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Radioimmunoassays for hFSH and hLH
Using an Immunoadsorbent Separation Technique and Human Serum as Standard Matrix

Radioimmunoassays for the determination of the gonadotropins hLH and hFSH employing standards based on a human serum matrix were developed. The serum was depleted of the glycoproteohormones (hLH, hFSH, hCG, hTSH) by an immunadsorption technique.

The binding of the immuncomplex (AgAb) and the phase separation was accomplished by a novel PEG accelerated double antibody solid phase technique.

The requirement of identity between standard and unknown serum sample was fulfilled by using serum matrix for standards. As a consequence identical reaction kinetics were obtained and systematic errors avoided. Especially in pediatric diagnoses the fluctuation of the plasma protein content does not influence the separation by the immunoadsorption method. The methodological characteristics of the assays permit a reliable determination of hLH and hFSH values, especially in the low concentration range, were the normal values of children are encountered.

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Maturation of pituitary gonadotropin secreting potentiality in puberty.

To investigate the pubertal maturation of gonadotropin (Gn) secretion, early and mid-pubertal girls were received different rates of LH-RH infusion (0.01 and 0.1μg/m²/min for 4h) and a pulse of LH-RH (10μg) at the end of the infusion. Serial blood samples were obtained and serum LH and FSH were measured by RIA. The releasing effect was assessed as the increment of Gn during infusion and the priming effect as that of in response to a pulse. Sexual maturity ratings were recorded according to Tanner (T). I) At the lower infusion rates, there were no elevations of LH in early pubertal girls, whereas in mid-pubertal girls (T3), serum LH levels were markedly increased during infusion. At higher infusion rates, these releasing effects in early pubertal girls were about the same as that on LH. II) In early pubertal girls, the priming effects of LH-RH were minimal at both infusion rates. On the other hand, in mid-pubertal girls, even after much lower rates of infusion (0.001μg/m²/min), the increments of LH by a pulse were significantly greater than that without prior infusion of LH-RH.

In conclusion, the releasing and priming effects of LH-RH on LH are clearly seen at the mid-pubertal stage (T3) and these observations may imply that pituitary synthesizing and releasing abilities of LH are rapidly maturing at this stage.

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Adrenal steroid excretion in childhood and the mechanism of adrenarche.

24h urine collections from a mixed longitudinal sample of 180 boys aged 3 to 16.5 years were analyzed for steroid metabolites by gas-liquid chromatography. As expected DHA excretion rose markedly over the whole age range but especially between ages 7-9; by contrast, although a substantial rise in THDOC and THS excretion was noted. THB and THF excretions did not increase more than could be explained by surface area changes. Enzymic activities at each step in the biosynthetic pathway were determined by ratios of metabolites excreted. A fall in 3β-hydroxysteroid dehydrogenation, especially of non-17 hydroxylated steroids, a marked fall of 21 hydroxylation of 17 hydroxylated steroids and a lack of change of 11β-hydroxylation contrasted with a marked rise in 17,20 lyase activity. Studies in patients with disorders of growth and puberty showed adrenal androgens to be ACTH stimulable and dexamethasone suppressible.

These results are consistent with the hypothesis that a relative decline in the ability to synthesize cortisol leads to a marginal increase in ACTH production which is responsible for the rise of adrenal androgens which constitutes adrenarche. It does not seem necessary to postulate the existence of a separate adrenal androgen stimulating hormone, at least in man.

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Hypogonadotropic hypogonadism (HH) in congenital adrenal hypoplasia (AH). Two associated congenital disorders?

Pubertal failure appears to be a regular association in adolescent males with the so-called cytomegalic type of AH, of which some 12 cases so far have been described. We have followed up two unrelated boys since birth. The diagnosis of AH was based on adrenal failure including severe salt loss since the newborn period, abnormally low plasma glucocorticoids even after prolonged ACTH administration and lack of aldosterone response to orthostasis with high renin. In spite of regular treatment, both pts. had delayed growth and bone maturation and no spontaneous puberty. At age 17 (BA=14) and 16 (BA=12) yrs, HCG produced a marked increase of serum testosterone (T) (< 0.2 → > 400 ng/ml) and a descent of inguinal small (< 2 ml) testes in both pts. Tests of the hypothalamo-pituitary axes showed an isolated lack of LH and FSH response to LHRH even during advanced puberty induced by HCG and T treatment. In contrast, a third pt. with idiopathic Addison's disease (first symptoms at 4 yrs.) had spontaneous puberty.

In conclusion, HH in AH may be do to lacking stimulation of the fetal gonadotropin secretion by the fetal adrenals.

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Changes in sensitivity of the gonadotropin-gonadal negative feedback axis (Gonadostat) in patients with gonadal dysgenesis (G.D.).

In 31 patients with G.D. adult castrate levels of urinary gonadotropins (mean±SEM = 3637±426 mIU/hr for FSH, and 2621±508 mIU/hr for LH) were obtained by a chronologic age of 11 and a bone age of 10. Oral, conjugated estrogen (CE) treatment in 18 individuals, ages 12-17, caused gonadotropin suppression to the prepubertal range (FSH <160, LH <90 mIU/hr) with 0.6 or 0.3 mg of CE daily, but not with 0.15 mg. According to published data in the acutely castrate woman, more than 2.5 mg of CE daily is needed to suppress LH and FSH into the normal adult range. All of 9 girls on continuous treatment with 0.6 or 0.3 mg of CE escaped from gonadotropin suppression with FSH (2700±527 mIU/hr) and LH (1460±265 mIU/hr) levels returning to the castrate range over a 9-30 mo period. In 5 agonadal girls, ages 12-15, who had previously been exposed to endogenous or exogenous estrogen, gonadotropins were not suppressed to prepubertal levels with 0.6 or 0.3 mg of CE. In contrast, in a 34-yr old woman with G.D. and no previous estrogen treatment, 0.3 mg of CE was sufficient to suppress FSH and LH excretion to the prepubertal range. Conclusions: 1) The gonadostat remains highly sensitive to estrogen in the absence of exposure to female sex steroids. 2) Escape from gonadotropin suppression during CE treatment suggests that further maturational changes occur with estrogen exposure. 3) Sex steroids themselves may modify the gonadostat.

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Steroidal puberty in girls with Turner's syndrome.

To study the role of the adrenal cortex versus the ovaries in steroidal puberty, we determined serum steroids in (125 samples from) 60 girls with Turner's syndrome (aged 6-20 years) and in 200 healthy girls. Pregnenolone, dehydroepiandrosterone (DHEA), progesterone, 17-hydroxyprogesterone, androstenedione, testosterone and dihydrotestosterone were measured with a radioimmunoassay after chromatography on Lipidex-5000. The levels of pregnenolone, progesterone and 17-hydroxyprogesterone were similar in the two groups. Testosterone and androstenedione levels were also not different in girls below age 10 years. But later the girls with Turner's syndrome had clearly lower levels, about 50% of the reference levels for testosterone and 60% for androstenedione. The early prepubertal rise in DHEA level was similar in the two groups, but at age 14.5 years the girls with Turner's syndrome had only about 80% of the reference levels. The ovaries thus seem responsible for most of the pubertal increase in circulating testosterone and androstenedione, and possibly a part of the late pubertal increase in DHEA.