β-succinyl-BSA) and the label (oestradiol-11α-tyrosine methyl ester). With some antibodies this gave 3-4 fold increase in sensitivity although in certain cases the assay specificity was compromised by cross reaction (16%) with oestrone.

Serum concentrations of gonadotrophins and oestradiol at 15 minute intervals throughout the night have been determined in 8 girls with central precocious puberty treated with D-Ser-GnRH analogue (Hoechst) and in 14 girls with delayed puberty treated with nocturnal pulsatile GnRH. We have observed a rise in oestradiol after the third or fourth LH pulse just as in normal girls (Boyar, 1974). This contrasts with our findings in boys in early puberty in whom testosterone rose after the first nocturnal LH pulse. These findings are important to the timing of blood samples to assess sex steroid secretion during puberty.

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U.Zumsteg*, J.L.Rime*, A.Blumberg* (Introd. by R.Zurbrügg), F. Hadžiselimović, J.Girard, R.Zurbrügg
Children's Hospitals Biel and Basel, Switzerland

LONG-TERM MANAGEMENT OF CENTRAL PRECOCIOUS PUBERTY WITH A LONG-ACTING INTRANASAL LHRH ANALOGUE($LHRH_a$)

6 girls and 1 boy(1.25-7.5 yrs at first symptoms) were treated for 1.1-2.1 yrs with intranasal $LHRH_a$ D-Ser(TBU)^{6}EA^{10}LHRH(buserelin), 24-46 mcg/kg/d, adjusted up to 30-80. Urinary LH and FSH (LH_u, FSH_u) and the response to an intranasal challenge with natural sequence LHRH were evaluated at regular intervals.

Secondary sexual characteristics regressed in 4 (1 girl afterwards excluded), stabilized in 1 and increased in 2 children. Height velocity (measurement interval 365±35 d) normalized, decreasing from 14.0 to 6.3 cm/y, always mean values, with a change of -5.6 in SDS related to chronological age(CA). During the last 6-13 mos SDS for bone age(BA) decreased in 5 children by -0.95 and stabilized in 1 girl. $\Delta BA/\Delta CA$ was 2.5 after the first 6.5-13 mos and fell to 0.6 during the last 6-13 mos. Gonadotrophins: Basal LH_u fell from 0.85 to 0.38 U/mmol creatinine and stimulated LH_u from 1.64 to 0.3. Basal FSH_u fell from 1.09 to 0.65 and stimulated FSH_u from 1.81 to 0.5. Testicular biopsy after 6 mos showed partial atrophy of Leydig cells and total atrophy in 2/3 of the tubuli after 13 mos coinciding with a regression of testicular volume restored after 6 wks off therapy and dose reduction.

Intranasal buserelin is thus an effective treatment of PP in terms of puberty ratings, height velocity and bone age. Basal and LHRH-stimulated urinary LH and FSH reliably reflect pituitary suppression suitable for dose adjustments.