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PATTERNS OF OVARIAN-STEROIDOGENIC RESPONSE TO GnRH ANALOG CHALLENGE AT ONSET OF PUBERTY IN GIRLS DIAGNOSED OF PREMATURE PUBARCHE DURING CHILDHOOD.

Post-pubertal girls diagnosed of premature pubarche (PP) during childhood show an increased incidence of functional ovarian hyperandrogenism (FOH). We assessed the ovarian-steroidogenic response to the GnRHa leuprolide acetate (500 μg sc) in 16 PP girls (chronological age (CA): 10.1 ± 1.0, bone age (BA): 10.8 ± 0.6) and in 10 controls (C) (CA: 11.9 ± 0.7, BA: 10.8 ± 0.5) at onset of true puberty (Tanner B2), to ascertain whether the supranormal 17-hydroxyprogesterone (17-OHP) response, characteristic of FOH, appears early in pubertal development; 21-hydroxylase and 3ß-hydroxysteroid dehydrogenase deficiencies had been ruled out in all.

Plasma LH and FSH levels were measured 0 and 6h post-GnRHa stimulation, and plasma estradiol (E2), and steroid intermediates were determined pre- and 24 h post-GnRHa challenge. GnRHa administration elicited pubertal gonadotropin responses and a 10-fold increase in plasma E2 levels in all subjects. Six PP girls had basal and post-stimulated androstenedione (D4-A) responses similar to those of C (100.3 ± 11.8 vs 93.5 ± 15.2; 133.7 ± 29.4 vs 137.8 ± 11.1 ng/dl respectively), whereas in the remaining 10, basal and post-GnRHa D4-A levels were significantly higher (198.8 ± 16.7 and 267.8 ± 9.9 ng/dl, $p<0.01$ and $p<0.007$, respectively). Baseline and post-stimulated plasma DHEA and DHEA-S levels were significantly higher in PP girls than in C; pre- and post-GnRH challenge plasma 17-OHP and testosterone (T) levels were similar in all. No correlations were found between D4-A, 17-OHP, DHEA, DHEA-S and T values post-GnRHa stimulation and values of the same steroids at PP diagnosis. Our results show that the distinct 17-OHP response post-GnRHa stimulation typical of FOH is not present at onset of true puberty in PP girls; disregulation of cytochrome P450c17a might occur later in puberty. Although 10 PP girls showed high basal and post-stimulated D4-A levels, the increase elicited by GnRHa was similar to that of C, ruling out ovarian hyperproduction of D4-steroids in early stages of pubertal development.

Long-term follow-up of these patients through later stages of puberty is necessary to assess the significance of these elevated D4-A levels in the eventual development of FOH.

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FSH AND hCG TREATMENT IN BOYS WITH RETENTIO TESTIS

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**Introduction**: The medical treatment of retentio testis remains controversial because of ineffectiveness and/or side-effects. FSH seems to influence the spontaneous descent of the testis; furthermore it induces LH receptors. Therefore we performed a double-blind, placebo-controlled study to investigate the effect of FSH with hCH (half the recommended WHO dose) versus hCG alone in retentio testis patients. **Methods**: 22 boys with retentio testis were investigated. Retractile testis were excluded. Group A (n = 14, 4 bilat, 10 unilat; mean age 3.15 yrs) was treated with 150 IU FSH 2x/wk during 2 weeks followed by 150 IU FSH and 250 IU hCG 2x/wk for another 4 weeks. Group B (n = 8, 2 bilat, 6 unilat; mean age 3.3 yrs) was treated with 250 IU hCG 2x/wk for 6 weeks. Testicular position, volume and consistency as well as the appearence of scrotum, length of penis were determined at week 0, 2, 4, 6 and 12 by 2 independent investigators. Blood investigation consisted of LH, FSH, T and SHBG. Successfull descent was considered when the testis reached a mid or low scrotal position at week 12. **Results**: In group A 6/18 testes descended successfully. In group B 5/10 testes descended successfully. Of the unsuccessfully treated patients 6 patients of group A and 4 of group B were operated. Of these patients 6/8 testes of group A and 4/5 testes of group B showed anatomical abnormalities, which could explain the lack of hormonal response. There were no significant differences in hormonal parameters between the 2 groups. In both groups no serious side effects were mentioned or observed. **Conclusions**: 1. Half the recommended WHO dose of hCG is sufficient to reach successful descent in 50 % of treated patients with no serious side-effects; this response rate is in agreement with the literature. 2. FSH does not seem to have an additional effect on the success rate. 3. Most of the unsuccessfully treated patients showed anatomical abnormalities at operation.

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FINAL HEIGHT AND LONG-TERM FOLLOW-UP OF 108 ADULT PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA.

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Worldwide, many patients with congenital adrenal hyperplasia (CAH) have already reached adulthood, but reports on the long-term outcome are still sparse. In our clinic population of grown-up CAH patients over 16 years of age, 108 subjects could be evaluated (68 females, 40 males). Simple virilizing CAH (SV-CAH) due to 21-hydroxylase deficiency (21-OHD) was present in 56 patients (38 females, 18 males), due to 11-hydroxylase deficiency in 3 patients (1 female, 2 males). Salt-losing 21-OHD (SL-CAH) occurred in 44 patients (24 females, 20 males), late-onset 21-OHD in 5 females. Final height in females was 156.6±5.9 (SD) cm (range:143.0-169.0 cm; n=68), in males 166.9±7.0 cm (range:150.9-181.1 cm; n=40). There was no significant difference between females and males in final height, expressed as standard deviation score (SDS). However, final height in both, females and males, was markedly lower than target height ($p<0.0001$). For each gender, measured final height did not differ between patients with SL-CAH and those with SV-CAH. Furthermore, younger grown-up CAH patients were not taller than older patients. On average, timing of pubertal development was normal, although menstrual irregularities and decreased testicular volumes were common. We conclude that despite adequate treatment CAH patients do not reach their full height potential.

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THE QUALITY OF LIFE IN ADULT FEMALE PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA (CAH). AN EVALUATION OF THE MEDICAL, SOCIAL AND PSYCHOLOGICAL CONSEQUENCES OF CAH IN ADULT FEMALE PATIENTS.

We report the results of a comprehensive, cross-sectional quality-of-life evaluation. All patients of the University Children's Hospital with the diagnosis of CAH above 18 years and raised as females were contacted and 2/3 (n=44) of the eligible patients (n=63) participated and were compared to a matched, healthy control group.

Most of the patients (48.9%) suffered from the simple-virilizing (sv-) CAH, 34% had the salt-wasting (sw-) form and 17 % the late-onset (lo-) form of CAH. In 35% of the patients genital virilization was pronounced (Prader stage 3 or 4); in 61% the correction was a combination of clitoral recession and vaginal reconstruction.

While patients were comparable to controls in most sociodemographic characteristics, a higher proportion of patients were living alone 52% versus 37%, and only 22% versus 38% of the control group had children (1 sv-, 3 sw-, 3 lo-CAH). The mean number of children, however, was 1.87 in both groups.

No major differences between groups were found in the quality-of-life assessment which pertained to physical state, psychological well-being, social integration and functional capacity. Patients differed from controls in reduced social competence and dominace (esp. sw-CAH). However, the major differences between the groups were apparent in the psychosexual identification with patients reporting to feel less feminine. Psychological adaptation was good in terms of high perceived social support.

Overall, the patients expressed a good quality-of-life both in the interview and the questionnaires with only few significant differences between the various clinical forms of CAH and the controls. However, the psychosexual identification is still problematic (esp. sw-CAH) and merits increased medical and psychological efforts.

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Identification of adrenoleukodystrophy gene and future therapy

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Adrenoleukodystrophy (ALD) is an X-linked disease characterized by progressive demyelination of the central nervous system (CNS) and adrenal insufficiency. Adrenal insufficiency may occur in boys with ALD who have not yet developed neurological symptoms and even remain the only clinical manifestation of ALD. However, when the neurologic manifestations associated with demyelination starts, no children escape rapid and severe deterioration leading to death within 2-4 years. The normal oxidation of very long chain fatty (VLCFA)-CoA in ALD patient's fibroblasts suggested that the gene coding for VLCFA-CoA synthetase was a candidate gene for ALD. Using positional cloning, we identified in Xq28 a gene partially deleted in 7% of ALD patients. Candidate exons were used to isolate cDNAs by exon-connection. The predicted protein sequence (745 aa) encode a peroxisomal transporter that may be involved in the import of the VLCFA-CoA synthetase but not the enzyme itself. We have moreover demonstrated that bone-marrow transplantation can correct or stabilize the evolution of the disease in 3 patients with the severe cerebral form. The use of autologous bone marrow after the insertion of a normal gene would circumvent the need for a histocompatible donor and may provide the most suitable gene therapy approach before attempting to deliver the ALD in the cells of CNS where it is expressed.

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HIGH FREQUENCY OF CARCINOMA-IN-SITU AND GONADOBLASTOMA IN CHILDREN AND ADOLESCENTS WITH ANDROGEN INSENSITIVITY (AI) AND GONADAL DYSGENESIS (GD). Jørn Müller, Niels E. Skakkebæk, Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark.

Individuals with AI and GD with a karyotype including a Y chromosome have a substantial increased risk of developing germ cell tumours as adults. We have previously reported a high frequency of carcinoma-in-situ (CIS) in children and adolescents with these disorders of sexual differentiation, and we herein update our experience with a total of 33 patients between 1 month and 20 years of age at the time of gonadectomy or biopsy. 21 patients with either complete or incomplete AI, and 12 patients with GD and 46,XY karyotype or 45,X/46,XY mosaicism were studied. The latter individuals had either female phenotype, ambiguous or male external genitalia. The gonadectomy and biopsy specimens were removed for prophylactic reasons, and neither ultrasound nor peroperative examination of the gonads raised suspicion of a germ cell tumour. The tissue was fixed in Stieve's or Cleland's fluid and analysed by conventional microscopy. The diagnosis of CIS and gonadoblastoma was made on morphological criteria. 5 (24%) of 21 patients with AI had CIS, and the preinvasive neoplasia was detected in patients with both complete and incomplete AI. 4 of 6 individuals with GD and a female phenotype had gonadoblastoma or CIS including a 9 year old girl with 46,XY GD, who additionally had areas with invasive neoplasia. 2 of 3 patients with 45,X/46,XY GD and ambiguous genitalia had CIS, and CIS was found in 3 of 6 males with GD. Thus, a total of 60% of the patients with GD had either CIS or gonadoblastoma. Since both CIS and gonadoblastoma can be considered to be preinvasive lesions, we recommend gonadectomy when the diagnosis of AI and GD is made, provided a female gender has been decided. In patients with GD and male phenotype, we suggest a biopsy at the time of diagnosis. If CIS is detected, either gonadectomy or close surveillance is advisable. If orchidectomy is not performed, a biopsy after puberty is recommended.